

METHOD OF TREATMENT OF ASTHMA

CROSS-REFERENCE TO RELATED PATENT APPLICATION

[0001] This specification claims the benefit of priority to U.S. Provisional Patent Application No. 63/607,314 (filed 7 December 2023). The entire text of the above-referenced patent application is incorporated by reference into this specification.

FIELD OF THE DISCLOSURE

[0002] The present disclosure provides methods for treating moderate or severe asthma in a particular subgroup of patients. The methods disclosed herein comprise administration of anti-IL-33 antibodies or antibody variants thereof, specifically tozorakimab.

BACKGROUND

[0003] The following discussion is provided to aid the reader in understanding the disclosure and does not constitute any admission as to the contents or relevance of the prior art.

[0004] Asthma is a chronic inflammatory disease of the airways characterized by bronchial hyperreactivity and reversible airflow limitation. International treatment guidelines for asthma recommend ICS as first line therapy (GINA 2020). For individuals who are symptomatic on medium dose ICS monotherapy, step-up therapy with LABA is the recommended next treatment option followed by other controller therapies including leukotriene receptor antagonists, theophylline, and oral corticosteroids. ‘Biologic agents’ (eg, omalizumab and benralizumab) that inhibit specific molecular targets such as IgE or Th2 cytokines and their respective receptors are reserved for those with severe uncontrolled asthma. Furthermore, all currently approved asthma controller therapies have little or no impact on the natural history of the disease (i.e., most people with moderate-severe asthma need life-long therapy). There is a clear unmet need for asthma therapies that not only better control symptoms, but lead to disease modification.

[0005] Numerous studies have shown a key role for IL-33 in asthma. The genes encoding IL-33 and ST2/IL1RL1 have been identified as major susceptibility loci for human asthma in several genome wide association studies (Bonnelykke et al 2014; Gudbjartsson et al 2009; Hirota et al 2011; Moffat et al 2010; Shrine et al 2019; Torgerson et al 2011; Wan et al 2012) and were among the few genes reproducibly found to be associated with asthma across diverse ethnic groups. In addition, a rare IL-33 loss-of-function mutation has been recently described

that reduces blood eosinophil counts and protects from asthma (Smith et al 2017). The protective effect remained, although weaker, after correcting for eosinophil counts, suggesting that IL-33 may influence asthma risk in part by controlling blood eosinophil count, and also through additional biological pathways (Mousas et al 2017). Two Phase II studies support a role for anti-IL-33 therapy in asthma treatment. In a proof-of-concept study involving adult patients with moderate-to-severe asthma, REGN3500 (itepekimab) monotherapy (ICS and LABA maintenance therapy were withdrawn during the trial) met the primary endpoint of improvement in loss of asthma control and significantly improved lung function compared to placebo, meeting a key secondary endpoint (NCT03387852). In a separate Phase II clinical study, a single IV dose of etokimab was administered to patients with uncontrolled moderate-to-severe asthma despite being on treatment with high dose combination ICS plus LABA therapy. Compared with a placebo group, asthmatics treated with etokimab had a significant improvement in lung function (FEV1) and a reduction in blood eosinophils (NCT03469934).

[0006] As with many other diseases, asthma patients present with notable variability in disease severity, disease onset and speed of progression. Due to this vast disease variability, different patient subgroups may be best served by different and more tailored treatments. Hence, a substantial unmet medical need remains.

[0007] The present disclosure is directed at solving one or more of the above-mentioned problems in the art. Accordingly, one or more aspects of the present disclosure and further instances thereof are defined hereinbelow.

[0008] tozorakimab is a human IgG1 mAb that binds to human IL-33. Tozorakimab binds full length and mature forms of human IL-33 with exceptionally high affinity and prevents IL-33 binding to soluble (sST2) and membrane-bound forms of ST2 (also known as IL-1RL1) receptor. Several clinical and non-clinical studies point to the IL-33/ST2 signaling axis playing a key role in the pathogenesis of asthma. The present disclosure describes the results of a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tozorakimab in adult participants with moderate-to-severe asthma in which a specific subgroup of patients was identified.

SUMMARY OF THE DISCLOSURE

[0009] In a first aspect, there is provided a method of treatment of a subject having moderate or severe asthma, the method comprising: administering to said subject an effective amount of

tozorakimab, wherein, in the 12 months prior to said administration the subject has had two or more asthma exacerbations.

[0010] In a second aspect there is provided a method of improving lung function in a subject having moderate or severe asthma, the method comprising: administering to said subject an effective amount of tozorakimab, wherein, in the 12 months prior to said administration the subject has had two or more asthma exacerbations.

[0011] In a third aspect there is provided a method of increasing preBD FEV₁ of a subject having moderate or severe asthma by at least 100ml, the method comprising: administering to said subject an effective amount of an IL-33 signaling axis antagonist, wherein in the 12 months prior to said administration the subject has had two or more asthma exacerbations. Optionally wherein the method is a method of treatment of a subject having moderate or severe asthma, by increasing preBD FEV₁ of the subject by at least 100ml.

[0012] In a fourth aspect there is provided a method of selecting a subject having moderate or severe asthma for treatment with an effective amount of tozorakimab, the method comprising: determining how many asthma exacerbations the subject has had in the past 12 months; selecting the subject for said treatment if the subject has had more than two asthma exacerbations in the past 12 months. Optionally the method may further comprise the step of administering an effective amount of tozorakimab to the subject.

[0013] In a fifth aspect there is provided tozorakimab for use in the treatment of moderate or severe asthma in a subject, wherein, in the 12 months prior to administration of tozorakimab the subject has had two or more asthma exacerbations.

[0014] In a sixth aspect there is provided tozorakimab for use in improving lung function in a subject having moderate or severe asthma, wherein, in the 12 months prior to administration of tozorakimab the subject as had two or more asthma exacerbations.

[0015] In a seventh aspect there is provided an IL-33 signaling axis antagonist for use in increasing preBD FEV₁ of a subject having moderate or severe asthma by at least 100ml, wherein in the 12 months prior to administration of the IL-33 signaling axis antagonist the subject has had two or more asthma exacerbations. Alternatively there is provided an IL-33 signaling axis antagonist for use in the treatment of moderate or severe asthma in a subject by increasing preBD FEV₁ of the subject by at least 100ml, wherein, in the 12 months prior to administration of the IL-33 signaling axis antagonist the subject as had two or more asthma exacerbations.

[0016] FRONTIER-3 (NCT04570657) is a phase II, randomized, double-blind, placebo-controlled study to assess tozorakimab (MEDI3506) in participants with asthma. This trial shows that whilst the primary endpoint was not met in the overall population, a particular subset of patients did meet the primary endpoint. In particular, the trial showed that those participants who had experienced a high number of exacerbations, at least 2 or more in the last year, exhibited enhanced therapeutic responses when administered tozorakimab. Surprisingly this specific group of patients showed improved lung function as measured by preBD FEV₁, showing around 200ml increase in their lung performance. The present disclosure aims to capture the treatment of said subsets of patients which may benefit more from treatment with such IL-33 signaling axis antagonists as tozorakimab.

[0017] Further features and instances of the above defined aspects are described hereinbelow in headed sections. Each section is combinable with any of the above mentioned aspects in any compatible combination.

DETAILED DESCRIPTION

[0018] *Definitions*

[0019] 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 instances, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain instances, 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.

[0020] As used herein, an “asthma exacerbation” or “exacerbation of asthma” refers to a change in a subject’s usual asthma symptoms that leads to any of the following: (a) (i) a temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable oral corticosteroid (OCS) background dose) for at least 3 consecutive days to treat symptoms of asthma worsening or (ii) a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids; (b) an emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or

urgent care centre) due to asthma that required systemic corticosteroids (as per the above) or (c) an in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours). A “hospitalised asthma exacerbation” is defined as any worsening of asthma that leads to (c.) above.

[0021] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, “an anti-IL-33 antibody” is understood to represent one or more anti-IL-33 antibodies. As such, the terms “a” (or “an”), “one or more,” and “at least one” can be used interchangeably herein.

[0022] “IL-33” protein as employed herein refers to interleukin 33, in particular a mammalian interleukin 33 protein, for example human protein deposited with UniProt number 095760. However, it clear that this entity is not a single species but instead exists as reduced and oxidized forms. Given the rapid oxidation of the reduced form in vivo, for example in the period 5 minutes to 40 minutes, and in vitro, prior art references to IL-33 may actually be references to the oxidized form. Furthermore, commercial assays may not effectively discriminate between the reduced and oxidized forms. The terms "IL-33" and "IL-33 polypeptide" are used interchangeably. In certain instances, IL-33 is full length. In another instance, IL-33 is mature, truncated IL-33 (amino acids 112-270). Recent studies suggest full length IL-33 is active (Cayrol and Girard, Proc Natl Acad Sci USA 106(22): 9021-6 (2009); Hayakawa et al., Biochem Biophys Res Commun. 387(1):218-22 (2009); Talabot-Ayer et al, J Biol Chem. 284(29): 19420-6 (2009)). However, N-terminally processed or truncated IL-33 including but not limited to aa 72-270, 79-270, 95-270, 99-270, 107-270, 109-270, 111-270, 112-270 may have enhanced activity (Lefrancais 2012, 2014). In another instance, IL-33 may include a full length IL-33, a fragment thereof, or an IL-33 mutant or variant polypeptide, wherein the fragment of IL-33 or IL-33 variant polypeptide retains some or all functional properties of active IL-33.

[0023] “Reduced IL-33” or “redIL-33” as employed herein refers to the form of the IL-33 that binds to ST2 and triggers ST2 mediated signaling. In particular cysteines 208, 227, 232 and 259 of the reduced form are not disulfide bonded.

[0024] It should be understood that references to “WT IL-33” or “IL-33” may refer to either the reduced or oxidised forms, or both, unless it is clear from the context within which it is used that one of the forms is meant.

[0025] As used herein, the terms “treat” or “treatment” refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0026] By “subject” or “individual” or “animal” or “patient” or “mammal,” is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired, except where the subject is defined as a ‘healthy subject’. Mammalian subjects include humans; domestic animals; farm animals; such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, cows, and so on.

[0027] “IL-33 signaling axis antagonist” as employed herein refers to any agent which attenuates IL-33 activity. Suitably, the IL-33 signaling axis antagonist may be selected from: an antibody, an antigen-binding fragment thereof, an aptamer, at least one heavy or light chain CDR of a reference antibody molecule, and at least six CDRs from one or more reference antibody molecules. Suitably, the IL-33 signaling axis antagonist is an antibody or binding fragment thereof. Suitably, the IL-33 signaling axis antagonist is an anti-IL-33 antibody or binding fragment thereof. Suitably, the anti-IL-33 antibody or binding fragment thereof specifically binds to IL-33.

[0028] “Antibody” is used in the broadest sense and encompasses various immunoglobulin molecules and antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity. In particular a full-length antibody or a molecule comprising a full-length antibody, for example a DVD-Ig molecule and the like.

[0029] A “binding fragment thereof” is interchangeable with “antigen binding fragment thereof” and refers to an epitope/antigen binding fragment of an antibody fragment, for

example comprising a binding region, in particular comprising 6 CDRs, such as 3 CDRs in heavy variable region and 3 CDRs in light variable region.

[0030] The term “effective amount” or “therapeutically effective amount” of an agent, e.g., tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical formulation comprising an tozorakimab or the IL-33 signaling axis antagonist refers to an amount sufficient to achieve benefit or a therapeutic effect, such as to ameliorate symptoms of a disease or condition e.g. an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0031] The terms “complementarity determining regions” and “CDRs” as used herein refer to the amino acid residues of an antibody or antigen-binding fragment that are responsible for antigen binding.

[0032] The term “immediately prior to administration” refers to the time up to and including 24 hours before administration e.g. 5 minutes, 10 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours or 24 hours before administration.

[0033] The term “pre-BD FEV₁”, “preBD FEV₁” or “pre-bronchodilator (BD) FEV₁” refers to pre-bronchodilator forced expiratory volume 1. This is a measurement of forced expiratory volume of a subject in 1 second before administration of bronchodilator.

[0034] The term “postBD-FEV₁” or “post-bronchodilator (BD)-FEV₁” refers to post-bronchodilator Forced expiratory volume 1. This is a measurement of forced expiratory volume of a subject in 1 second after administration of bronchodilator.

[0035] The term “preBD-FVC” or “pre-bronchodilator (BD) forced vital capacity (FVC)” refers to bronchodilator Forced vital capacity. This is the total amount of air exhaled by a subject during a forced expiratory volume test or FVC test before administration of bronchodilator.

[0036] The term “postBD-FVC” or “post-bronchodilator (BD)-FVC” refers to post-bronchodilator forced vital capacity. This is the total amount of air exhaled by a subject during a forced expiratory volume test or FVC test after administration of bronchodilator.

[0037] The term “bronchodilator” is a substance which dilates the bronchi and bronchioles, decreasing resistance in the respiratory airways and increasing airflow to the lungs. Suitable

bronchodilators include a short-acting beta agonist (SABA) such as albuterol (90 1-1g metered dose) or salbutamol (1 00 1-1g metered dose) or equivalent (Sorkness et al, J Appl Physiol. 1 04(2):394-403, 2008).

[0038] The term “tidal volume” indicates the amount of air inhaled or exhaled during normal breathing of a subject.

[0039] The term “minute volume” indicates the total amount of air exhaled per minute of a subject.

[0040] The term “vital capacity” indicates the total volume of air that can be exhaled by a subject after inhaling as much as possible.

[0041] The term “functional residual capacity” indicates the amount of air left in the lungs of a subject after exhaling normally.

[0042] The term “residual volume” indicates the amount of air left in the lungs of a subject after exhaling as much as possible.

[0043] The term “total lung volume” indicates the total volume of the lungs of a subject when filled with as much air as possible.

[0044] The term “forced expiratory flow” indicates the average rate of flow of air expired by a subject during the middle half of the FVC test.

[0045] The term “peak expiratory flow rate (PEF)” indicates the fastest rate that a subject can force air out of the lungs during a forced expiratory volume test or FVC test, typically measured in Litres/minute.

[0046] The term “forced expiratory volume (FEV)” is amount of air expired by a subject during the first, second, and third seconds of the FVC test. The term FEV₁ as explained above is the amount of air expired by a subject during the first second of the FVC test.

[0047] The term “forced vital capacity” (FVC) or the forced vital capacity test is a measurement of the total amount of air exhaled forcefully and quickly by a subject after inhaling as much as possible.

[0048] The term “placebo group” refers to a group of control subjects having the same characteristics as the subject to be treated, who have not received the tozorakimab or the IL-33 signaling axis antagonist but who have received a placebo. Suitably the placebo is a pharmacologically inert preparation or composition. Suitably the placebo may contain the same ingredients as a pharmaceutical composition containing the tozorakimab or the IL-33 signaling

axis antagonist with the exception that it does not contain the active tozorakimab or IL-33 signaling axis antagonist.

[0049] Subject

[0050] The methods and medical uses are practiced in respect of a subject. Suitably the subject may be a human. Suitably the subject may be undergoing medical care. Suitably the subject may be an individual requesting medical care. Suitably the subject is male or female. Suitably the subject is an adult or a child. Suitably the term ‘subject’ is used herein interchangeably with the term ‘patient’.

[0051] Suitably the subject has asthma, is suspected of having asthma, or has symptoms consistent with asthma. Suitably the subject having asthma may mean the subject has a diagnosis of asthma. The subject may have a documented history of asthma, suitably for at least 1 year.

[0052] Suitably the subject has moderate or severe asthma, or moderate-to-severe asthma, or has symptoms consistent with moderate or severe, or moderate-to-severe asthma. Suitably the subject having moderate or severe asthma, or moderate-to-severe asthma, may mean the subject has a diagnosis of moderate or severe asthma, or moderate-to-severe asthma. The subject may have a documented history of moderate or severe asthma, or moderate-to-severe asthma, suitably for at least 1 year. Suitably any references herein to the subject having asthma may be taken as a reference to the subject having moderate or severe asthma.

[0053] Asthma is a chronic inflammatory disease of the airways affecting 1-18% of the population in different countries and is characterized by bronchial hyperreactivity and reversible airflow limitation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough. The etiology of asthma is thought to be multi-factorial and there are recognizable clusters of demographic, clinical and/or pathophysiological phenotypes. In patients with more severe phenotypes, some phenotype-guided treatment are available. However, no strong relationship between pathological symptoms and clinical presentations and response to therapies have been established.

[0054] Different asthma subtypes have been identified, including allergic asthma, non-allergic asthma, late-onset asthma (which typically tends to be non-allergic), asthma with persistent airflow limitation (which is linked to airway wall remodeling, leading to a long-standing, persistent, irreversible airflow limitation), and asthma with obesity (which is typically linked to

a non/low eosinophilic mechanism of action). Suitably subjects treated by the present disclosure may have any type or origin of asthma.

[0055] In some instances, the subject may have early-onset asthma. As defined herein “early-onset” asthma refers to a subject diagnosed with asthma before the age of 25, preferably before the age of 18. Diagnosis may be made by a clinician, for example, using any one of a number of well-known methods for diagnosing asthma. It is to be understood that methods disclosed herein for use in early-onset asthma sufferers are not confined to subjects below the age of 25 (or 18, even). For example, the methods of treatment described herein may be used in an adult (defined herein as someone above the age of 18) but who has been suffering from asthma since before the age of 25.

[0056] There are different levels of asthma severity, which are currently assessed retrospectively from the level of treatment required to control symptoms and exacerbations. The severity index comprises three main groups: mild asthma, moderate asthma, and severe asthma. Severity of asthma is defined on the GINA scale by the level of treatment required to gain adequate control of symptoms. The GINA scale is defined in the “Pocket Guide for Asthma Management and Prevention,” Global Initiative for Asthma; 2019. Unless otherwise stated herein, references to “moderate asthma” or “severe asthma” are in accordance with the definitions on the GINA scale. For instance, moderate asthma refers to asthma that has a Global Initiative for Asthma (GINA) scale of 3 or less, suitably a GINA scale of 2 or 3 (i.e. GINA step 2 or step 3), and severe asthma refers to asthma that requires high intensity treatment (e.g., GINA Step 4 and Step 5) to maintain good control, or where good control is not achieved despite high intensity treatment (GINA, Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA) December 2012)

[0057] Suitably, the subjects treated by the present disclosure are suffering from moderate asthma, severe asthma, or moderate-to-severe asthma. In some instances, the subjects have asthma which is not well-controlled on controller or reliever standard of care therapies defined in steps 1 and 2 of the GINA scale. Suitably therefore the subjects treated by the present disclosure may have uncontrolled asthma. Suitably the subjects may have moderate asthma uncontrolled on standard of care therapy, severe asthma uncontrolled on standard of care therapy, or moderate-to-severe asthma uncontrolled on standard of care therapy. Standard of care (SOC) therapy is as defined in the GINA scale.

[0058] Asthma may be diagnosed or assessed by a number of different measures, including:

[0059] Airway inflammation evaluated using a standardized single-breath Fraction of Exhaled Nitric Oxide (FeNO) (ATS, Am J Respir Crit Care Med. 171(8):912-30, 2005). FeNO has not been established for confirming asthma diagnosis but elevated FeNO has been associated with asthma characterized by a Type 2 airway inflammation.

[0060] Determining the atopic status. This can be identified by a skin prick test with common environmental allergens or by measuring the level of specific IgE in serum. As with FeNO, allergy tests do not rule in or rule out a diagnosis of asthma but the presence of atopy increases the probability that a patient with respiratory symptoms has allergic asthma.

[0061] Bronchial provocation testing. These tests monitor variable airflow limitation to assess airway hyperresponsiveness (AHR). Subjects can be challenged with chemical agents such as methacholine. Such tests are moderately sensitive to the diagnosis of asthma.

[0062] The Asthma Control Questionnaire (ACQ) 6 is a patient-reported questionnaire assessing asthma symptoms (i.e., night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use and FEV₁ (Juniper et al, Oct 1999). The ACQ-6 is a shortened version of the ACQ that omits the FEV₁ measurement from the original ACQ score. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of 0.75 indicate well-controlled asthma, scores between 0.75 and 1.5 indicate partly-controlled asthma, and a score > 1.5 indicates uncontrolled asthma (Juniper et al, Respir Med. 100(4):616-21, 2006). Individual changes of at least 0.5 are considered to be clinically meaningful (Juniper et al, Respir Med. 99(5):553-8, 2005). Suitably, the subjects treated by the present disclosure may have an ACQ-6 score of ≥ 0.75 , ≥ 0.80 , ≥ 0.85 , ≥ 0.90 , ≥ 0.95 , ≥ 1.0 , ≥ 1.05 , ≥ 1.10 , ≥ 1.15 , ≥ 1.20 , ≥ 1.25 , ≥ 1.30 , ≥ 1.35 , ≥ 1.40 , ≥ 1.45 , ≥ 1.5 , before administration of tozorakimab or the IL-33 signaling axis antagonist. Suitably, the subjects treated by the present disclosure may have an ACQ-6 score of ≥ 1.5 , before administration of tozorakimab or the IL-33 signaling axis antagonist.

[0063] Suitably any parameters relating to lung function described herein such as pre-BD FEV₁, post-BD FEV₁, FEV₁, pre-BD FVC, post-BD FVC, FVC, PEF etc. are measured by spirometry. Suitably this may be home spirometry or in-clinic spirometry. Suitably, unless otherwise stated all spirometry measurements are in-clinic.

[0064] Spirometry is performed according to ATS/European Respiratory Society (ERS) guidelines (Miller et al, Eur Respir J. 26(1):153-61, 2005). For example, multiple forced

expiratory efforts (at least 3 but no more than 8) is performed at each spirometry session and the 2 best efforts that meet ATS/ERS acceptability and reproducibility criteria are recorded. The best efforts will be based on the highest FEV₁. The maximum flow-volume exhalation volume (FEV₁) of the 2 best efforts will be used for the analysis. Both the absolute measurement (for FEV₁ and forced vital capacity (FVC)) and the percentage of predicted normal value will be recorded using appropriate reference values. The highest FVC will be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV₁).

[0065] Post-bronchodilator (Post-BD) spirometry testing is assessed after the subject has performed pre-BD spirometry. Pre-BD FEV₁ is measured as defined above using spirometry before administration of a suitable bronchodilator to the subject. To measure post-BD FEV₁, maximal bronchodilation is induced using a short-acting beta agonist (SABA) such as albuterol (90 1-1g metered dose) or salbutamol (1 00 1-1g metered dose) or equivalent with a spacer device for a maximum of 8 total puffs (Sorkness et al, J Appl Physiol. 1 04(2):394-403, 2008). The highest pre- and post-BD FEV₁ obtained after 4, 6, or 8 puffs is used to determine reversibility and for analysis. Reversibility algorithm is as follows: %Reversibility= (post-BD FEV₁- pre-BD FEV₁) x 1 00/pre-BD FEV₁

[0066] Suitably, the subjects treated by the present disclosure may have a %Reversibility of greater than or equal to 12% and greater than or equal to 200 ml (for example, 15 to 60 min after administration of 4 puffs of albuterol/salbutamol).

[0067] Suitably in the 12 months prior to administration of tozorakimab or the IL-33 signaling axis antagonist, the subject has had two or more exacerbations of asthma. Suitably, the subject to be treated by the present disclosure may have a specific blood eosinophil count <300 cells/μl. In some instances, the specific blood eosinophil count is the blood eosinophil count determined prior to administration. This can also be referred to as the “baseline” of blood eosinophil count. In some instances, the methods of treatment described herein may comprise a further step of selecting a subject having a specific blood eosinophil count. The subject may be selected from a group of subjects comprising a blood eosinophil count of <300 cells/μl. The results show that the response of patients to tozorakimab is not dependent on a specific baseline blood eosinophil count (FIG. 5A and 5B). Nevertheless, a blood eosinophil count of below <300 cells/μl is generally considered “low EOS”. Subjects with a low EOS asthma endotype have particularly limited treatment options, even when considering currently approved biologics.

[0068] In some instances, the blood eosinophil count is the blood eosinophil count immediately prior to administration of the tozorakimab or the IL-33 signaling axis antagonist. The blood eosinophil count may be measured immediately prior to administration of the tozorakimab or the IL-33 signaling axis antagonist. Suitably the blood eosinophil count is measured from a sample, suitably from a blood sample collected, or which has been obtained, from the subject up to 24 hours before said administration of the tozorakimab or the IL-33 signaling axis antagonist.

[0069] Suitably, the subject may be over 40 years old. Suitably subject may be less than 75 years old. Suitably the subject may be between 40 and 75 years old. Suitably the subject may be between 40-45 years old, 45-50 years old, 50-55 years old, 55-60 years old, 60-65 years old, 65-70 years old, or 70-75 years old.

[0070] Suitably, the subject may be up to date with vaccines, suitably with vaccines for respiratory diseases. Suitably the subject has received pneumococcus and influenza vaccines.

[0071] Suitably the subject may have received treatment for asthma, or is currently receiving treatment for asthma. Suitably the subject may have, or be receiving, a documented stable regimen of treatment for asthma. Suitably said treatment may comprise one or more currently available asthma medications. Suitably the subject may have received, or is currently receiving any one or more of the following medications:

- Inhaled corticosteroids such as Fluticasone (Flovent HFA, Arnuity Ellipta, others), Budesonide (Pulmicort Flexhaler), Mometasone (Asmanex Twisthaler), Beclomethasone (Qvar RediHaler), Ciclesonide (Alvesco)

- Leukotriene modifiers such as Montelukast (Singulair), Zafirlukast (Accolate), Zileuton (Zyflo)

- Long-acting beta agonists (LABAs) such as Salmeterol (Serevent), Formoterol

- Long-acting muscarinic antagonists (LAMAs) such as tiotropium (Spiriva Respimat)

- Combination therapies such as Fluticasone and salmeterol (Advair Diskus, AirDuo Digihaler, others), Budesonide and formoterol (Symbicort), Mometasone and formoterol (Dulera) and Fluticasone and vilanterol (Breo Ellipta)

- Theophylline

- Short-acting beta agonists such as albuterol (ProAir HFA, Ventolin HFA, others) or Levalbuterol (Xopenex HFA)

- Ipratropium (Atrovent HFA) or a combination of ipratropium and albuterol (Combivent)

- Oral corticosteroids such as Prednisone or Methylprednisolone

[0072] Suitably the subject may have received said asthma treatment for ≥ 3 months.

[0073] Suitably the subject may have a normal body mass index (BMI). Suitably therefore the subject may have a BMI of $\geq 19 \text{ kg/m}^2$ and $\leq 35 \text{ kg/m}^2$. Suitably the subject may have a BMI of $\geq 19 \text{ kg/m}^2$ and $\leq 30 \text{ kg/m}^2$, $\geq 19 \text{ kg/m}^2$ and $\leq 25 \text{ kg/m}^2$.

[0074] *Method of treatment and method of improvement of lung function*

[0075] Suitably, treatment of a subject having asthma as described herein results in improving the lung function of the subject. Suitably therefore in any of the methods of treatment or medical uses described herein the treatment of asthma is effected by improving lung function of the subject.

[0076] In some instances the lung function of the subject may be compared to the lung function of a control subject. Suitably the control subject is a subject having asthma, suitably moderate or severe asthma, who has not received treatment with tozorakimab or the IL-33 signaling axis antagonist (which may be a subject from a placebo group).

[0077] Suitably the improvement in lung function may be measured by pulmonary function tests such as spirometry and plethysmography. Suitably therefore, the improvement in lung function may be any one of the following: a higher tidal volume, a higher minute volume, a higher vital capacity, a higher functional residual capacity, a higher residual volume, a higher total lung capacity, a higher forced vital capacity (FVC), a higher forced expiratory capacity (FEV₁) which may be a higher pre-BD FEV₁ or a higher post-BD FEV₁, a higher forced expiratory flow, and a higher peak expiratory flow rate (PEF), or alternatively may be a reduction in the use of rescue medication or a reduction in the rate of exacerbations of the subject compared to a control subject having asthma, suitably moderate or severe asthma, who has not received the tozorakimab or the IL-33 signaling axis antagonist (which may be a subject from a placebo group).

[0078] Alternatively the lung function of the subject may equally be compared to the baseline lung function of the same subject i.e. before administration of the tozorakimab or the IL-33 signaling axis antagonist. The improvement of the lung function may be an improvement in the lung function of the subject after administration of the tozorakimab or the IL-33 signaling axis antagonist compared to baseline, i.e. compared to before administration of the tozorakimab or the IL-33 signaling axis antagonist. Suitably therefore, the improvement in lung function may be any one of the following: a higher tidal volume, a higher minute volume, a higher vital capacity, a higher functional residual capacity, a higher residual volume, a higher total lung capacity, a higher forced vital capacity (FVC), a higher forced expiratory capacity (FEV₁) which may be a higher pre-BD FEV₁ or a higher post-BD FEV₁, a higher forced expiratory flow, and a higher peak expiratory flow rate (PEF), or alternatively may be a reduction in the use of rescue medication or a reduction in the rate of exacerbations of the subject compared to the baseline measurement in the same subject i.e. before administration of the tozorakimab or the IL-33 signaling axis antagonist to the subject. Suitably immediately prior to the administration of the tozorakimab or the IL-33 signaling axis antagonist to the subject.

[0079] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma may result in increasing preBD FEV₁ of the subject. PreBD FEV₁ of the subject may be compared to the preBD FEV₁ of a control subject having asthma who has not received the tozorakimab or the IL-33 signaling axis antagonist (such as a subject from a placebo group). Alternatively, preBD FEV₁ of the subject may be compared to the baseline preBD FEV₁ of the same subject i.e. before administration of the tozorakimab or the IL-33 signaling axis antagonist to the subject.

[0080] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 100ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 100ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 100ml at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least

100ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0081] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 105ml, at least 110ml, at least 115ml, at least 120ml, at least 125ml, at least 130ml, at least 135ml, at least 140ml, at least 145ml, at least 150ml, at least 155ml, at least 160ml, at least 165ml at least 170ml, at least 175ml, at least 180ml, at least 185ml, at least 190ml, at least 195ml, at least 200ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 105ml, at least 110ml, at least 115ml, at least 120ml, at least 125ml, at least 130ml, at least 135ml, at least 140ml, at least 145ml, at least 150ml, at least 155ml, at least 160ml, at least 165ml at least 170ml, at least 175ml, at least 180ml, at least 185ml, at least 190ml, at least 195ml, at least 200ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 105ml, at least 110ml, at least 115ml, at least 120ml, at least 125ml, at least 130ml, at least 135ml, at least 140ml, at least 145ml, at least 150ml, at least 155ml, at least 160ml, at least 165ml at least 170ml, at least 175ml, at least 180ml, at least 185ml, at least 190ml, at least 195ml, at least 200ml at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by at least 105ml, at least 110ml, at least 115ml, at least 120ml, at least 125ml, at least 130ml, at least 135ml, at least 140ml, at least 145ml, at least 150ml, at least 155ml, at least 160ml, at least 165ml at least 170ml, at least 175ml, at least 180ml, at least 185ml, at least 190ml, at least 195ml, at least 200ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0082] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by around 200ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by around 200ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by around 200ml at 16

weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing preBD FEV₁ of the subject by around 200ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0083] In some instances, the increase in preBD-FEV₁ of the subject is achieved by week 16 after administration of an effective amount of the tozorakimab or the IL-33 signaling axis antagonist. In some instances, the increase in preBD-FEV₁ of the subject is achieved by week 24 after administration of an effective amount of the tozorakimab or the IL-33 signaling axis antagonist.

[0084] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma may result in increasing home FEV₁ of the subject. Home FEV₁ is the FEV₁ of the subject measured at home, the home FEV₁ of the subject may be compared to the home FEV₁ of a control subject having asthma who has not received the tozorakimab or the IL-33 signaling axis antagonist (such as a subject from a placebo group). Alternatively, home FEV₁ of the subject may be compared to the baseline home FEV₁ of the same subject i.e. before administration of the tozorakimab or the IL-33 signaling axis antagonist to the subject.

[0085] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least 60ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least 60ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least 60ml at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least 60ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0086] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least 65ml, at least 70ml, at least 75ml, at least 80ml, at least 85ml, at least 90ml, at least 95ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in

increasing home FEV₁ of the subject by at least at least 65ml, at least 70ml, at least 75ml, at least 80ml, at least 85ml, at least 90ml, at least 95ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least at least 65ml, at least 70ml, at least 75ml, at least 80ml, at least 85ml, at least 90ml, at least 95ml at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by at least at least 65ml, at least 70ml, at least 75ml, at least 80ml, at least 85ml, at least 90ml, at least 95ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0087] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by around 95ml. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by around 95ml compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by around 95ml at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing home FEV₁ of the subject by around 95ml at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0088] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma may result in increasing PEF of the subject. PEF of the subject may be compared to the PEF of a control subject having asthma who has not received the tozorakimab or the IL-33 signaling axis antagonist (such as a subject from a placebo group). Alternatively, PEF of the subject may be compared to the baseline PEF of the same subject i.e. before administration of the tozorakimab or the IL-33 signaling axis antagonist to the subject.

[0089] In some instances, the treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min compared to a control or to baseline.

Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0090] In some instances, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min, at least 5.5L/min, at least 6L/min, at least 6.5L/min, at least 7L/min, at least 7.5L/min, at least 8L/min, at least 8.5L/min, at least 9L/min. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min, at least 5.5L/min, at least 6L/min, at least 6.5L/min, at least 7L/min, at least 7.5L/min, at least 8L/min, at least 8.5L/min, at least 9L/min compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min, at least 5.5L/min, at least 6L/min, at least 6.5L/min, at least 7L/min, at least 7.5L/min, at least 8L/min, at least 8.5L/min, at least 9L/min at 16 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by at least 5L/min, at least 5.5L/min, at least 6L/min, at least 6.5L/min, at least 7L/min, at least 7.5L/min, at least 8L/min, at least 8.5L/min, at least 9L/min at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0091] In one instance, treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by about 9L/min. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by about 9L/min compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by about 9L/min at 16 weeks after

administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline. Suitably treatment of a subject having asthma or improving lung function in a subject having asthma results in increasing PEF of the subject by about 9L/min at 24 weeks after administration of the tozorakimab or the IL-33 signaling axis antagonist, compared to a control or to baseline.

[0092] In some instances, increasing preBD-FEV₁ or increasing PEF of the subject is relative to a baseline level. The baseline may be the level in a subject having asthma before administration of an effective amount of an tozorakimab or the IL-33 signaling axis antagonist. In some instances, the baseline is the level in the same subject prior to said administration of the effective amount of an tozorakimab or the IL-33 signaling axis antagonist.

[0093] In some instances, the treatment of a subject having asthma or improving lung function in a subject having asthma results in reducing the rate of exacerbations in a subject having asthma, after administration of the tozorakimab or the IL-33 signaling axis antagonist. In some instances, the rate of exacerbations is reduced by at least 10%, 15%, 20%, 25%, or by at least 30%. Suitably the rate of exacerbations is reduced by at least 20%, or by at least 25%, or by at least 30%. Suitably the rate of exacerbations is reduced by at least 10%, 15%, 20%, 25%, or by at least 30% compared to the rate of exacerbations of a control subject having asthma who has not received the tozorakimab or the IL-33 signaling axis antagonist. Suitably the rate of exacerbations is reduced by at least 20%, by at least 25%, by at least 30% compared to the rate of exacerbations of a control subject having asthma who has not received the tozorakimab or the IL-33 signaling axis antagonist. Suitably the rate of exacerbations is reduced by at least 10%, 15%, 20%, 25%, or by at least 30%, suitably by at least 20%, by at least 25%, by at least 30%, compared to a subject from the placebo group. Alternatively, the rate of exacerbations is reduced by at least 10%, 15%, 20%, 25%, or by at least 30%, suitably by at least 20%, by at least 25%, by at least 30%, compared to the rate of exacerbations in the same subject prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, suitably during the 12 months preceding the administration of the tozorakimab or the IL-33 signaling axis antagonist.

[0094] In some instances, the rate of exacerbations is reduced over a 16 week period after administration of an effective amount of the tozorakimab or the IL-33 signaling axis antagonist. Suitably the reduction in the rate of exacerbations is achieved by week 16 after administration of an effective amount of the tozorakimab or the IL-33 signaling axis antagonist.

[0095] *Selecting a subject*

[0096] This disclosure is furthermore related to a method of selecting a subject having asthma for treatment. Suitably any other method according to the present disclosure may further comprise a step of selecting a subject. The methods according to the present disclosure may involve selecting a subgroup of subjects who may benefit more from administration of the tozorakimab or the IL-33 signaling axis antagonist compared to simply any subject.

[0097] Suitably the method of selecting the subject having asthma for treatment comprises determining how many exacerbations the subject has had in the past 12 months. Suitably this may be determined by a patient questionnaire or by consulting medical records.

[0098] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have had 2 or more exacerbations in the past 12 months.

[0099] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if in the 12 months prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, the subject has had 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, 20 or more exacerbations of asthma.

[0100] Suitably historical exacerbations, suitably those in the 12 months preceding treatment may be evidenced by any of the following: Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalised/treated with systemic corticosteroids for an asthma exacerbation; Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic corticosteroids; Evidence of prescriptions for systemic corticosteroids used during an exacerbation; A documented conversation between the Investigator (or delegate) and a participant who is already on an OCS action plan, including the information necessary to assess Inclusion Criterion 19; A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with corticosteroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

[0101] Suitably the exacerbations of asthma may be mild, moderate or severe. Suitably therefore the method of selecting a subject having asthma for treatment comprises a step of

selecting a subject if in the 12 months prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, the subject has had two or more mild, moderate or severe exacerbations of asthma. Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if in the 12 months prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, the subject has had two or more moderate or severe exacerbations of asthma. Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if in the 12 months prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, the subject has had two or more severe exacerbations of asthma. Suitable definitions of 'exacerbations' of asthma are provided hereinabove.

[0102] Suitably the method of selecting a subject for treatment may further comprise a step of measuring the blood eosinophil count of the subject, suitably in a sample obtained from the subject. Suitably the sample is a blood sample. Suitably the method of selecting a subject having asthma for treatment may further comprise an initial step of taking or obtaining a sample from the subject. Suitably taking or obtaining a blood sample from the subject. Suitably said sample is taken or obtained from the subject prior to administration of the tozorakimab or the IL-33 signaling axis antagonist, suitably immediately prior to administration of the tozorakimab or the IL-33 signaling axis antagonist. Suitably said sample is taken or obtained from the subject up to 24 hours before said administration of the tozorakimab or the IL-33 signaling axis antagonist.

[0103] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have a blood eosinophil count of from <300 cells/ μ l.

[0104] Suitably, the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they are over 40 years old. Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they are less than 75 years old. Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they are between 40 and 75 years old. Suitably the subject may be between 40-45 years old, 45-50 years old, 50-55 years old, 55-60 years old, 60-65 years old, 65-70 years old, or 70-75 years old.

[0105] Suitably, the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they are up to date with vaccines, suitably with vaccines for respiratory diseases. Suitably the method of selecting a subject having asthma for treatment

comprises a step of selecting a subject if they have received pneumococcus and influenza vaccines.

[0106] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have received treatment for asthma, or are currently receiving treatment for asthma. Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have received, or are receiving, a documented stable regimen of treatment for asthma. Suitably said treatment may comprise one or more currently available asthma medications. Suitably the subject may have received, or is currently receiving any one or more of the following medications:

- Inhaled corticosteroids such as Fluticasone (Flovent HFA, Arnuity Ellipta, others), Budesonide (Pulmicort Flexhaler), Mometasone (Asmanex Twisthaler), Beclomethasone (Qvar RediHaler), Ciclesonide (Alvesco)
- Leukotriene modifiers such as Montelukast (Singulair), Zafirlukast (Accolate), Zileuton (Zyflo)
- Long-acting beta agonists (LABAs) such as Salmeterol (Serevent), Formoterol
- Long-acting muscarinic antagonists (LAMAs) such as tiotropium (Spiriva Respimat)
- Combination therapies such as Fluticasone and salmeterol (Advair Diskus, AirDuo Digihaler, others), Budesonide and formoterol (Symbicort), Mometasone and formoterol (Dulera) and Fluticasone and vilanterol (Breo Ellipta)
- Theophylline
- Short-acting beta agonists such as albuterol (ProAir HFA, Ventolin HFA, others) or Levalbuterol (Xopenex HFA)
- Ipratropium (Atrovent HFA) or a combination of ipratropium and albuterol (Combivent)
- Oral corticosteroids such as Prednisone or Methylprednisolone

[0107] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have received said asthma treatment for ≥ 3 months.

[0108] Suitably the method of selecting a subject having asthma for treatment comprises a step of selecting a subject if they have a normal body mass index (BMI). Suitably therefore the subject may have a BMI of $\geq 19 \text{ kg/m}^2$ and $\leq 35 \text{ kg/m}^2$. Suitably the subject may have a BMI of $\geq 19 \text{ kg/m}^2$ and $\leq 30 \text{ kg/m}^2$, $\geq 19 \text{ kg/m}^2$ and $\leq 25 \text{ kg/m}^2$.

[0109] *IL-33 signaling axis antagonist*

[0110] Suitably, tozorakimab or any other IL-33 signaling axis antagonist referred to herein reduces, inhibits or neutralizes IL-33 activity. Interleukin-33 (IL-33), also known as IL-1F11, is a member of the interleukin-1 (IL-1) cytokine family that is encoded by the IL33 gene. IL-33 is a 270 amino acid protein consisting of two domains: a homeodomain and a cytokine (IL-1 like) domain. The homeodomain contains a nuclear localization signal (NLS). IL-33 is known to exist in different forms; a reduced form (redIL-33) and an oxidised form (oxIL-33). Previous studies have shown that the reduced form is rapidly oxidised under physiological conditions to form at least one disulphide bond in the oxidised form, and that the two forms likely have different binding patterns and effects.

[0111] IL-33 is constitutively expressed in multiple cell types, including structural cells, such as smooth muscle, epithelial, and endothelial cells. It has been reported that IL-33 expression can also be induced by inflammatory factors in macrophages and dendritic cells. Cellular stress caused by environmental triggers, such as allergens, toxins, and pathogens, and mechanistic insult can lead to IL-33 release. Free IL-33 associates with a heterodimeric IL-33 receptor complex composed of suppression of tumorigenicity 2 (ST2) protein and interleukin-1 receptor accessory protein (IL-1 RacP) to activate the AP-1 and NF- κ B pathways through the adaptor protein myeloid differentiation primary response 88 (MyD88) and possibly MyD88-adaptor-like (Mal) protein. IL-33 stimulates numerous cell types, including innate lymphoid type II cells (ILC2), mast cells, basophils, eosinophils, and dendritic cells, to promote an immune response. It was previously discovered that the reduced form of IL-33 binds to ST2, and is in fact the only known ligand of the ST2 receptor expressed by Th2 cells and mast cells. Soluble ST2 (sST2) is thought to be a decoy receptor that prevents reduced-IL-33 signaling.

[0112] The terms "interleukin 1 receptor-like 1 (IL1RL)" and "ST2" used interchangeably herein, refer to any native ST2 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. ST2 is also referred to in the art as DER4, T1, and FIT-1. The term encompasses "full-length," unprocessed ST2, as well as any form of ST2 that results from processing in the cell. At least

four isoforms of ST2 are known in the art, including soluble (sST2, also known as IL 1 RL 1-a) and transmembrane (ST2L, also known as IL 1 RL 1-b), which arise from differential mRNA expression from a dual promoter system, and ST2V and ST2LV, which arise from alternative splicing. The domain structure of ST2L includes three extracellular immunoglobulin-like C2 domains, a transmembrane domain, and a cytoplasmic Toll/Interleukin-1 receptor (TIR) domain. sST2 lacks the transmembrane and cytoplasmic domains contained within ST2L and includes a unique 9 amino acid (a.a.) C-terminal sequence (see, e.g., Kakkar et al. Nat. Rev. Drug Disc. 40 7: 827-840, 2008). sST2 can function as a decoy receptor to inhibit soluble IL-33. The term also encompasses naturally occurring variants of ST2, e.g., splice variants (e.g., ST2V, which lacks the third immunoglobulin motif and has a unique hydrophobic tail, and ST2LV, which lacks the transmembrane domain of ST2L) or allelic variants. The amino acid sequence of an exemplary human ST2 can be found, for example, under UniProtKB accession number 001638. ST2 is a part of the IL-33 receptor along with the co-receptor protein IL-1 RacP. Binding of IL-33 to ST2 and the co-receptor interleukin-1 receptor accessory protein (IL-1 RacP) forms a 1:1:1 ternary signaling complex to promote downstream signal transduction (Lingel et al. Structure 17(10): 1398-1410, 2009, and Liu et al. Proc. Nat. Acad. Sci. 11 0(37): 14918-14924, 2013).

[0113] More recently, it was found that the oxidised form of IL-33 also has physiological effects. It was discovered that oxidised IL-33 does not bind ST2, but instead binds to the receptor for advanced glycation end products (RAGE) and signals through this alternative pathway. It has surprisingly been discovered that RAGE complexes with epithelial growth factor receptor (EGFR) as part of the oxidised IL-33 pathway. Reduced IL-33 is rapidly converted to oxidised IL-33 which then binds to RAGE and complexes with EGFR to stimulate EGFR activity. It is believed that antagonists that can bind to either form of IL-33 may effectively prevent signaling of oxidised IL-33. This may be either directly by binding to oxidised IL-33 itself, or indirectly by inhibiting conversion of reduced IL-33 to oxidised IL-33, both of which in turn will prevent stimulation of RAGE and stimulation of EGFR.

[0114] Suitably by 'IL-33 signaling axis antagonist' it is meant any molecule which inhibits or reduces the activity of any of the components of a signaling pathway activated by IL-33, either the reduced or oxidised form. Suitable signaling pathways activated by IL-33 may be the ST2 pathway or the RAGE pathway. Suitably therefore tozorakimab or another IL-33 signaling axis antagonist may inhibit or reduce the activity of any of the components of the ST2 pathway

and/or the RAGE pathway. Suitably in some instances, the IL-33 signaling axis antagonist may be an antibody, variant or antigen binding fragment thereof which inhibits or reduces the activity of one or more components of the ST2 pathway and/or the RAGE pathway.

[0115] ‘ST2 pathway’ as employed herein refers to the IL-33/ST2 system where reduced IL-33 recognition by ST2 promotes dimerization with IL-1RAcP on the cell surface and within the cell recruitment of receptor complex components MyD88, TRAF6 and IRAK1-4 to intracellular TIR domain. Thus ST2 dependent signaling/effects may be interrupted and attenuated by perturbing the interaction of IL-33 with ST2 or alternatively by interrupting the interaction with IL-1RAcP.

[0116] ‘RAGE pathway’ as employed herein refers to the oxidised IL-33/RAGE-EGFR system where oxidised IL-33 recognition by RAGE promotes complexing with EGFR within cell membranes. Thus RAGE-EGFR mediated signaling/effects may be interrupted and attenuated by perturbing the interaction of oxidised IL-33 with RAGE, or by interrupting the conversion of reduced IL-33 into oxidised IL-33.

[0117] It is contemplated herein that antibodies, binding fragments, or antibody variants that specifically bind to and inhibit components of the IL-33 signaling axis may be useful for the treatment of asthma. One instance of which is the antibody tozorakimab. In another instance, the antibody may be itepekimab. In another instance, the antibody may be astegolimab.

[0118] Suitably tozorakimab or the IL-33 signaling axis antagonist is an antibody, variant or antigen binding fragment thereof which specifically binds to and inhibits one or more components of the IL-33/ST2 signaling axis. Suitably tozorakimab or the IL-33 signaling axis antagonist is an antibody, variant or antigen binding fragment thereof which specifically binds to and inhibits the IL-33 receptor complex. Suitably tozorakimab or the IL-33 signaling axis antagonist is an antibody, variant or antigen binding fragment thereof which specifically binds to and inhibits ST2. Suitably tozorakimab or the IL-33 signaling axis antagonist is an antibody, variant or antigen binding fragment thereof which specifically binds to and inhibits IL-1 RacP.

[0119] In some instances, tozorakimab or the IL-33 signaling axis antagonist binds to and inhibits IL-33. In some instances, tozorakimab or the IL-33 signaling axis antagonist is an antibody, variant or antigen binding fragment thereof which specifically binds to and inhibits IL-33.

[0120] Suitably, therefore, the tozorakimab or the IL-33 signaling axis antagonist used herein is a binding molecule which may be selected from: an antibody, an antigen-binding fragment

thereof, an aptamer, at least one heavy or light chain CDR of a reference antibody molecule, and at least six CDRs from one or more reference antibody molecules.

[0121] Suitably, tozorakimab or the IL-33 signaling axis antagonist is an antibody, or variant thereof i.e. any antibody that binds specifically to and inhibits IL-33, which is effective in the treatment of asthma.

[0122] Suitably, the antibody or antigen binding fragment thereof is selected from: naturally-occurring, polyclonal, monoclonal (Mabs), recombinant, multispecific, mouse, human, humanized such as complementarity-determining region (CDR)-grafted, primatized, chimeric, and antibody variants, including single chain, monomeric antibodies, and/or bispecific, as well as fragments or derivatives thereof.

[0123] Suitably, the IL-33 signal axis antagonist is an antibody or an antigen binding fragment thereof. Suitably, the antigen binding fragment may be an epitope-binding fragment, e.g., Fab' and F(ab')₂, Fd, Fvs, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), fragments comprising either a VL or VH domain, or fragments produced by a Fab expression library. Suitably the Fab and F'ab') fragments may be generated by enzymatic cleavage of full-length antibodies. Other antigen binding fragments include those generated by recombinant DNA techniques, such as the expression of recombinant plasmids containing nucleic acid sequences encoding antibody variable regions. Suitably, the antibody or antigen binding fragment thereof may be a minibody, a diabody, a triabody, a tetrabody, or a single chain antibody. Suitably, the antibody or antigen binding fragment thereof is a monoclonal antibody. ScFv molecules are known in the art and are described, e.g., in U.S. Pat. No. 5,892,019. In some instances, the anti-IL-33 antibody variant or antigen binding fragment thereof is selected from the group consisting of a diabody, a triabody, a tetrabody, a Fab fragment, single domain antibody, scFv, wherein the dose is adjusted such that the binding sites to be equimolar to those dosed by bivalent antibodies.

[0124] Monoclonal antibodies may be modified for use as therapeutics or diagnostic". "Monoclonal antibody" or "monoclonal antibody composition" as used herein refers to polypeptides, including antibodies, bispecific antibodies, etc., that have substantially identical amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0125] One instance 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.

[0126] In another instance, a monoclonal antibody is a "humanized" antibody. Methods for humanizing non-human antibodies are well known in the art. See U.S. Pat. Nos. 5,585,089 and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. Humanization can be performed, for example, using methods described in the art (Jones et al., 1986, Nature 321 :522-25; Riechmann et al., 1998, Nature 332:323-27; Verhoeyen et al., 1988, Science 239:1534-36), by substituting at least a portion of a rodent complementarity-determining region for the corresponding regions of a human antibody.

[0127] Antibody molecules of the disclosure can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2, etc.), or subclass of immunoglobulin molecule. In one instance, tozorakimab or the IL-33 signaling axis antagonist is an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, or an IgG4 antibody. In some instances, the tozorakimab or the IL-33 signaling axis antagonist useful in the present methods is a monoclonal IgG1 antibody.

[0128] In some instances, the IL-33 signaling axis antagonist is an anti-IL-33 antibody, anti-ST2 antibody anti-IL1-RacP antibody, a binding fragment, or a variant thereof. Suitably, the anti-IL-33 antibody, variant, or binding fragment thereof specifically binds to IL-33, either reduced or oxidised IL-33.

[0129] In some instances, the IL-33 signaling axis antagonist is an anti-IL-33 antibody, binding fragment, or variant thereof. Suitably any anti-IL-33 antibody, binding fragment, or variant thereof may be used in the methods of the disclosure.

[0130] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof specifically binds to redIL-33 with a binding affinity (K_d) of less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M,

10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. Suitably, the binding affinity to redIL-33 is less than 5×10^{-14} M (i.e. 0.05 pM). Suitably, the binding affinity is as measured using Kinetic Exclusion Assays (KinExA) or BIACORE™, suitably using KinExA, using protocols such as those described in WO2016/156440 (see *e.g.*, Example 11), which is hereby incorporated by reference in its entirety. Anti-IL-33 antibodies, binding fragments, or antibody variants thereof that bind to redIL-33 with this binding affinity appear to bind tightly enough to redIL-33 to prevent dissociation of the binding molecule/redIL-33 complex within biologically relevant timescales. Without wishing to be bound by theory, this binding strength is thought to prevent release of the antigen prior to degradation of the antibody/antigen complex *in vivo*, such that redIL-33 is not released and cannot undergo conversion from redIL-33 to oxIL-33. Thus, when binding to redIL-33 with this binding affinity, the anti-IL-33 antibody, binding fragment, or antibody variant thereof can inhibit or attenuate the activity of oxIL-33 by preventing its formation.

[0131] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof may specifically bind to redIL-33 with an on rate ($k(\text{on})$) of greater than or equal to $10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $10^4 \text{ M}^{-1} \text{ sec}^{-1}$ or $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. For example, anti-IL-33 antibody, binding fragment, or antibody variant thereof of the disclosure may bind to redIL-33 or a fragment or variant thereof with an on rate ($k(\text{on})$) greater than or equal to $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$. Suitably, the $k(\text{on})$ rate is greater than or equal to $10^7 \text{ M}^{-1} \text{ sec}^{-1}$.

[0132] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof may specifically bind to redIL-33 with an off rate ($k(\text{off})$) of less than or equal to $5 \times 10^{-1} \text{ sec}^{-1}$, 10^{-1} sec^{-1} , $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$ or 10^{-3} sec^{-1} . For example, anti-IL-33 antibody, binding fragment, or antibody variant thereof of the disclosure may be said to bind to redIL-33 or a fragment or variant thereof with an off rate ($k(\text{off})$) less than or equal to $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, 10^{-5} sec^{-1} , $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$ or 10^{-7} sec^{-1} . Suitably, the $k(\text{off})$ rate is less than or equal to 10^{-3} sec^{-1} . IL-33 is an alarmin cytokine released rapidly and in high concentrations in response to inflammatory stimuli. redIL-33 is converted to the oxidised approximately 5-45 mins after release into the extracellular environment. Thus, to prevent conversion of redIL-33 to oxIL-33, the anti-IL-33 antibody, binding fragment, or antibody variant thereof described herein may bind to redIL-33 with these $k(\text{on})$ and/or $k(\text{off})$ rates. Without wishing to be bound by theory, these $k(\text{on})/k(\text{off})$ rates are thought to ensure that

the anti-IL-33 antibody, binding fragment, or antibody variant thereof can bind rapidly to redIL-33 before it converts to oxIL-33, thereby reducing the formation of oxIL-33.

[0133] In various instances, the anti-IL-33 antibody, binding fragment, or antibody variant thereof may be an inhibitory antibody, capable of inhibiting IL-33 or a fragment thereof as defined herein. In various instances, an inhibitory antibody may be capable of inhibiting the association of IL-33 or a fragment thereof with the IL-33 receptor complex, ST2 and/or IL-1 RacP.

[0134] Suitable anti-IL-33 antibodies for use in the methods of the disclosure are known in the art and may comprise any of the following anti-IL-33 antibodies: 33_640087-7B (as described in WO2016/156440), ANB020 known as Etokimab (as described in WO2015/106080), 9675P (as described in US2014/0271658), A25-3H04 (as described in US2017/0283494), Ab43 (as described in WO2018/081075), IL33-158 (as described in US2018/0037644), 10C12.38.H6. 87Y.581 IgG4 (as described in WO2016/077381) or binding fragments thereof, each of the documents being incorporated herein by reference. All of these antibodies are referenced in Table 1.

[0135] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of a variable heavy domain (VH) and a variable light domain (VL) pair selected from Table 1. Pair 1 corresponds to the VH and VL domain sequences of 33_640087-7B described in WO2016/156440. 33_640087-7B is also known as tozorakimab . Pairs 2-7 correspond to VH and VL domain sequences of antibodies described in US2014/0271658. Pairs 8-12 correspond to VH and VL domain sequences of antibodies described in US2017/0283494. Pair 13 corresponds to the VH and VL domain sequences of ANB020, described in WO2015/106080. Pairs 14-16 correspond to VH and VL domain sequences of antibodies described in WO2018/081075. Pair 17 corresponds to VH and VL domain sequences of IL33-158 described in US2018/0037644. Pair 18 corresponds to VH and VL domain sequences of 10C12.38.H6. 87Y.581 IgG4 described in WO2016/077381.

[0136] Table 1: Exemplary anti-IL-33 antibody VH and VL pairs

Pair	SEQ ID NO:	HCVR amino acid sequence	SEQ ID NO:	LCVR amino acid sequence

1	SEQ ID NO: 1	EVQLLESGGGLVQPGGG LRLSCAASGFTFSSYAMS WVRQAPGKGLEWVSGIS AIDQSTYYADSVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARQKFMQ LWGGGLRYPFGYWGQG TMVTVSS	SEQ ID NO: 19	SYVLTQPPSVSVSPGQTASITCSG EGMGDKYAAWYQQKPGQSPVLV IYRDTKRPSGIPERFSGSNSGNTAT LTISGTQAMDEADYYCGVIQDNT GVFGGGTKLTVL
2	SEQ ID NO: 2	EVQLVESGGGLVQPGGG LRLSCAASGFTFRSFAMS WVRQAPGKGLELVSDLR TSGGSTYYADSVKGRLTI SRDNSKNTLYLQMNSLR AEDTAVYYCAKSHYSTS WFGGFDYWGQGTLLVTV SS	SEQ ID NO: 20	DIQMTQSPSSVSASVGDRVITICR ASQGFSSWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTD FTLTITNLQPEDFATYYCQQANSF PLTFGGGTKVEIK
3	SEQ ID NO: 3	QVQLQESGPGLVKPSETL SLTCTVSGGSISSYYWSW IRQPPGKGLELIGYIYYS STNYPNPSLKSRTISVDT SKNHFSKLSSVTAADT AVYYCARSQYTSSWYGS FDIWGQGTMTVTVSS	SEQ ID NO: 21	DIQMTQSPSSVSASVGDRVITICR ASQGISTWLAWFQQKPGKAPKLL IYAASLTQGGVPSRFSGSGSGPEF TLTISSLQPEDFATYYCQQANSFP WTFGQGTKVEIK
4	SEQ ID NO: 4	QVQLVQSGAEVKKPGAS VKVSCKASGYTFNSYGIS WVRQAPGQGLEWMGWI SSHNGNSHYVQKFQGRV SMTTDTSTSTAYMELRS LRSDDTAVYYCARHSYT TSWYGGFDYWGQGTLLV TVSS	SEQ ID NO: 22	DIQMTQSPSSVSASVGDRVITICR ASQGFSSWLAWYQQKPGKAPQL LIYAASSLQSGVPSRFSGSGSGSD FTLTISSLQPEDFATYYCQQANSF PLTFGGGTKVEIK

5	SEQ ID NO: 5	EVQLVESGGGLVQPGGS LRLSCAASGFTFSSYALT WVRQAPGKGLEWVSFIS GSGGRPFYADSVKGRFTI SRDNSKNMLYLQMNSLR AEDTAIYYCAKSLYTTS WYGGFDSWGQGLVTV SS	SEQ ID NO: 23	DIQMTQSPSSVSASVGDRVITICR ASQGVVSWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQSNSFP FTLGPGTKVDIK
6	SEQ ID NO: 6	EVQLVESGGGLVQPGGS LRLSCAASGFTFSNYAM TWVRQAPGKGLEWVSTI SGSGDNTYYADSVQGRF TISRGHSKNTLYLQMNSL RAEDTAVYYCAKPTYSR SWYGAFDFWGQGTMTVT VSS	SEQ ID NO: 24	DIQMTQSPSSVSASVGDRVITICR ASQGISSWLAWYQQKPGKAPQLL IYAASRLQSGVPSRFRWGSGSGTDF TLTISSLQPEDFATYYCQQANNFP FTFGPGTKVDIK
7	SEQ ID NO: 7	EVQLVESGGNLEQPGGS LRLSCTASGFTFSRSAMN WVRRAPGKGLEWVSGIS GSGGRTYADSVKGRFT ISRDNSKNTLYLQMNSLS AEDTAAYYCAKDSYTTS WYGGMDVWGHGTTVT V SS	SEQ ID NO: 25	DIQMTQSPSSVSASVGDRVITICR ASQGIFSWLAWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFAIYYCQQANSVPI TFGQGTRLEIK
8	SEQ ID NO: 8	EVQLLESGGGLVQPGGS LRLSCAASGFTFSDYYM NWVRQAPGKGLEWVSSI SRYSSYIYYADSVKGRFT ISRDNSKNTLYLQMNSL RAEDTAVYYCARDIGGM DVWGQGLVTVSS	SEQ ID NO: 26	QSVLTQPPSASGTPGQRVTISCTG SSSNIGAVYDVHWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGT SASLAISGLRSEDEADYYCQTYDS SRWVFGGGTKLTVL

9	SEQ ID NO: 9	EVQLLESGGGLVQPGGS LRLSCAASGFTFSNYYM HWVRQAPGKGLEWVSSI SARSRYHYYADSVKGRF TISRDN SKNTLYLQMNSL RAEDTAVYYCARLATRH NAFDIWGQGTLVTVSS	SEQ ID NO: 27	QSVLTQPPSASGTPGQRVTISCSG SSSNIGNNAVSWYQQLPGTAPKL LIYASNM RVIGVPDRFSGSKSGTS ASLAISGLRSEDEADYYCGAWDD SQKALVFGGGTKLTVL
10	SEQ ID NO: 10	EVQLLESGGGLVQPGGS LRLSCAASGFTFSNYYM HWVRQAPGKGLEWVSSI SARSSYIYYADSVKGRFT ISRDN SKNTLYLQMNSL RAEDTAVYYCARLATRN NAFDIWGQGTLVTVSS	SEQ ID NO: 28	QSVLTQPPSASGTPGQRVTISCSG SSSNIGRNAVNWYQQLPGTAPKL LIYASNM RVSGVPDRFSGSKSGTS ASLAISGLRSEDEADYYCWA WD DSQKVG VFGGGTKLTVL
11	SEQ ID NO: 11	EVQLLESGGGLVQPGGS LRLSCAASGFTFSRYYM HWVRQAPGKGLEWVSSI SAQSSHIYYADSV EGRFT ISRDN SKNTLYLQMNSL RAEDTAVYYCARLATRQ NAFDIWGQGTLVTVSS	SEQ ID NO: 29	QSVLTQPPSASGTPGQRVTISCSG SSSNIGRNAVNWYQQLPGTAPKL LIYASNMRRSGVPDRFSGSKSGTS ASLAISGLRSEDEADYYCSAWDD SQKV VVFGGGTKLTVL
12	SEQ ID NO: 12	EVQLLESGGGLVQPGGS LRLSCAASGFTFSNYYM HWVRQAPGKGLEWVSSI SARSSYLYYADSVKGRF TISRDN SKNTLYLQMNSL RAEDTAVYYCARLATRH VAFDIWGQGTLVTVSS	SEQ ID NO: 30	QSVLTQPPSASGTPGQRVTISCSG SSSNIGNNAVNWYQQLPGTAPKL LIYASNMRRPGVPDRFSGSKSGTS ASLAISGLRSEDEADYYCEAWDD SQKAVVFGGGTKLTVL
13	SEQ ID NO: 13	MRAWIFFLLCLAGRALA QVQLMQSGAEVKKPGAS VKV SCKASGYTFTSYWM HWVRQAPGQGLEWMGT	SEQ ID NO: 31	MRAWIFFLLCLAGRALADIQLTQ SPSFLSASVGDRV TITCKASQDVG TAVAWYQQKPGKAPKLLIYWAS TRHTGVPSRFSGSGSGTEFTLTISS

		IYPRNSNTDYNQKFKAR VTMTRDTSTSTVYMELS SLRSED TAVYYCARPLY YYLTSPPTLFWGQGLV TVSS		LQPEDFATYYCQQAKTYPFTFGS GTKLEIKR
14	SEQ ID NO: 14	EVQLVETGGGLIQPGGSL RLSCAASGFTFSSYAMS WVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARTLHGIR AAYDAFIIWGQGLVTV SS	SEQ ID NO: 32	EIVLTQSPGTLSSLSPGERATLSCRA SQSVGINLSWYQQKPGQAPRLLIY GASHRATGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCHQYSQSPPF TFGGGTKVEIK
15	SEQ ID NO: 15	EVQLVETGGGLIQPGGSL RLSCAASGFTFSFYAMS WVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARTLHGIR AAYDAFIIWGQGLVTV SS	SEQ ID NO: 33	EIVLTQSPGTLSSLSPGERATLSCRA SQSVGINLSWYQQKPGQAPRLLIY GASHRLTGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCHQYSQPPPF TFGGGTKVEIK
16	SEQ ID NO: 16	EVQLVETGGGLIQPGGSL RLSCAASGFTFSFYAMS WVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRFTI SRDNSKNTLYLQMNSLR AEDTAVYYCARTIHGIR AAYDAFIIWGQGLVTV SS	SEQ ID NO: 34	EIVLTQSPGTLSSLSPGERATLSCRA SQSVGINLSWYQQKPGQAPRLLIY GASHRLTGIPDRFSGSGSGTDFTL TISRLEPEDFAVYYCHQYSQPPPF TFGGGTKVEIK
17	SEQ ID	EVQLVESGGGLVQPGGS LRLSCAASGFTFSSYWM YWVRQAPGKGLEWVAA	SEQ ID	DIQMTQSPSSLSASVGDRVITITCK ASQNINKHLDWYQQKPGKAPKL LIYFTNNLQTGVPSRFSGSGSGTD

	NO: 17	ITPNAGEDYYPESVKGRF TISRDNAKNSLYLQMNS LRAEDTAVYYCARGHY YYTSYSLGYWGQGTTLVT VSS	NO: 35	FTLTISSLQPEDFATYYCFQYNQG WTFGGGTKVEIK
18	SEQ ID NO: 18	EVQLVESGGGLVQPGGS LRLSCAASGFTFSSFSMS WVRQAPGKGLEWVATIS GGKTFTDYVDSVKGRFT ISRDDSKNTLYLQMNSL RAEDTAVYYCTRANYG NWFFEYWGQGTTLVTSS	SEQ ID NO: 36	EIVLTQSPATLSLSPGERATLSCRA SESVAKYGLSLLNWFQQKPGQPP RLLIFAASNRGSGIPARFSGSGSGT DFTLTISSLEPEDFAVYYCQQSKE VPFTFGQGTKVEIK

[0137] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:1 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:19. These CDRs correspond to those derived from tozorakimab 33_640087-7B (as described in WO2016/156440), which binds reduced IL-33 and inhibits its conversion to oxidised IL-33. Tozorakimab or 33_640087-7B is described in full in WO2016/156440 which is incorporated by reference herein.

[0138] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:7 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:25. These CDRs correspond to those derived from the antibody 9675P. 9675P is described in full in US2014/0271658 which is incorporated by reference herein.

[0139] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:11 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID

NO:29. These CDRs correspond to those derived from the antibody A25-3H04. A25-3H04 is described in full in US2017/0283494 which is incorporated by reference herein.

[0140] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:13 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:31. These CDRs correspond to those derived from the antibody ANB020. ANB020 is described in full in WO2015/106080 which is incorporated by reference herein.

[0141] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:16 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:34. These CDRs correspond to those derived from the antibody Ab43. Ab43 is described in full in WO2018/081075 which is incorporated by reference herein.

[0142] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:17 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:35. These CDRs correspond to those derived from the antibody IL33-158. IL33-158 is described in full in US2018/0037644 which is incorporated by reference herein.

[0143] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises the complementarity determining regions (CDRs) of the heavy chain variable region (HCVR) comprising the sequence of SEQ ID NO:18 and the complementarity determining regions (CDRs) of light chain variable region (LCVR) comprising the sequence of SEQ ID NO:36. These CDRs correspond to those derived from the antibody 10C12.38.H6. 87Y.581 IgG4. 10C12.38.H6. 87Y.581 IgG4 is described in full in WO2016/077381 which is incorporated by reference herein.

[0144] Suitably the skilled person knows of available methods in the art to identify CDRs within the heavy and light variable regions of an antibody or antigen-binding fragment thereof. Suitably the skilled person may conduct sequence-based annotation, for example. The regions between CDRs are generally highly conserved, and therefore, logic rules can be used to determine CDR location. The skilled person may use a set of sequence-based rules for

conventional antibodies (Pantazes and Maranas, Protein Engineering, Design and Selection, 2010), alternatively or additionally he may refine the rules based on a multiple sequence alignment. Alternatively, the skilled person may compare the antibody sequences to a publicly available database operating on Kabat, Chothia or IMGT methods using the BLASTP command of BLAST+ to identify the most similar annotated sequence. Each of these methods has devised a unique residue numbering scheme according to which it numbers the hypervariable region residues and the beginning and ending of each of the six CDRs is then determined according to certain key positions. Upon alignment with the most similar annotated sequence, for example, the CDRs can be extrapolated from the annotated sequence to the non-annotated sequence, thereby identifying the CDRs. Suitable tools/databases are: the Kabat database, Kabatman, Scaling, IMGT, Abnum for example.

[0145] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a variable heavy domain (VH) and variable light domain (VL) pair selected from Table 1.

[0146] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH domain of the sequence of SEQ ID NO:1 and a VL domain of the sequence of SEQ ID NO:19.

[0147] Suitably the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises 3 CDRs in a heavy chain variable region according to SEQ ID NO:1.

[0148] Suitably, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises 3 CDRs in a light chain variable region according to SEQ ID NO:19.

[0149] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises 3 CDRs in a heavy chain variable region according to SEQ ID NO:1, and 3 CDRs in a light chain variable region according to SEQ ID NO:19.

[0150] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a variable heavy domain (VH) and a variable light domain (VL) having VH CDRs 1-3 having the sequences SEQ ID NO: 37, 38 and 39, respectively, wherein one or more VHCDRs have 3 or fewer single amino acid substitutions, insertions and/or deletions.

[0151] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH domain which comprises VHCDRs 1-3 of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39, respectively.

[0152] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH domain which comprises VHCDRs 1-3 consisting of SEQ ID NO: 37, SEQ ID NO: 38 and SEQ ID NO: 39, respectively.

[0153] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a variable heavy domain (VH) and a variable light domain (VL) having VL CDRs 1-3 having the sequences of SEQ ID NO: 40, 41 and 42, respectively, wherein one or more VLCDRs have 3 or fewer single amino acid substitutions, insertions and/or deletions.

[0154] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VL domain which comprises VLCDRs 1-3 of SEQ ID NO: 40, SEQ ID NO: 41 and SEQ ID NO: 42, respectively.

[0155] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VL domain which comprises VLCDRs 1-3 consisting of SEQ ID NO: 40, SEQ ID NO: 41 and SEQ ID NO: 42, respectively.

[0156] Suitably, therefore, the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VHCDR1 having the sequence of SEQ ID NO: 37, a VHCDR2 having the sequence of SEQ ID NO: 38, a VHCDR3 having the sequence of SEQ ID NO: 39, a VLCDR1 having the sequence of SEQ ID NO: 40, a VLCDR2 having the sequence of SEQ ID NO: 41, and a VLCDR3 having the sequence of SEQ ID NO: 42.

[0157] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH and VL, wherein the VH has an amino acid sequence at least 90%, for example 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identical to a VH according to SEQ ID NO: 1.

[0158] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH and VL, wherein a VH disclosed above, has a sequence with 1, 2, 3 or 4 amino acids in the framework deleted, inserted and/or independently replaced with a different amino acid.

[0159] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH and VL, wherein the VL has an amino acid sequence at least 90%, for example 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identical to a VL according to SEQ ID NO: 19.

[0160] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH and VL, wherein a VL disclosed above has a sequence with 1, 2, 3 or 4 amino acids in the framework independently deleted, inserted and/or replaced with a different amino acid.

[0161] S

[0162] Suitably, therefore the anti-IL-33 antibody, binding fragment, or antibody variant thereof comprises a VH and VL, wherein the VH has an amino acid sequence consisting of SEQ ID NO: 1, and the VL has an amino acid sequence consisting of SEQ ID NO: 19.

[0163] In some instance the anti-IL-33 antibody, binding fragment, or variant thereof useful in the present methods comprises a heavy chain set forth in SEQ ID NO: 43 or a sequence 80, 85, 90 or 95% identical thereto and/or a light chain set forth in SEQ ID NO: 44 or a sequence 80, 85, 90 or 95% identical thereto. In some instances, the heavy chain has the sequence set forth in SEQ ID NO: 43 and the light chain has the sequence set forth in SEQ ID NO: 44. In some instances, the anti-IL-33 antibody, binding fragment, or variant thereof useful in the present methods comprises a heavy chain consisting of the sequence set forth in SEQ ID NO: 43, and a light chain consisting of the sequence set forth in SEQ ID NO: 44.

[0164] In some instances, the IL-33 signaling axis antagonist is the antibody 33_640087_7B, as disclosed in WO2016/156440, which is incorporated herein by reference. 33_640087_7B, also referred to in the art as MEDI3506 or tozorakimab. Therefore in some instances of the present disclosure the IL-33 signaling axis antagonist is tozorakimab.

[0165] Tozorakimab is a monoclonal antibody that binds to IL-33 and potently and specifically blocks all forms of IL-33 to prevent their signaling. Tozorakimab is an example of an IL-33 signaling axis antagonist. Tozorakimab also inhibits the conversion of redIL-33 to the oxidised form (oxIL-33), which has been shown to induce signaling via RAGE and induce epithelial cell proliferation. Suitably any of the characteristics defined above in relation to IL-33 signaling axis antagonists or anti-IL-33 antibodies apply to tozorakimab.

[0166] Tozorakimab is an exemplary anti-IL-33 antibody having : (a) a heavy chain variable region comprising a VHCDR1 having the sequence as set forth in SEQ ID NO: 37, a VHCDR2 having the sequence of SEQ ID NO: 38, a VHCDR3 having the sequence of SEQ ID NO: 39; and (b) a light chain variable region a VLCDR1 having the sequence of SEQ ID NO: 40, a VLCDR2 having the sequence of SEQ ID NO: 41, and a VLCDR3 having the sequence of SEQ ID NO: 42.

[0167] Tozorakimab also comprises a VH domain having the amino acid sequence as set forth in SEQ ID NO: 1 and a VL domain having the amino acid sequence as set forth in SEQ ID NO: 19.

[0168] Tozorakimab is an IgG1 antibody, the sequence of the full length heavy and light chain of tozorakimab, including the IgG1 chain, is set forth in SEQ ID NOs: 43 and 44, respectively.

[0169] In some instances, therefore, the antibody is tozorakimab, or a binding fragment or variant thereof. Suitably therefore in some instances, the IL-33 signaling axis antagonist is tozorakimab, or a binding fragment or variant thereof. Suitably therefore in some instances, the IL-33 signaling axis antagonist is tozorakimab.

[0170] In some instances, the IL-33 signaling axis antagonist is an anti-IL-33 antibody, binding fragment, or antibody variant thereof that has similar, or the same, pharmacokinetic (pK) characteristics as tozorakimab in humans.

[0171] In particular, an anti-IL-33 antibody, binding fragment, or antibody variant for use in the present methods may have a similar, or the same, half-life in humans as tozorakimab. The anti-IL-33 antibody, binding fragment, or antibody variant having a similar, or the same, half-life in humans as tozorakimab, when administered at a dose of 30 mg Q2W, may have a half-life of about 10 to about 20 days, about 12 to about 15 days, or of about 12.7 days. The anti-IL-33 antibody, binding fragment, or antibody variant having a similar, or the same, half-life in humans as tozorakimab, when administered at a dose of 100 mg Q2W, may have a half-life of about 10 to about 20 days, about 12 to about 15 days, or of about 13.2 days. The anti-IL-33 antibody, binding fragment, or antibody variant having a similar, or the same, half-life in humans as tozorakimab, when administered at a dose of 300 mg Q2W, may have a half-life of about 10 to about 20 days, about 12 to about 15 days, or of about 14.8 days.

[0172] In some instances, the IL-33 antibody, binding fragment, or variant thereof may competitively inhibit binding of IL-33 to tozorakimab (as described in WO2016/156440). WO2016/156440 discloses that tozorakimab binds to redIL-33 with particularly high affinity and attenuates both ST-2 and RAGE-dependent IL-33 signaling. An antibody, binding fragment, or variant thereof is said to competitively inhibit binding of a reference antibody to a given epitope if it specifically binds to that epitope to the extent that it blocks, to some degree, binding of the reference antibody to the epitope. Competitive inhibition may be determined by any method known in the art, for example, solid phase assays such as competition ELISA assays, Dissociation-Enhanced Lanthanide Fluorescent Immunoassays (DELFI[®], Perkin

Elmer), and radioligand binding assays. For example, the skilled person could determine whether an antibody, binding fragment, or variant thereof competes for binding to IL-33 by using an *in vitro* competitive binding assay, such as the HTRF assay described in WO2016/156440, paragraphs 881-886, which is incorporated herein by reference. For example, the skilled person could label tozorakimab with a donor fluorophore and mix multiple concentrations with fixed concentration samples of acceptor fluorophore labelled-redIL-33. Subsequently, the fluorescence resonance energy transfer between the donor and acceptor fluorophore within each sample can be measured to ascertain binding characteristics. To elucidate competitive binding antibody molecules, the skilled person could first mix various concentrations of a test binding molecule with a fixed concentration of the labelled tozorakimab antibody. A reduction in the FRET signal when the mixture is incubated with labelled IL-33 in comparison with a labelled antibody-only positive control would indicate competitive binding to IL-33. An antibody, binding fragment, or variant thereof may be said to competitively inhibit binding of the reference antibody to a given epitope by at least 90%, at least 80%, at least 70%, at least 60%, or at least 50%.

[0173] *Pharmaceutical composition*

[0174] In some instances, the effective amount of the tozorakimab or the IL-33 signaling axis antagonist is comprised in a pharmaceutical composition, comprising one or more excipients. Suitably, the tozorakimab or the IL-33 signaling axis antagonist is administered to the subject in the form of a pharmaceutical composition.

[0175] Suitably, any references herein to 'a/the tozorakimab or a/the IL-33 signaling axis antagonist' may also refer to a pharmaceutical composition comprising an/the tozorakimab or a/the IL-33 signaling axis antagonist. Suitably the pharmaceutical composition may comprise one or more IL-33 signaling axis antagonists.

[0176] The pharmaceutical compositions may be formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Thus, the pharmaceutical compositions may comprise, in addition to the active ingredient (i.e. the anti-IL-33 antibody), a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other material well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the

efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be by injection, e.g. intravenous or subcutaneous.

[0177] For subcutaneous injection, the pharmaceutical composition may be an aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability.

[0178] The pharmaceutical composition may be a liquid formulation provided in the form of containers with defined volume, including sealed and sterilized plastic or glass vials, ampoules and syringes, as well as in the form of large volume containers like bottles. Suitably, in the methods described herein, the pharmaceutical composition is a liquid formulation.

[0179] Suitably, the anti-IL-33 antibody, may be present within the pharmaceutical composition at a concentration of from 100 mg/ml to 200 mg/ml, more suitably 150 mg/ml. In particular, when an antibody dose of 300 mg is used, the antibody (particularly tozorakimab) may be provided in 2 ml of a 150 mg/ml liquid composition.

[0180] Suitably, the anti-IL-33 antibody may be buffered to a pH of 5.2 to 5.7, most suitably 5.5 (e.g. ± 0.1). The selection of such a pH confers significant stability to the pharmaceutical composition.

[0181] It will be appreciated that references to a "pharmaceutically acceptable excipient" includes references to any excipient conventionally used in pharmaceutical compositions. Such excipients may typically include one or more surfactant, inorganic or organic salt, stabilizer, diluent, solubilizer, reducing agent, antioxidant, chelating agent, preservative and the like.

[0182] Suitably, the surfactant is present within the pharmaceutical composition in an amount of from 0.001% to 0.1% (w/w). Suitably, the surfactant is polysorbate-80 (PS-80).

[0183] The anti-IL-33 antibody (particularly tozorakimab) may be provided in a pharmaceutical composition comprising L-histidine and/or L-histidine hydrochloride, L-arginine hydrochloride and polysorbate 80. The composition may in particular comprise 20 mM ± 10 % L-histidine/L-histidine hydrochloride, e.g. 20 mM ± 2.5 %, 5 % or 7.5 % L-histidine/L-histidine hydrochloride. That is to say L-histidine/L-histidine hydrochloride may be present in the composition at a concentration from 18-22, 18.5-21.5, 19-21 or 19.5-20.5 mM, suitably at a concentration of 20 mM.

[0184] The composition may in particular comprise 220 mM ± 10 % L-arginine hydrochloride, e.g. 220 mM ± 2.5 %, 5 % or 7.5 % L-arginine hydrochloride. For instance, L

arginine hydrochloride may be present in the composition at a concentration from 200-240, 205-235, 210-230 or 215-225 mM, suitably at a concentration of 220 mM.

[0185] The composition may in particular comprise 0.03 % w/v $\pm$ 10 % polysorbate 80, e.g. 0.03 % w/v $\pm$ 2.5 %, 5 % or 7.5 % polysorbate 80. For instance, polysorbate 80 may be present in the composition at a concentration from 0.027-0.033, 0.028-0.032 or 0.029-0.031 % w/v, suitably at a concentration of 0.03 % w/v.

[0186] The composition may have a pH from 5.2-5.7, 5.3-5.6 or 5.4-5.5, suitably 5.5.

In a particular instance the pharmaceutical composition comprises 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride and 0.03 % polysorbate 80, and has a pH of 5.5. Suitably the pharmaceutical composition also comprises 150 mg/ml tozorakimab. When the composition comprises 150 mg/ml tozorakimab, a 300 mg dose of the antibody can be administered in 2 ml of the composition.

[0187] *Administration Regimens*

[0188] The present disclosure also relates to dosage regimens of tozorakimab or an IL-33 signaling axis antagonist, which finds particular effectiveness in the treatment of asthma.

[0189] A dosage regimen is made up of one or more doses of a controlled size, administered throughout a treatment window. Where there is more than one dose, the doses are separated by a dosing interval. The tozorakimab or the IL-33 signaling axis antagonist is administered in a therapeutically effective amount. As defined hereinabove, an “effective amount” or “therapeutically effective amount” of an agent, e.g., a pharmaceutical formulation comprising an anti-IL-33 antibody, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0190] In some instances, therefore, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered at a dose that achieves at least 80%, 85% or 90% target engagement in the lung. In some instances, the dose achieves at least 90% target engagement in the lung. In some instances, the dose achieves at least 91%, 92%, 93% or 94% target engagement in the lung. In some instances the % target engagement is achieved at trough concentration.

[0191] Methods of administering the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof to a subject in need thereof are well known to or are readily determined by those skilled in the art, and are described hereinbelow.

[0192] The size of the dose of tozorakimab or the IL-33 signaling axis antagonist may be expressed in terms of weight of the tozorakimab or the IL-33 signaling axis antagonist. In certain instances, the tozorakimab or the IL-33 signaling axis antagonist is administered in a dose of about 400 to about 800 mg, about 450 to about 750 mg, about 500 to about 700 mg, about 510 to about 690 mg, about 520 to about 680 mg, about 530 to about 670 mg, about 540 to about 660 mg, about 550 to about 650 mg, about 560 to about 640 mg, about 570 to about 630 mg, about 580 to about 620 mg, about 590 to about 630 mg, or about 600 mg. In some instances, the dose is 600 mg.

[0193] In some instances, the tozorakimab or the IL-33 signaling axis antagonist is formulated for subcutaneous injection at 150 mg/mL, such that a 600 mg dose is administered as a 4 mL treatment. A 600 mg dose of the tozorakimab or the IL-33 signaling axis antagonist may be administered as two concurrent 300 mg dosages. As used herein, “concurrent” doses refer to doses which are administered simultaneously, or sequentially with no or only a minimal time period (e.g. less than 1 hour, less than 30 minutes, less than 15 minutes, less than 5 minutes) separating them.

[0194] In some instances, the tozorakimab or the IL-33 signaling axis antagonist is administered in a dose of about 200 to about 400 mg, about 250 to about 350 mg, about 260 to about 340 mg, about 270 to about 330 mg, about 280 to about 320 mg, about 290 to about 310 mg, about 295 to about 305 mg or about 300 mg.

[0195] In some instances, the dose is 300 mg. In some instances, the tozorakimab or the IL-33 signaling axis antagonist is formulated for subcutaneous injection at 150 mg/mL, such that a 300 mg dose is administered as a 2 mL treatment. In some instances, a 300 mg dose of the tozorakimab or the IL-33 signaling axis antagonist may be administered as two concurrent 150 mg dosages. As used herein, “concurrent” doses refer to doses which are administered simultaneously, or sequentially with no or only a minimal time period (e.g. less than 1 hour, less than 30 minutes, less than 15 minutes, less than 5 minutes) separating them.

[0196] In some instances, the dose is 150 mg. In some instances, the tozorakimab or the IL-33 signaling axis antagonist is formulated for subcutaneous injection at 150 mg/mL, such that a 150 mg dose is administered as a 1 mL treatment. The size of the dose of tozorakimab or the IL-33 signaling axis antagonist may be expressed in terms of the plasma drug concentration provided by the dose, as the amount of active compound manipulated so as to provide a plasma drug concentration of a certain level. By varying the amount, bioavailability, or

timing/frequency of the antibody or variant administered, the skilled person can control the plasma concentration in the subject. As plasma concentrations vary across time with drug uptake and clearance, they may be expressed in various standardized ways – for example as a maximum, minimum (trough) or across time.

[0197] In some instances, the dose is selected so as to provide a $C_{\max,ss}$ (the observed maximum concentration at steady state) of between about 20 and about 50 $\mu\text{g/mL}$, between about 25 and about 45 $\mu\text{g/mL}$, between about 30 and about 40 $\mu\text{g/mL}$, between about 35 and about 40 $\mu\text{g/mL}$, or about 37 $\mu\text{g/mL}$. In some instances, the $C_{\max,ss}$ is that observed during the dosing period. In this context, the “dosing period” refers to the time between two consecutive doses.

[0198] The tozorakimab serum concentration can be measured (and therefore used to determine $C_{\max,ss}$) anti-drug antibody reagents in a suitable assay format to capture and detect tozorakimab from a biological sample (e.g. blood). In some instances, the assay may use an anti-IgG1 capture mAb and a stabilised tozorakimab antigen labelled with a detectable marker. The detectable marker can be quantified in order to determine the concentration of tozorakimab. I

[0199] Administration of the tozorakimab or the IL-33 signaling axis antagonist is performed as multiple doses separated by a dosing interval. In some instances, the dosing interval is 2 weeks (14 days), 3 weeks (21 days), 4 weeks (28 days) or 5 weeks (35 days). In some instances, the dosing interval is 4 weeks (28 days). In some instances, the dosing interval is about 4 weeks (i.e. 28 ± 4 days). In some instances, the dosing interval is about 2 weeks (i.e. 14 ± 4 days).

[0200] Therefore, as used herein, a dose of 600 mg with a 4 week dosing window (Q4W) may be substituted 300 mg administered every 2 weeks (Q2W) all which provides a dosing regimen equivalent to 600 mg every 4 weeks. Thus, in some instances, the dose is about 300 mg Q2W.

[0201] In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered to the subject every 2 weeks (Q2W), 4 weeks (Q4W) or 8 weeks (Q8W).

[0202] In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered at about 300 mg Q2W. In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is

administered at about 600 mg Q4W. In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered at about 300 mg Q4W.

[0203] In some instances, the effective amount of the tozorakimab or the IL-33 signaling axis antagonist is a dose of between 300mg to 600mg. The effective amount of an tozorakimab or the IL-33 signaling axis antagonist may be a dose of between 300mg to 600mg of tozorakimab.

[0204] In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered to the subject at a dose of 600 mg every 4 weeks (Q4W). In some instances, tozorakimab or a pharmaceutical composition thereof is administered to the subject at a dose of 600 mg every 4 weeks (Q4W). In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered to the subject at a dose of 300 mg every 2 weeks (Q2W). In some instances, tozorakimab or pharmaceutical composition thereof is administered to the subject at a dose of 300 mg every 2 weeks (Q2W).

[0205] When the dosing interval is expressed as a number of weeks, a margin of error is permissible such that a week may be expressed as 7 days $\pm$ 1 day. In some instances, a week may be expressed as 7 days $\pm$ 0.5 days, 7 days $\pm$ 0.25 days, or exactly 7 days. Where the dosing interval is multiple weeks, the margins of error in each week may be combined. For example, in some instances, the dosing interval is 4 weeks $\pm$ 4 days. In some instances, the dosing interval is 4 weeks $\pm$ 3 days. In some instances, the dosing interval is 4 weeks $\pm$ 2 days. In some instances, the dosing interval is 4 weeks $\pm$ 1 day. In some instances, the dosing interval is exactly 4 weeks. In some instances, the dosing interval is 8 weeks $\pm$ 4 days. In some instances, the dosing interval is 8 weeks $\pm$ 3 days. In some instances, the dosing interval is 8 weeks $\pm$ 2 days. In some instances, the dosing interval is 8 weeks $\pm$ 1 day. In some instances, the dosing interval is exactly 8 weeks.

[0206] In some instances, the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered during a “treatment window”, which as used herein refers to a period commencing at the administration of the first dose and running until the final dose of the tozorakimab or the IL-33 signaling axis antagonist or pharmaceutical composition thereof is administered. The date the first dose is administered is referred to as “Day 1” or “Week 0”, with Week 1 commencing 7 days later, Week 2 commencing 7 days after that, and so on. In some instances, the treatment window is 16 weeks long (i.e. running from Week 0 to Week 15) and the dosing interval is 4 weeks, such that a total of 4 doses are

administered (on Week 0, 4, 8 and 12 respectively). In some instances, the treatment window is 12 weeks long, and the dosing interval is 4 weeks, such that doses are administered Days 1 (Week 0), 29 ± 4 (Week 4), 57 ± 4 (Week 8), and 85 ± 4 (Week 12).

[0207] In some instances, the treatment window is 12 weeks, 14 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, 24 weeks, 26 weeks, 28 weeks, 30 weeks, 32 weeks, 34 weeks, 36 weeks, 38 weeks, 40 weeks, 42 weeks, 44 weeks, 46 weeks, 48 weeks, 50 weeks, 52 weeks or more. In some instances, the treatment window is 52 weeks or more. In some instances, the treatment window is 48 weeks or more. In one instance, the treatment window is 24 weeks. In one instance, the treatment window is 24 weeks long, and the dosing interval is 4 weeks.

[0208] *Route of administration*

[0209] Methods of administering the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof to a subject in need thereof are well known to or are readily determined by those skilled in the art.

[0210] Suitably, the route of administration of the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof may be parenteral. Suitably, the term parenteral as used herein includes, e.g., intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal, or vaginal administration.

[0211] Suitably, parenteral formulations may be a single bolus dose, an infusion or a loading bolus dose followed with a maintenance dose. These compositions may be administered at specific fixed or variable intervals, e.g., once a day, or on an "as needed" basis.

[0212] In some instances, the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject subcutaneously. In some instances, the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject by injection. In some instances, the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject by subcutaneous injection.

[0213] The disclosure will now be described with reference to the following figures.

FIGURES

[0214] FIG. 1 shows Tozorakimab 600mg Q4W significantly improved clinic preBD-FEV₁ by 0.195L (87.8 - 301.9) at Week 16 vs placebo in a subgroup of participants with ≥ 2

exacerbations in previous 12 months having moderate or severe asthma recruited into the FRONTIER-3 trial (Stat Sig. P value < 0.1).

[0215] FIG. 2 shows Tozorakimab 600 mg Q4W has greater efficacy for improving clinic preBD-FEV₁ compared to a placebo in a subgroup of participants with ≥ 2 exacerbations in previous 12 months having moderate or severe asthma recruited into the FRONTIER-3 trial (Stat Sig. P value < 0.1).

[0216] FIG. 3 shows Tozorakimab 600 mg Q4W has greater efficacy for improving home FEV₁ compared to a placebo in a subgroup of participants with ≥ 2 exacerbations in previous 12 months having moderate or severe asthma recruited into the FRONTIER-3 trial (Stat Sig. P value < 0.1).

[0217] FIG. 4 shows Tozorakimab 600 mg Q4W has greater efficacy for improving PEF compared to a placebo in a subgroup of participants with ≥ 2 exacerbations in previous 12 months having moderate or severe asthma recruited into the FRONTIER-3 trial (Stat Sig. P value < 0.1).

[0218] FIG. 5A shows tozorakimab had a similar effect on home FEV₁ secondary endpoint in the ITT (entire treated cohort) compared to placebo in subjects with either > or < 300 EOS at baseline.

[0219] FIG. 5B shows tozorakimab had a similar effect on PEF secondary endpoint in the ITT (entire treated cohort) compared to placebo in subjects with either > or < 300 EOS at baseline.

EXAMPLES

[0220] **Example 1: A Phase II, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of MEDI3506 (tozorakimab) in Adult Participants with Uncontrolled Moderate-to-severe Asthma**

[0221] Study Design

[0222] This was a Phase II, randomised, double-blind, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, pharmacokinetics (PK) and immunogenicity of MEDI3506 (hereafter referred to as tozorakimab) in adult participants with uncontrolled moderate-to-severe asthma on top of standard of care (SoC). Participants who failed screening could be re-screened.

[0223] Participants were centrally assigned to randomized intervention using a randomization and trial supply management system in a 1:1:1 ratio to receive either 600 or 300 mg

tozorakimab, or placebo, every 4 weeks (Q4W) by subcutaneous (SC) injection for a total of 4 doses. The randomization was stratified according to participation in the cough sub-study. As tozorakimab and placebo are not identical, study intervention was handled by an unblinded study intervention manager at the site and was administered by an unblinded study team member who was not involved in the management of study participants. Participants were required to take their asthma controller therapy regularly throughout the screening, intervention and follow-up periods.

[0224] Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of tozorakimab compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	• As measured in clinic, change from baseline to Week 16 in pre-BD FEV ₁ (L).
Secondary	
• To further assess the effect of tozorakimab compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	• As measured in clinic, change from baseline to Weeks 8 and 16 in post-BD FEV ₁ (L).
• To assess the PK of tozorakimab in adult participants with uncontrolled moderate-to-severe asthma.	• Serum tozorakimab concentration-time profiles during the intervention and follow-up periods.
• To assess the immunogenicity of tozorakimab in adult participants with uncontrolled moderate-to-severe asthma.	• ADA during the intervention and follow-up periods.
• To assess the effect of tozorakimab compared with placebo on asthma control in adult participants with uncontrolled moderate-to-severe asthma.	• Change from baseline to Week 16 in ACQ-6 score. • Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16. • Proportion of participants achieving ACQ-6 well controlled status (defined as ACQ-6 score ≤ 0.75 at Week 16).

• To assess the effect of tozorakimab compared with placebo on health status in adult participants with uncontrolled moderate-to-severe asthma.	• Change from baseline to Week 16 in SGRQ score. • Proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16.
• To assess the effect of tozorakimab compared with placebo on CompEx in adult participants with uncontrolled moderate-to-severe asthma.	• Time to first CompEx event based on the period from baseline to Week 16. • CompEx annualised event rate.
• To assess the effect of tozorakimab compared with placebo on concentration of FeNO in adult participants with uncontrolled moderate-to-severe asthma.	• Percent change from baseline to Week 16 in concentration of FeNO in exhaled breath.

ACQ-6 = asthma control questionnaire-6; ADA = anti-drug antibody(ies); BD = bronchodilator; CompEx = composite endpoint for severe exacerbations of asthma; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV₁ = forced expiratory volume in the first second; L = litres; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PCR = polymerase chain reaction; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's respiratory questionnaire; tozorakimab = MEDI3506.

[0225] Target Population and Sample Size

[0226] Eligible participants were adults (18 to < 65 years of age inclusive) with documented physician-diagnosed asthma of early onset, defined as development of asthma before the age of 25 years. Asthma was to have been diagnosed > 12 months prior to Study Visit 1 (SV1). Participants were to have been treated with medium to high dose inhaled corticosteroids (ICS) defined as total daily dose of > 250 µg fluticasone dry powder or equivalent, for at least 12 months prior to SV1 and on a stable dose for ≥ 3 months prior to SV1 and receiving stable long-acting beta agonist therapy for ≥ 3 months prior to SV1 (this may be as a fixed-dose combination product, or a separate inhaler). Treatment with additional asthma controller therapies eg, long acting muscarinic antagonists, leukotriene receptor antagonists, theophylline (≥ 1 month at a stable dose) prior to SV1 was also allowed. Participants were to have an asthma

control questionnaire-6 (ACQ-6) score of ≥ 1.5 at each of SV1, SV2, and SV4 (randomisation) and morning pre-bronchodilator (BD) forced expiratory volume in the first second (FEV₁) < 85% predicted normal at SV1.

[0227] Approximately 228 participants were to be randomised 1:1:1 (tozorakimab 600 mg: tozorakimab 300 mg: placebo) to achieve 216 evaluable participants (72 participants per treatment group). A sample size of 216 participants would provide at least 80% power to detect a statistically significant difference in change from baseline to Week 16 in pre-BD FEV₁, assuming a difference of 150 mL between placebo and tozorakimab, a between-participant standard deviation (SD) of 420 mL and a one-sided- 10% alpha level.

[0228] Up to 60 participants were intended to be included in the cough sub-study (approximately 20 participants per treatment group). However, given the exploratory nature of the sub-study and that it may not have been activated in all countries, randomisation of participants not included in the sub-study was not restricted and sub-study recruitment was not achieved. The sub-study was considered exploratory and no formal power calculations were performed.

[0229] Investigational Product and Comparator(s): Dosage, Mode of Administration

[0230] Tozorakimab was manufactured by AstraZeneca and supplied as a solution for SC injection in 1 mL vials. Tozorakimab was administered at 300, and 600 mg per dose every 4 weeks for a total of 4 doses. In the 300 mg group, participants received 2 mL tozorakimab as 1 × 2 mL syringe, plus 2 mL placebo as 1 × 2 mL syringe. In the 600 mg group, participants received 4 mL tozorakimab as 2 × 2 mL syringes. In the placebo group, participants received 2 × 2 mL syringes of placebo.

[0231] Duration of Treatment

[0232] Participants were enrolled in this study for up to 29 weeks. The study comprised 3 periods including the screening period of up to 5 weeks, an intervention period of 16 weeks, and a follow-up period of 8 weeks.

[0233] Efficacy Assessments

[0234] Spirometry (Pre- and Post-bronchodilation)

The Global Lung Function Initiative equations were used to determine the PNV and are pre- programmed into the spirometer, any suitable spirometer may be used. FEV₁, expressed as percent of the PNV, will be calculated as follows:

$$FEV1\% \text{ of PNV} = (FEV1_{\text{measured}}/FEV1_{\text{PNV}}) \times 100$$

Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 4 inhalations. It is highly recommended to use a spacer device for this procedure.

After a gentle and complete exhalation, up to a maximum of 4 inhalations of salbutamol (100 µg metered dose) or albuterol (90 µg metered dose) should be administered using a spacer device. In rare cases where a participant has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45 µg metered dose, up to a maximum of 4 inhalations) can be used (Sorkness et al 2008). A nebuliser should not be used. A lower total dose (eg, 2 inhalations instead of 4 and if required up to a maximum of 4 puffs) can be used if there is a concern about any effect on the participant's safety; the reason should be noted in the participant's medical record.

The highest technically acceptable pre-and post-BD FEV1 will be used to determine reversibility. Reversibility is calculated as follows:

$$FEV1\% \text{ Reversibility} = (post-BD \text{ FEV1} - pre-BD \text{ FEV1})/pre-BD \text{ FEV1} \times 100$$

At-home Spirometry

During the study period, participants will be required to monitor lung function at home twice daily using an at-home spirometry device.

[0235] Fractional Exhaled Nitric Oxide

Airway inflammation will be evaluated using a standardised single-breath FeNO test. A single exhalation technique recommended by the manufacturer will be followed (Allakhverdi et al 2007; Alving et al 2017). The FeNO test will be performed prior to AO and spirometry. Participants should follow the relevant medication and other restrictions beforehand (Sections 6.5.3 and 5.3). If any of the above restrictions are not met, and the assessment cannot be sufficiently delayed on the day the assessment should be rescheduled within the allowed visit window.

The NIOX VERO® Airway Inflammation Monitor will be used to measure FeNO. Instructions for use of this monitor will be provided in a separate user's manual. NIOX

VERO® sensors will be replaced as recommended by the manufacturer. The vendor supplying the equipment will be responsible for ensuring that the equipment and procedures for the measurement of FeNO are validated prior to the start of the study.

If possible, all post-randomisation FeNO assessments should be performed within ± 1.5 hours of the time that the randomisation FeNO was performed.

[0236] Asthma Control Questionnaire-6

The ACQ (Juniper et al 1999) was developed to measure asthma control and has been fully validated for use in adults and children 6 to 17 years of age. International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimise asthma control (minimisation of symptoms, activity limitation, bronchoconstriction, and rescue BD use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ was developed to meet these criteria by measuring both the adequacy of asthma control and change in asthma control, which occur either spontaneously or as a result of treatment.

In the ACQ-6, participants are asked to recall how their asthma has been during the previous week by responding to one BD use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores > 1.5 indicate not well-controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered clinically meaningful.

[0237] St. George's Respiratory Questionnaire

[0238] The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into two parts: part one 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 three domain 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 domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones and Forde 2009).

[0239] Assessment and Documentation of Asthma Exacerbations

[0240] During the study, an asthma exacerbation will be defined as a change in the participant's usual asthma symptoms that leads to any of the following:

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

b. An emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).

c. An in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours).

A hospitalised asthma exacerbation is defined as any worsening of asthma that leads to (c.) above. Note: for each exacerbation, the criterion/criteria met to confirm exacerbation status should be documented.

The list below defines what is acceptable documentation for historical exacerbations, suitably those in the 12 months preceding treatment:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalised/treated with systemic corticosteroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic corticosteroids.
- Evidence of prescriptions for systemic corticosteroids used during an exacerbation.

- A documented conversation between the Investigator (or delegate) and a participant who is already on an OCS action plan, including the information necessary to assess Inclusion Criterion 19.

- A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with corticosteroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

The guidance below defines assessment of asthma exacerbations. The start of an exacerbation is defined as the earliest of the following:

- Start date of systemic corticosteroids or temporary increase in a stable OCS background dose.
- Date of emergency room or urgent care visits requiring systemic corticosteroids.
- Date of hospital admission due to asthma.

The end date of an exacerbation is defined as the latest of the following:

- Last date of systemic corticosteroids or temporary increase in a stable OCS background dose.
- Date of discharge from emergency room or urgent care visit.
- Date of hospital discharge.

If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation in the statistical analysis.

All asthma exacerbations that occur during the treatment period and follow-up, must be recorded in the exacerbation eCRF.

Daily eDiary

During the study period, participants will be required to take their asthma controller therapy regularly and complete an eDiary twice daily.

At SV1, participants will receive a handheld eDiary device to complete twice-daily, daily and non-daily PRO assessments during the study. Participants will be provided training on the use of the handheld device. Daily assessments will include night-time and daytime asthma symptoms (morning and evening diary, respectively), use of inhaled rescue medication in response to worsening symptoms, nights with awakenings due to asthma symptoms (morning diary only) and background medication use. The PEF data (obtained from the home peak flow meter) will be captured at the conclusion of the morning and evening eDiary entry.

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night-time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

The number of doses of rescue medication (1 dose unit = 1 puff on inhaler) taken will be recorded by the participant in the eDiary twice daily. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening.

The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning.

Nocturnal awakenings due to asthma symptoms will be recorded by the participant in the daily eDiary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response.

Background (inhaled ICS/LABA) medication administration use will be recorded once daily in the daily eDiary as “yes” or “no” response.

[0241] CompEx

CompEx is a combination of exacerbations of asthma and diary events (ie, combination of eDiary variables). CompEx is a composite surrogate endpoint for exacerbations of asthma, recently developed by AstraZeneca (it is not yet a regulatory-approved clinical endpoint). Diary

events are defined by the threshold and slope criteria using the following morning/evening (AM/PM) diary variables:

- PEF
- Symptom score (0 –3)
- Use of rescue medication

CompEx can predict treatment efficacy on exacerbations in early development before running traditional long-term exacerbation trials. CompEx can be used broadly in the assessment of new therapeutic interventions for asthma (Fuhlbrigge et al 2017; note: the referenced publication used the term ‘severe exacerbation’ but used the same definition as used for ‘exacerbation’ in this protocol; therefore, the term ‘exacerbation’ has been used in this section for internal consistency of the protocol.)

[0242] Statistical Analyses

[0243] Efficacy analyses were performed using the Intent-to-treat (ITT) population. The primary estimand was a ‘Treatment Policy’ estimand, as follows: the difference in mean change from baseline in pre-BD FEV₁ at Week 16 (tozorakimab – placebo) was to be estimated using a repeated measures mixed effects analysis of covariance model, for the ITT population. This included all available data from all visits up to and including Week 16, irrespective of whether the participant discontinued study intervention or received rescue therapy.

[0244] A similar approach was taken for the analysis of ACQ-6, St George’s respiratory questionnaire (SGRQ), and fractional exhaled nitric oxide (FeNO). The difference in mean change from baseline in post-BD FEV₁ at Weeks 8 and 16 was to be estimated using a repeated measures mixed effects analysis of covariance model, similar to that described for the primary efficacy analysis. Data may have been log transformed prior to analysis where appropriate. Time to first composite endpoint for severe exacerbations of asthma (CompEx) event was to be analysed using a Cox proportional hazard model, with treatment fitted as a covariate.

[0245] Study Population

[0246] Of the 478 patients screened, 235 participants were randomized in 52 study centres across 7 countries in a 1:1:1 ratio to receive either placebo (81 participants), tozorakimab 300 mg (77 participants), or tozorakimab 600 mg (77 participants). At the end of the study, all

participants had either completed (225 [95.7%] participants) or discontinued (10 [4.3%] participants) treatment. Overall, 227 (96.6%) participants completed the study.

[0247] Demographics and disease characteristics were representative of the intended population of adults with uncontrolled moderate-to-severe asthma and with the exception of a lower proportion of female participants in the placebo group (53.1%) compared with the tozorakimab group (69.5%) otherwise similar across the treatment groups.

[0248] Summary of Efficacy Results

[0249] Primary Endpoint

[0250] No statistically significant difference from placebo was demonstrated for either the tozorakimab 300 mg or tozorakimab 600 mg group *as a whole* in change from baseline at Week 16 in pre-BD FEV₁ as measured in the clinic (300 mg: least square mean [LSMean] difference [tozorakimab – placebo] of 0.036 L [80% confidence interval (CI): -0.038, 0.111], p = 0.267; 600 mg: LSMean difference of 0.004 L [80% CI: -0.071, 0.079], p = 0.473).

[0251] However, a statistically significant improvement in week 16 pre-BD FEV₁ as measured in the clinic was seen in the tozorakimab 600 mg Q4W group for a subgroup of participants having had ≥ 2 exacerbations in the 12 months prior to administration of tozorakimab (see Table below). For this group tozorakimab 600mg Q4W improved clinic FEV₁ by 0.195L (87.8, 301.9) at Week 16 *vs* placebo. This improvement was also reflected in the endpoint of home pre-BD FEV₁ in the same group of participants. A significant improvement of 95mL (23.0, 167.6) at week 16 of pre-BD FEV₁ as measured at home, compared to placebo, was also seen in the tozorakimab 600 mg Q4W group for participants having had ≥ 2 exacerbations in the 12 months prior to administration of tozorakimab.

	Tozorakimab Dose A Participants were randomised to receive tozorakimab Dose A by subcutaneous (SC) injection.	Tozorakimab Dose B Participants were randomised to receive tozorakimab Dose B by SC injection.	Placebo Participants were randomised to receive placebo by SC injection.
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	Number of Participants Analyzed:	45		47		52	
Change from Baseline to Week 16 in Pre-BD FEV₁ as Measured in the Study Clinic: Analysis per Number of Exacerbations in Last 12 Months Units: litres	Category	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
1 Exacerbation in Last 12 Months	Number Analyzed:	45 Participants		47 Participants		52 Participants	
		0.188	0.065	0.042	0.070	0.165	0.062
≥ 2 Exacerbations in Last 12 Months	Number Analyzed:	31 Participants		30 Participants		29 Participants	
		0.059	0.067	0.194	0.065	-0.018	0.069

[0252] Secondary Endpoints

• No statistically significant difference at Week 8 or Week 16 was observed compared with placebo for either the tozorakimab 300 mg or 600 mg group for post-BD FEV₁ as measured in the clinic.

- No statistically significant difference was observed between either the tozorakimab 300 mg or 600 mg groups, and placebo for the change from baseline to Week 16 in ACQ-6 score.

- Although a numerically higher proportion of participants achieved a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16 in both the tozorakimab 300 mg and tozorakimab 600 mg groups compared with placebo, this difference between groups in the proportion of responders was not clinically meaningful.

- There was no statistically significant difference in the proportion of participants in either the tozorakimab 300 mg or tozorakimab 600 mg groups achieving well controlled status in their ACQ-6 score at Week 16 compared with placebo.

- No statistically significant difference was observed between either the tozorakimab 300 mg or 600 mg groups, and placebo for the change from baseline to Week 16 in SGRQ domain and total scores.

- There was no statistically significant difference in the proportion of participants in either the tozorakimab 300 mg or tozorakimab 600 mg groups achieving a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16 compared with placebo.

- There was no statistically significant difference in either the tozorakimab 300 mg or tozorakimab 600 mg groups in the time to first CompEx event based on the period from baseline to Week 16 compared with the placebo group.

- Although there was a numerically lower CompEx annual event rate through Week 16 in the tozorakimab 600 mg group (0.69) than the tozorakimab 300 mg (0.86) or placebo groups (0.99), but the difference between either of the tozorakimab groups and placebo was not statistically significant.

[0253] Other endpoints however were shown to be improved in the above group of participants who received tozorakimab 600 mg Q4W and had ≥ 2 exacerbations in the 12 months prior to administration of tozorakimab: PEF (peak expiratory flow AM/PM) was significantly improved in this group, by 9.212 L/min (0.071, 18.352) at week 16 compared to placebo.

[0254] Conclusion(s)

- The study did not meet its primary objective. No statistically significant, or clinically meaningful difference from placebo was demonstrated for either the tozorakimab 300 mg or tozorakimab 600 mg group *as a whole* in change from baseline at Week 16 pre-BD FEV₁ as measured in the clinic for the ITT population.

- The study did however meet other endpoints in a particular population. In a subgroup of participants, a significant improvement in Week 16 pre-BD FEV₁ as measured in the clinic was achieved. This subgroup of participants were those who received tozorakimab 600 mg Q4W and had ≥ 2 exacerbations in the 12 months prior to administration of tozorakimab.

SEQUENCES

[0255] Further to the sequences listed in Table 1, we provide the following additional sequences:

MEDI3506 VHCDR1 SEQ ID NO 37: SYAMS

MEDI3506 VHCDR2 SEQ ID NO 38: GISAIQSTYYADSVKG

MEDI3506 VHCDR3 SEQ ID NO 39: QKFMQLWGGGLRYPFGY

MEDI3506 VLCDR1 SEQ ID NO 40: SGEGMGDKYAA

MEDI3506 VLCDR2 SEQ ID NO 41: RDTKRPS

MEDI3506 VLCDR3 SEQ ID NO 42: GVIQDNTGV

SEQ ID NO:43 MEDI3506 heavy chain

EVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGISAID
QSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARQKFMQLWGGGLRYPF
GYWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:44 MEDI3506 light chain

SYVLTQPPSVSVSPGQTASITCSGEGMGDKYAAWYQQKPGQSPVLVIYRDTKRPS
GIPERFSGSNSGNTATLTISGTQAMDEADYYCGVIQDNTGVFGGGTKLTVLGQPKAAPS
VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA
ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

CLAIMS

What is claimed is:

1. A method of treatment of a subject having moderate or severe asthma, the method comprising: administering to said subject an effective amount of tozorakimab, wherein, in the 12 months prior to said administration the subject has had two or more asthma exacerbations.
2. A method of improving lung function in a subject having moderate or severe asthma, the method comprising: administering to said subject an effective amount of tozorakimab, wherein, in the 12 months prior to said administration the subject has had two or more asthma exacerbations.
3. A method of increasing preBD FEV₁ of a subject having moderate or severe asthma by at least 100ml, the method comprising: administering to said subject an effective amount of an IL-33 signaling axis antagonist, wherein in the 12 months prior to said administration the subject has had two or more asthma exacerbations.
4. The method of claim 3 wherein the method of increasing preBD FEV₁ of a subject having moderate or severe asthma by at least 100ml is a method of treatment of a subject having moderate or severe asthma by increasing preBD FEV₁ of the subject by at least 100ml.
5. The method of any one of claims 1 to 4, wherein, prior to said administration the subject comprises a blood eosinophil count of <300 cells/ μ l.
6. The method of claim 5, wherein the subject is selected from a group of subjects comprising said blood eosinophil count prior to said administration.
7. The method of claim 5 or 6, wherein the method further comprises a step of selecting a subject having said blood eosinophil count prior to said administration.
8. The method of any one of claims 1 or 5-7, wherein treatment of a subject having moderate or severe asthma results in improving lung function of the subject.
9. The method of any one of claims 1 to 8, wherein treatment of a subject having moderate or severe asthma, or improvement of lung function of a subject having moderate or severe asthma, or increasing preBD FEV₁ of a subject having moderate or severe asthma, results in increasing

pre-bronchodilator (BD) FEV₁ of the subject by at least 100ml, 105ml, 110ml, 115ml, 120ml, 125ml, 130ml, 1345ml, 140ml, 145ml, 150ml, 155ml, 160ml, 165ml, 170ml, 175ml, 180ml, 185ml, 190ml, 195ml, or by at least 200ml, optionally by about 200ml.

10. The method of any one of claims 1 to 9, wherein treatment of a subject having moderate or severe asthma, or improvement of lung function of a subject having moderate or severe asthma, or increasing preBD FEV₁ of a subject having moderate or severe asthma, further results in increasing peak expiration flow (PEF) of the subject by at least 5L/min, at least 5.5L/min, at least 6L/min, at least 6.5L/min, at least 7L/min, at least 7.5L/min, at least 8L/min, at least 8.5L/min, or by at least 9L/min, optionally by about 9L/min.

11. The method of claim 9 or 10, wherein the increase in preBD-FEV₁ or PEF of the subject is achieved by week 16 after administration of the effective amount of tozorakimab or the IL-33 signaling axis antagonist.

12. The method of any one of claims 9 to 11, wherein the increase in preBD-FEV₁ or PEF of the subject is achieved by week 24 after administration of the effective amount of tozorakimab or the IL-33 signaling axis antagonist.

13. The method of any one of claims 1 to 12, wherein the treatment of a subject having moderate or severe asthma or improvement of lung function of a subject having moderate or severe asthma, or increasing preBD FEV₁ of a subject having moderate or severe asthma, results in reducing the rate of asthma exacerbations in the subject.

14. The method of claim 13, wherein the rate of asthma exacerbations is reduced by at least 20%, by at least 25%, by at least 30%, optionally by about 30%, after administration of an effective amount of tozorakimab, or the IL-33 signaling axis antagonist compared to a control subject having moderate or severe asthma who has not received tozorakimab or the IL-33 signaling axis antagonist.

15. The method of claim 13 or 14, wherein the rate of asthma exacerbations is reduced over a 24 week period.

16. The method of any one of claims 1 to 15, wherein the subject has early-onset asthma.

17. The method of any one of claims 1 to 16, wherein the asthma is severe asthma.

18. A method of selecting a subject having moderate or severe asthma for treatment with an effective amount of tozorakimab, the method comprising: determining how many asthma exacerbations the subject has had in the past 12 months; selecting the subject for said treatment if the subject has had more than two asthma exacerbations in the past 12 months.
19. The method of claim 18, wherein said method further comprises selecting the subject for said treatment if the blood eosinophil count of the subject is <300 cells/ μ l.
20. The method of claim 18 or 19, wherein said method further comprises administering an effective amount of tozorakimab to the subject.
21. The method of any one of claims 9 to 15, wherein increasing pre-bronchodilator (BD) FEV₁ of the subject, increasing PEF of the subject, and reducing the rate of asthma exacerbations in the subject, is relative to a baseline level.
22. The method of claim 21, wherein the baseline is the level in a subject prior to administration of the effective amount of tozorakimab or IL-33 signaling axis antagonist.
23. The method of any one of claims 3 to 22, wherein the IL-33 signaling axis antagonist is an antibody, an antigen binding fragment, or a variant thereof.
24. The method of claim 23, wherein the antibody is an anti-IL-33 antibody, anti-ST2 antibody anti-IL1-RacP antibody, an antigen binding fragment, or a variant thereof.
25. The method of claim 23 or 24, wherein the antibody is an anti-IL-33 antibody, an antigen binding fragment, or variant thereof.
26. The method of any one of claims 23 to 25, wherein the anti-IL-33 antibody, antigen binding fragment, or variant thereof comprises a VH domain comprising a VHCDR1 having the sequence set forth in SEQ ID NO:37, a VHCDR2 having the sequence set forth in SEQ ID NO:38, a VHCDR3 having the sequence set forth in SEQ ID NO:39, and a VL domain comprising a VLCDR1 having the sequence set forth in SEQ ID NO:40, a VLCDR2 having the sequence set forth in SEQ ID NO:41, and a VLCDR3 having the sequence set forth in SEQ ID NO:42.

27. The method of any one of claims 23 to 26, wherein the anti-IL-33 antibody, an antigen binding fragment, or variant thereof comprises a VH domain having the sequence set forth in SEQ ID NO: 1 or a sequence 80, 85, 90 or 95% identical thereto, and a VL domain having the sequence set forth in SEQ ID NO: 19 or a sequence 80, 85, 90 or 95% identical thereto.
28. The method of any one of claims 23 to 27, wherein the anti-IL-33 antibody, an antigen binding fragment, or variant thereof comprises a heavy chain having the sequence set forth in SEQ ID NO:43 or a sequence 80, 85, 90 or 95% identical thereto and a light chain having the sequence set forth in SEQ ID NO:44 or a sequence 80, 85, 90 or 95% identical thereto.
29. The method of any one of claims 23 to 28, wherein the antibody is tozorakimab.
30. The method of any one of claims 1 to 29, wherein the effective amount of tozorakimab or the IL-33 signaling axis antagonist is comprised in a pharmaceutical composition, comprising one or more excipients.
31. The method of any one of claims 1 to 30, wherein the effective amount of tozorakimab or the IL-33 signaling axis antagonist is a dose of between 300mg to 600mg.
32. The method of any one of claims 1 to 31, wherein the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject every 2 weeks (Q2W), 4 weeks (Q4W) or 8 weeks (Q8W).
33. The method of any one of claims 1 to 32, wherein the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject at a dose of 600 mg every 4 weeks (Q4W).
34. The method of any one of claims 1 to 33, wherein the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject at a dose of 300 mg every 2 weeks (Q2W).
35. The method of any one of claims 1 to 34, wherein the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject subcutaneously.

36. The method of any one of claims 1 to 35, wherein the tozorakimab or the IL-33 signaling axis antagonist or a pharmaceutical composition thereof is administered to the subject by injection.