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(54) Title: METHODS FOR TREATING OR PREVENTING ASTHMA BY ADMINISTERING AN IL-4R ANTAGONIST

(57) Abstract: Methods for treating or preventing asthma (e.g., allergic asthma, asthma associated with allergic bronchopulmonary aspergillosis (ABPA), moderate-to-severe asthma, persistent asthma or the like) and associated conditions (e.g., ABPA, ABPA comorbid with asthma, ABPA comorbid with cystic fibrosis (CF), ABPA comorbid with asthma and CF) in a subject are provided. Methods comprising administering to a subject in need thereof a therapeutic composition comprising an interleukin-4 receptor (IL-4R) antagonist, such as an anti-IL-4R antibody or antigen-binding fragment thereof, are provided.

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METHODS FOR TREATING OR PREVENTING ASTHMA BY ADMINISTERING AN IL-4R ANTAGONIST

RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 63/004,084, filed April 2, 2020, U.S. Provisional Application No. 62/877,031, filed July 22, 2019, U.S. Provisional Application No. 62/874,747, filed July 16, 2019, and European Application No. 20315237.6, filed May 7, 2020, the contents of which are incorporated by reference in their entireties for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates to the treatment and/or prevention of asthma, e.g., allergic asthma, and related conditions, e.g., allergic bronchopulmonary aspergillosis (ABPA). The invention relates to the administration of an interleukin-4 receptor (IL-4R) antagonist to treat or prevent asthma, e.g., allergic asthma, asthma associated with ABPA, or the like, in a patient in need thereof. The invention also relates to the administration of an interleukin-4 receptor (IL-4R) antagonist to treat or prevent ABPA in a patient in need thereof, e.g., ABPA comorbid with asthma, ABPA comorbid with cystic fibrosis and/or ABPA comorbid with both asthma and cystic fibrosis.

BACKGROUND

[0003] Asthma is a chronic inflammatory disease of the airways characterized by airway hyper responsiveness, acute and chronic bronchoconstriction, airway edema and mucus plugging. The inflammation component of asthma is thought to involve many cell types, including mast cells, eosinophils, T lymphocytes, neutrophils, epithelial cells, and their biological products. Patients with asthma most often present with symptoms of wheezing, shortness of breath, cough, and chest tightness. For most asthma patients, a regimen of controller therapy and bronchodilator therapy provides adequate long-term control. Inhaled corticosteroids (ICS) are considered the "gold standard" in controlling asthma symptoms, and inhaled beta2-agonists are the most effective bronchodilators currently available. Studies have shown that combination therapy of an ICS with an inhaled long-acting beta2-agonist (LABA)

provides better asthma control than high doses of ICS alone. Consequently, combination therapy has been the recommended treatment for subjects who are not controlled on low doses of ICS alone.

[0004] Nonetheless, it is estimated that 5% to 10% of the population with asthma has symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. Furthermore, this severe asthma population accounts for up to 50% of the total health cost through hospital admissions, use of emergency services, and unscheduled physician visits. There is an unmet need for a new therapy in this severe asthma population as many of these patients are poorly responsive to ICS due to a number of cellular and molecular mechanisms. In addition, the long term adverse effects of systemic and inhaled corticosteroids on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Although a large portion of asthma patients are managed reasonably well with current treatments, patients with severe uncontrolled asthma (e.g., severe corticosteroid-refractory asthma or steroid-intolerant asthma) have few therapeutic treatment options that can adequately control the disease. The consequence of unresponsiveness to therapy or lack of compliance with therapy is loss of asthma control and ultimately asthma exacerbation.

[0005] An estimated 45% of patients with severe asthma require systemic glucocorticoids to control their disease, and to prevent life-threatening exacerbations associated with increased risk of permanent damage to lung tissue, progressive fixed airway obstruction, and accelerated decline in lung function. However, systemic glucocorticoids act non-selectively and are associated with significant multi-organ toxicities and broad immunosuppression. There is a need for safer and more effective targeted therapies that prevent exacerbations and lung function impairment, improve asthma symptoms and control, and reduce or obviate the need for oral glucocorticoids.

[0006] Approximately 20% of patients with asthma have uncontrolled, moderate-to-severe disease with recurrent exacerbations and persistent symptoms despite maximized standard-of-care controller therapy. This population is at an increased risk of morbidity (especially exacerbations) and accounts for significant healthcare resources. These patients have substantially reduced lung function, despite maximum treatment, and are destined to inexorably further lose lung function. No currently approved treatments have been shown to slow this inexorable decline in these patients, or to consistently and meaningfully increase lung function.

[0007] Type 2-high asthma is the most prevalent type of persistent, uncontrolled asthma (Fahy (2015) Nat. Rev. Immunol. 15:57-65). It includes the overlapping phenotypes allergic asthma (characterized by increased expression of specific immunoglobulin E (IgE) to aeroallergens) and eosinophilic asthma (characterized by blood and/or airway/tissue eosinophilia) (Fahy, *Supra*; Campo et al. (2013) J. Investig. Allergol. Clin. Immunol. 23:76-88; Wenzel (2012) Clin Exp Allergy 42:650-8).

[0008] Allergic sensitization is a strong risk factor for asthma inception and severity in children and in adults (Gough et al. (2015) Pediatr. Allergy Immunol. 26:431-437). Current allergic asthma therapies that address symptoms and the ongoing inflammatory process of the disease do not affect the underlying, dysregulated immune response and, therefore, are very limited in controlling allergic asthma progression (Dhami et al. (2017) Eur. J. Allergy Clin. Immunol. 72(12):1825-1848)).

[0009] ABPA is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus species* (e.g., *A. fumigatus*) colonized in airways. ABPA most often occurs in subjects having asthma or cystic fibrosis.

[0010] ABPA is clinically characterized by wheezing, dyspnea, respiratory exacerbations, bronchial hyperreactivity, hemoptysis or productive cough (expectoration of brownish black mucus plugs in 31 to 69% of patients), central bronchiectasis with mucus plugging, and markedly elevated IgE and blood and tissue eosinophilia.

[0011] There are currently no approved drugs specific for ABPA. The current mainstay of treatment is systemic corticosteroids, and antifungals are used as an adjuvant therapy. However, greater than 50% of ABPA patients are undertreated or not treated effectively either due to limitations in treatment efficacy or the considerable side effects of corticosteroids. Accordingly, patients with ABPA have a high unmet medical need.

[0012] Cystic fibrosis (CF), also known as mucoviscidosis, is a genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections. Other signs and symptoms include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in males among others. Subjects may have varying degrees of symptoms.

[0013] CF is inherited in an autosomal recessive manner. It is caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Those with a single working copy are carriers and otherwise mostly

normal. CFTR is involved in production of sweat, digestive fluids, and mucus. When CFTR is not functional, secretions, which are usually thin, instead become thick. The condition is diagnosed by a sweat test and genetic testing. Screening of infants at birth takes place in some areas of the world.

[0014] There is no cure for cystic fibrosis. Lung infections are treated with antibiotics which may be given intravenously, inhaled, or by mouth. Sometimes the antibiotic azithromycin is used long term. Inhaled hypertonic saline and salbutamol may also be useful. Lung transplantation may be an option if lung function continues to worsen. Pancreatic enzyme replacement and fat-soluble vitamin supplementation are important, especially in the young. The average life expectancy is between 42 and 50 years in the developed world. While CF is a multi-organ disease, lung problems are the dominant cause of morbidity and mortality. Other CF symptoms include pancreatic insufficiency, intestinal obstruction, elevated electrolyte levels in sweat (the basis of the most common diagnostic test), and male infertility. CF is most common among people of Northern European ancestry and affects about one out of every 2,500 to 4,000 newborns. About one in 25 people are carriers. While treatments for CF are available, more effective therapies are needed.

[0015] A need exists for novel targeted therapies for the treatment and/or prevention of asthma, e.g., allergic asthma, asthma associated with ABPA, and the like, as well as disorders such as ABPA, including ABPA that is comorbid with CF, ABPA that is comorbid with asthma, and ABPA that is comorbid with both asthma and CF.

BRIEF SUMMARY OF THE INVENTION

[0016] According to one aspect, a method for treating a subject having allergic asthma is provided. The method includes administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

[0017] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 150 cells/μl or at least about 300 cells/μl.

[0018] In certain exemplary embodiments, the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 25 ppb, or at least about 20 ppb.

[0019] In certain exemplary embodiments, the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

[0020] In certain exemplary embodiments, the allergen is selected from the group consisting of animal (e.g., dust mite (e.g., *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*), cockroach, cat or dog), fungus (e.g., *Alternaria alternata*, *Cladosporium herbarum* or *Aspergillus fumigatus*) and plant.

[0021] In certain exemplary embodiments, the allergen is selected from the group consisting of cat dander, dog dander, German cockroach and Oriental cockroach.

[0022] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[0023] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[0024] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[0025] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[0026] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[0027] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[0028] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[0029] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations.

[0030] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[0031] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0032] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0033] In certain exemplary embodiments, the antibody is dupilumab.

[0034] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma.

[0035] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0036] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0037] According to another aspect, a method for treating a subject having allergic asthma is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil level of at least about 300 cells/μl.

[0038] In certain exemplary embodiments, the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 25 ppb, or at least about 20 ppb.

[0039] In certain exemplary embodiments, the subject has a total serum IgE level of at least about 700 IU/mL.

[0040] In certain exemplary embodiments, the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

[0041] In certain exemplary embodiments, the allergen is selected from the group consisting of dust mite, cockroach, cat dander, dog dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, German cockroach and Oriental cockroach.

[0042] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[0043] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[0044] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w)

[0045] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[0046] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[0047] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[0048] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[0049] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations.

[0050] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[0051] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0052] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0053] In certain exemplary embodiments, the antibody is dupilumab.

[0054] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma.

[0055] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0056] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0057] According to another aspect, a method for treating a subject having allergic asthma is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 20 ppb.

[0058] In certain exemplary embodiments, the subject has a baseline FeNO level of at least 25 ppb.

[0059] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 150 cells/μl. In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 300 cells/μl.

[0060] In certain exemplary embodiments, the subject has a total serum IgE level of at least about 700 IU/mL.

[0061] In certain exemplary embodiments, the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

[0062] In certain exemplary embodiments, the allergen is selected from the group consisting of dust mite, cockroach, cat dander, dog dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, German cockroach and Oriental cockroach.

[0063] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[0064] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[0065] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[0066] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[0067] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[0068] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[0069] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[0070] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations.

[0071] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[0072] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0073] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0074] In certain exemplary embodiments, the antibody is dupilumab.

[0075] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0076] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0077] In another aspect, a method of improving lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%) in a subject having allergic asthma is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

[0078] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0079] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0080] In certain exemplary embodiments, the antibody is dupilumab.

[0081] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma.

[0082] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0083] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0084] In another aspect, a method of reducing annualized severe asthma exacerbations in a subject having allergic asthma is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R),

wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

[0085] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0086] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0087] In certain exemplary embodiments, the antibody is dupilumab.

[0088] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma.

[0089] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0090] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0091] In another aspect, a method of improving Asthma Control Questionnaire (ACQ-5) score in a subject having allergic asthma is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

[0092] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[0093] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[0094] In certain exemplary embodiments, the antibody is dupilumab.

[0095] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma.

[0096] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid allergic asthma and comorbid cystic fibrosis.

[0097] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[0098] In another aspect, a method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

[0099] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

[00100] In certain exemplary embodiments, the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L. In certain exemplary embodiments, the allergen is *Aspergillus fumigatus*.

[00101] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00102] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00103] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00104] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[00105] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment

thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00106] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00107] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00108] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations. In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%). In certain exemplary embodiments, treatment results in a decrease in the total serum IgE level. In certain exemplary embodiments, treatment results in a decrease in serum *Aspergillus fumigatus*-specific IgE. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00109] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00110] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00111] In certain exemplary embodiments, the antibody is dupilumab.

[00112] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00113] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00114] In another aspect, a method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L.

[00115] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 300 cells/μl.

[00116] In certain exemplary embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL.

[00117] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

[00118] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00119] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00120] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00121] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[00122] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

[00123] In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00124] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00125] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00126] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations. In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%). In certain exemplary embodiments, treatment results in a decrease in the total serum IgE level. In certain exemplary embodiments, treatment results in a decrease in serum *Aspergillus fumigatus*-specific IgE. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00127] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00128] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00129] In certain exemplary embodiments, the antibody is dupilumab.

[00130] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00131] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00132] In another aspect, a method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR

sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

[00133] In certain exemplary embodiments, the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L.

[00134] In certain exemplary embodiments, the allergen is *Aspergillus fumigatus*.

[00135] In certain exemplary embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL.

[00136] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00137] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00138] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

[00139] In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00140] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00141] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00142] In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations. In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%). In certain exemplary embodiments, treatment results in a decrease in the total serum IgE level. In certain exemplary embodiments, treatment results in a decrease in serum *Aspergillus fumigatus*-specific IgE. In

certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00143] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00144] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00145] In certain exemplary embodiments, the antibody is dupilumab.

[00146] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00147] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00148] In another aspect, a method of improving lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%) in a subject having asthma associated with allergic bronchopulmonary aspergillosis (ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

[00149] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00150] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00151] In certain exemplary embodiments, the antibody is dupilumab.

[00152] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00153] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00154] In another aspect, a method of reducing annualized severe asthma exacerbations in a subject having asthma associated with allergic bronchopulmonary aspergillosis (ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

[00155] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00156] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00157] In certain exemplary embodiments, the antibody is dupilumab.

[00158] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00159] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00160] In another aspect, a method of improving Asthma Control Questionnaire (ACQ-5) score in a subject having asthma associated with allergic bronchopulmonary aspergillosis

(ABPA) is provided, comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

[00161] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00162] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00163] In certain exemplary embodiments, the antibody is dupilumab.

[00164] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled allergic asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00165] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00166] In another aspect, a method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, is provided. In some embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL.

[00167] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

[00168] In certain exemplary embodiments, the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L. In certain exemplary embodiments, the allergen is *Aspergillus fumigatus*.

[00169] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00170] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00171] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00172] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

[00173] In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00174] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00175] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00176] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[00177] In certain exemplary embodiments, treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00178] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00179] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00180] In certain exemplary embodiments, the antibody is dupilumab.

[00181] In certain exemplary embodiments, the subject has asthma. In certain exemplary embodiments, treatment results in a reduction in annualized asthma exacerbations.

[00182] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00183] In another aspect, a method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, is provided.

[00184] In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 300 cells/µl. In certain exemplary embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL. In certain exemplary embodiments, the subject has a baseline blood eosinophil count of at least about 500 cells/µl.

[00185] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00186] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00187] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00188] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance

dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

[00189] In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00190] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00191] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00192] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[00193] In certain exemplary embodiments, treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00194] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00195] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00196] In certain exemplary embodiments, the antibody is dupilumab.

[00197] In certain exemplary embodiments, the subject has asthma. In certain exemplary embodiments, treatment results in a reduction in annualized asthma exacerbations.

[00198] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00199] In another aspect, a method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl, is provided.

[00200] In certain exemplary embodiments, the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L. In certain exemplary embodiments, the allergen is *Aspergillus fumigatus*.

[00201] In certain exemplary embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL.

[00202] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

[00203] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

[00204] In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00205] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

[00206] In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00207] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00208] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00209] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[00210] In certain exemplary embodiments, treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00211] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00212] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00213] In certain exemplary embodiments, the antibody is dupilumab.

[00214] In certain exemplary embodiments, the subject has asthma. In certain exemplary embodiments, treatment results in a reduction in annualized asthma exacerbations.

[00215] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00216] In another aspect, a method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, wherein the subject has a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, or a baseline blood eosinophil count of at least about 500 cells/μl, is provided.

[00217] In certain exemplary embodiments, the subject has at least two of a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl. In certain exemplary embodiments, the subject has a total serum IgE level of at least about 1000 IU/mL,

an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl.

[00218] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses. In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen. In certain exemplary embodiments, a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

[00219] In certain exemplary embodiments, the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

[00220] In certain exemplary embodiments, the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof. In certain exemplary embodiments, each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

[00221] In certain exemplary embodiments, the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

[00222] In certain exemplary embodiments, a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

[00223] In certain exemplary embodiments, treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

[00224] In certain exemplary embodiments, treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels. In certain exemplary embodiments, treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels. In certain exemplary embodiments, FeNO (ppb) is reduced.

[00225] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00226] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00227] In certain exemplary embodiments, the antibody is dupilumab.

[00228] In certain exemplary embodiments, the subject has moderate-to-severe uncontrolled asthma. In certain exemplary embodiments, treatment results in a reduction in annualized severe asthma exacerbations.

[00229] In certain exemplary embodiments, the subject exhibits comorbid asthma. In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00230] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00231] In another aspect, a method for treating a subject having asthma comprising administering to the subject two or more doses of an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject is further administered a vaccine, is provided.

[00232] In certain exemplary embodiments, administration of the antibody or antigen-binding fragment thereof is temporarily suspended prior to administering the vaccine.

[00233] In certain exemplary embodiments, the vaccine is administered at least 7 days after the antibody or antigen-binding fragment thereof was last administered to the subject. In certain exemplary embodiments, the vaccine is administered between about 7 days and about 60 days after the antibody or antigen-binding fragment thereof was last administered to the subject.

[00234] In certain exemplary embodiments, administration of the antibody or antigen-binding fragment thereof is resumed following administration of the vaccine.

[00235] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered between about 1 day and about 90 days after administration of the vaccine. In certain exemplary embodiments, the antibody or antigen-binding fragment thereof is administered about 7 days after administration of the vaccine. In certain exemplary

embodiments, the antibody or antigen-binding fragment thereof is administered about 14 days after administration of the vaccine.

[00236] In certain exemplary embodiments, the antibody or an antigen-binding fragment thereof is administered about 21 days after administration of the vaccine.

[00237] In certain exemplary embodiments, efficacy of the antibody or antigen-binding fragment thereof is not decreased by administration of the vaccine.

[00238] In certain exemplary embodiments, forced expiratory volume (FEV_1) of the subject is approximately the same before and after administration of the vaccine.

[00239] In certain exemplary embodiments, vaccine efficacy in the subject is not decreased by administration of the antibody or antigen-binding fragment thereof.

[00240] In certain exemplary embodiments, the subject develops a seroprotective neutralization titer after administration of the vaccine.

[00241] In certain exemplary embodiments, the vaccine is a live vaccine. In certain exemplary embodiments, the vaccine comprises a live-attenuated yellow fever virus. In certain exemplary embodiments, the vaccine is specific against yellow fever virus.

[00242] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00243] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00244] In certain exemplary embodiments, the antibody is dupilumab.

[00245] In certain exemplary embodiments, the subject exhibits comorbid cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00246] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00247] In another aspect, a method for administrating a vaccine to a subject, wherein before, during, or after administration of the vaccine, the subject is administered at least one dose of an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three

heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, is provided.

[00248] In certain exemplary embodiments, the subject has a type 2 inflammatory disease. In certain exemplary embodiments, the type 2 inflammatory disease is selected from the group consisting of one or any combination of asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSsNP), eosinophilic esophagitis (EoE), atopic dermatitis (AD), food and environmental allergies, aspirin exacerbated respiratory disease (AERD), and respiratory disease exacerbated by other non-steroidal anti-inflammatory drugs (NSAID).

[00249] In certain exemplary embodiments, the vaccine is administered to the subject about 1 day to about 90 days after the last dose of the antibody or an antigen-binding fragment thereof.

[00250] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

[00251] In certain exemplary embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain sequence of SEQ ID NO: 9 and a light chain sequence of SEQ ID NO: 10.

[00252] In certain exemplary embodiments, the antibody is dupilumab.

[00253] In certain exemplary embodiments, the subject exhibits asthma. In certain exemplary embodiments, the subject exhibits cystic fibrosis. In certain exemplary embodiments, the subject exhibits comorbid asthma and comorbid cystic fibrosis.

[00254] In certain exemplary embodiments, the subject is an adult. In certain exemplary embodiments, the subject is an adolescent. In certain exemplary embodiments, the subject is a child.

[00255] Other embodiments will become apparent from a review of the ensuing detailed description, drawings, tables and accompanying claims.

BRIEF DESCRIPTION OF THE FIGURES

[00256] The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings. The file of this patent contains at least one drawing/photograph executed in color. Copies of this patent with color

drawing(s)/photograph(s) will be provided by the Office upon request and payment of the necessary fee.

[00257] Fig. 1A – Fig. 1E depict the effect of dupilumab on annualized severe exacerbation rates. **Fig. 1A** shows that dupilumab reduced the overall annualized severe exacerbation rates in the overall allergic asthma subgroup as well as in the overall asthma subgroup that did not meet the criteria for allergic asthma. **Fig. 1B** depicts the effect of dupilumab in an allergic asthma subgroup as well as in an asthma subgroup that did not meet the criteria for allergic asthma, wherein the subjects had blood eosinophil levels of ≥150 cells/μL. **Fig. 1C** depicts the effect of dupilumab in an allergic asthma subgroup as well as an asthma subgroup that did not meet the criteria for allergic asthma, wherein the subjects had blood eosinophil levels of ≥300 cells/μL. **Fig. 1D** depicts the effect of dupilumab in an allergic asthma subgroup as well as in an asthma subgroup that did not meet the criteria for allergic asthma, wherein the subjects had a baseline blood FeNO of ≥25 ppb. **Fig. 1E** depicts the effect of dupilumab in an allergic asthma subgroup as well as in an asthma subgroup that did not meet the criteria for allergic asthma, wherein the subjects had serum total IgE >700 IU/mL. CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; q2w, every 2 weeks.

[00258] Fig 2. depicts the effect of dupilumab on FEV_1 (L) in the overall allergic asthma subgroup and in the overall asthma subgroup that did not meet the criteria for allergic asthma. **Fig. 2A** depicts the change in baseline FEV_1 during a 52-week treatment period in the overall allergic asthma subgroup, and depicts the magnitude of effects in subgroups that were further defined by baseline blood eosinophil levels, FeNO levels, or baseline serum total IgE levels at week 12. **Fig. 2B** depicts the change in the baseline FEV_1 during a 52-week treatment period in the overall asthma subgroup that did not meet the criteria for allergic asthma, and depicts the magnitude of effects in subgroups that were further defined by baseline blood eosinophil levels, FeNO levels, or baseline serum total IgE levels at week 12.

[00259] Fig 3. depicts the effect of dupilumab on asthma control (as measured by ACQ-5) during the 52-week treatment period in the overall allergic asthma subgroup and the overall asthma subgroup that did not meet the criteria for allergic asthma. ACQ-5, 5-item asthma control questionnaire; LS, least squares; q2w, every 2 weeks; SE, standard error.

[00260] Fig. 4A – Fig. 4C depict the effect of dupilumab on various biomarkers. **Fig. 4A** depicts the effect of dupilumab on serum total IgE levels. **Fig. 4B** depicts the effect of dupilumab on FeNO levels. **Fig. 4C** depicts the effect of dupilumab on serum TARC levels

during the 52-week treatment period in the overall allergic asthma subgroup and the overall asthma subgroup that did not meet the criteria for allergic asthma (exposed population). CI, confidence interval; FeNO, fractional exhaled nitric oxide; q2w, every 2 weeks; TARC, thymus and activation-regulated chemokine.

[00261] Fig. 5A – Fig. 5H depict the effect of dupilumab on antigen-specific serum IgE levels during the 52-week treatment period in the allergic asthma subgroup. **Fig. 5A** depicts the effect of dupilumab on antigen-specific serum IgE levels ≥0.35 kU/mL (exposed population) in an allergic asthma subgroup exposed to *A. fumigatus*. **Fig. 5B** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to cat dander. **Fig. 5C** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to *D. farinae*. **Fig. 5D** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to *D. pteronyssinus*. **Fig. 5E** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to dog dander. **Fig. 5F** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to German cockroach. **Fig. 5G** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to *A. tenuis/alternata*. **Fig. 5H** depicts the effect of dupilumab on antigen-specific serum IgE levels in an allergic asthma subgroup exposed to and *C. herbarum/hormodendrum*. CI, confidence interval; q2w, every 2 weeks.

[00262] Fig. 6A- Fig. 6B show statistical analyses of IgE ≥700IU/ml patients. **Fig. 6A** depicts a histogram of the residuals to ensure normal distribution. **Fig. 6B** depicts a q-q plot showing a normal distribution.

[00263] Fig. 7 depicts the annualized rate of severe exacerbations during a 52-week treatment period for patients with allergic bronchopulmonary aspergillosis (ABPA) in an intention to treat (ITT) population.

[00264] Fig. 8 depicts least squares (LS) mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) at weeks 24 and 52 in an ITT population.

[00265] Fig. 9 depicts total serum IgE levels at week 52 in a patient population that was exposed to *Aspergillus fumigatus* (Af).

[00266] Fig. 10 depicts total serum Af-specific IgE levels at week 52 in a patient population that was exposed to Af.

[00267] Fig. 11 graphically depicts absolute FeNO (ppb) levels at week 52 in a patient population that was exposed to Af.

[00268] Fig. 12 graphically depicts the effect of dupilumab q2w on annualized severe exacerbation rate during the 52-week treatment period in ITT patient population with serologic evidence of ABPA.

[00269] Fig. 13 graphically depicts the effect of dupilumab q2w on pre-bronchodilator FEV1 (L) during the 52-week treatment period in ITT patient population with serologic evidence of ABPA.

[00270] Fig. 14 graphically depicts the effect of dupilumab q2w on ACQ-5 score during the 52-week treatment period in ITT patient population with serologic evidence of ABPA.

[00271] Fig. 15A – Fig. 15B graphically depict the effect of dupilumab q2w on serum total IgE (IU/mL) (**Fig. 15A**) and *A. fumigatus*-specific serum IgE (IU/mL) (**Fig. 15B**) during the 52-week treatment period in exposed patients with serologic evidence of ABPA.

[00272] Fig. 16A – Fig. 16D graphically depict the effect of dupilumab q2w on type 2 biomarkers during the 52-week treatment period in exposed patients with serologic evidence of ABPA. FeNO (ppb) (**Fig. 16A**), TARC (pg/mL) (**Fig. 16B**), eotaxin-3 (pg/mL) (**Fig. 16C**), and peripheral blood eosinophils (cells/μL) (**Fig. 16D**).

[00273] Fig. 17A – Fig. 17B graphically depict plaque reduction neutralization titers ($PRNT_{50}$) of neutralizing YFV-17D antibody pre-and post-vaccination. **Fig. 17A** depicts matched neutralization titers for 23 patients where pre-vaccination titers were obtained. **Fig. 17B** depicts pre- and post-vaccination data for all patients. In **Fig. 17B**, patients with dupilumab concentrations lower than the mean C_{trough} concentration of 37.4 mg/L are indicated in black circles, whereas those patients with serum concentrations greater than 37.4 mg/L are indicated in open circles. A titer <1:10 is defined as seronegative and those values were designated '1'. **Fig. 17A – Fig. 17B** shows that all 37 vaccinated patients had seroprotective yellow fever neutralization titers post-vaccination.

[00274] Fig. 18 graphically depicts (log) PRNT titer increase (post- vs. pre-titer) vs. pre-vaccination dupilumab concentration. Pre-vaccination PK samples were collected on the same day of YFV administration in 15 out of 23 patients. All 13 patients with serum dupilumab concentrations > 37.4 mg/L had seroprotective PRNT titers after YFV. Twelve of these patients demonstrated an increase in post-vaccination titers, while one of these 13 patients did not demonstrate an increase in titer, but was already within a seroprotective threshold at

baseline. The fold change in PRNT titer level for these patients is demonstrated in **Fig. 18**. Pre-titer <1:10, 10 was used to calculate the titer-fold increase.

[00275] Fig. 19 graphically depicts mean absolute FEV_1 (L) before and after yellow fever vaccination in patients with yellow fever vaccination in the LTS12551 study. **Fig. 19** shows that the FEV_1 was stable between the visit before the YFV was administered and at the first visit after YFV was administered. BL: baseline of the parent study; Pre-YF: the last visit before yellow fever vaccination; Post-YF: the first visit after yellow fever vaccination; FU: follow-up visit.

[00276] Fig. 20 graphically depicts the mean change from baseline in FEV1 (L) before and after yellow fever vaccination in patients with yellow fever vaccination in the LTS12551 study. **Fig. 20** shows that the FEV1 was stable between the visit before the YFV was administered and at the first visit after YFV was administered. BL: baseline of the parent study; Pre-YF: the last visit before yellow fever vaccination; Post-YF: the first visit after yellow fever vaccination; FU: follow-up visit.

DETAILED DESCRIPTION

[00277] Before the invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, because the scope of the invention will be limited only by the appended claims.

[00278] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[00279] As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

[00280] As used herein, the terms "treat," "treating," or the like, mean to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

[00281] Although any methods and materials similar or equivalent to those described herein can be used in the practice of the invention, the typical methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Methods for Reducing the Incidence of Asthma and/or ABPA Exacerbations

[00282] Methods for reducing the incidence of asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA (ABPA, ABPA associated with asthma, ABPA associated with CF, ABPA associated with asthma and CF, or the like) exacerbations in a subject in need thereof comprising administering a pharmaceutical composition comprising an IL-4R antagonist to the subject are provided. According to certain embodiments, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4R. Exemplary anti-IL-4R antibodies that can be used in the context of the methods featured here are described elsewhere herein.

[00283] As used herein, the expression "asthma exacerbation" means an increase in the severity and/or frequency and/or duration of one or more symptoms or indicia of asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like). An "asthma exacerbation" also includes any deterioration in the respiratory health of a subject that requires and or is treatable by a therapeutic intervention for asthma (such as, e.g., steroid treatment, inhaled corticosteroid treatment, hospitalization, etc.). There are two types of asthma exacerbation events: a loss of asthma control (LOAC) event and a severe exacerbation event.

[00284] As used herein, the expression "allergic bronchopulmonary aspergillosis exacerbation" or "ABPA exacerbation" means an increase in the severity and/or frequency and/or duration of one or more symptoms or indicia of ABPA including, but not limited to, wheezing, dyspnea, respiratory exacerbations, bronchial hyperreactivity, hemoptysis, productive cough (expectoration of brownish-black mucus plugs), central bronchiectasis with mucus plugging, markedly elevated total IgE, markedly elevated Af-specific IgE, and tissue eosinophilia.

[00285] According to certain embodiments, an ABPA exacerbation occurs in a subject having an HLA-DR2 serotype (e.g., subtype HLA-DRB1*1501, subtype *HLA-DRB1*1503, or subtype *HLA-DRB1*1601) or an HLA-DR5 serotype (e.g., subtype HLA-DRB1*1101,

subtype HLA-DRB1*1104, or subtype HLA-DRB1*1202), optionally wherein the subject and has an increased susceptibility of developing ABPA when exposed to Af antigen relative to a subject that does not have one of these serotypes and/or subtypes.

[00286] According to certain embodiments, a loss of asthma control (LOAC) event is defined as one or more of the following: (a) greater than or equal to 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days; (b) an increase in ICS greater than or equal to 4 times the dose at visit 2; and (c) use of systemic corticosteroids for greater than or equal to 3 days; or (d) hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.

[00287] In certain instances, an asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) exacerbation may be categorized as a "severe asthma exacerbation event." A severe asthma (e.g., severe allergic asthma) exacerbation event means an incident requiring immediate intervention in the form of treatment with either systemic corticosteroids or with inhaled corticosteroids at four or more times the dose taken prior to the incident. According to certain embodiments, a severe asthma (e.g., severe allergic asthma) exacerbation event is defined as a deterioration of asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) requiring: use of systemic corticosteroids for greater than or equal to 3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. The general expression "asthma exacerbation" therefore includes and encompasses the more specific subcategory of "severe asthma exacerbations." Accordingly, methods for reducing the incidence of severe asthma exacerbations in a patient in need thereof are included.

[00288] A "reduction in the incidence" of an asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or an ABPA exacerbation means that a subject who has received a pharmaceutical composition comprising an IL-4R antagonist experiences fewer asthma or ABPA exacerbations (i.e., at least one fewer exacerbation) after treatment than before treatment, or experiences no asthma exacerbations for at least 4 weeks (e.g., 4, 6, 8, 12, 14, or more weeks) following initiation of treatment with the pharmaceutical composition. A "reduction in the incidence" of an asthma and/or an ABPA exacerbation alternatively means that, following administration of the pharmaceutical composition, the likelihood that a subject experiences an asthma exacerbation is decreased by

at least 10% (e.g., 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, or more) as compared to a subject who has not received the pharmaceutical composition.

[00289] Methods for reducing the incidence of asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA exacerbations in a subject in need thereof comprising administering a pharmaceutical composition comprising an IL-4R antagonist to the subject as well as administering to the subject one or more maintenance doses of an inhaled corticosteroid (ICS) and/or one or more maintenance doses of a second controller, e.g., a long-acting beta-agonist (LABA) or a leukotriene receptor antagonist (LTA), are provided. Suitable ICSs include, but are not limited to, fluticasone (e.g., fluticasone propionate, e.g., Flovent™), budesonide, mometasone (e.g., mometasone furoate, e.g., Asmanex™), flunisolide (e.g., Aerobid™), dexamethasone acetate/phenobarbital/theophylline (e.g., Azmacort™), beclomethasone dipropionate HFA (Qvar™), and the like. Suitable LABAs include, but are not limited to, salmeterol (e.g., Serevent™), formoterol (e.g., Foradil™), and the like. Suitable LTAs include, but are not limited to, montelukast (e.g., Singulaire™), zafirlukast (e.g., Accolate™), and the like.

[00290] Methods for reducing the incidence of asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA exacerbations in a subject in need thereof comprising administering a pharmaceutical composition comprising an IL-4R antagonist to the subject as well as administering to the subject one or more reliever medications to eliminate or reduce one or more asthma-associated symptoms, are provided. Suitable reliever medications include, but are not limited to, quick-acting $beta_2$-adrenergic receptor agonists such as, e.g., albuterol (i.e., salbutamol, e.g., Proventil™, Ventolin™, Xopenex™ and the like), pirbuterol (e.g., Maxair™), metaproterenol (e.g., Alupent™) and the like.

Methods for Improving Asthma-Associated and/or ABPA-Associated Parameters

[00291] Methods for improving one or more asthma-associated and/or ABPA-associated parameters in a subject in need thereof, wherein the methods comprise administering a pharmaceutical composition comprising an IL-4R antagonist to the subject, are also provided. A reduction in the incidence of an asthma exacerbation and/or an ABPA exacerbation (as described above) may correlate with an improvement in one or more asthma-associated

parameters and/or ABPA-associated parameters; however, such a correlation is not necessarily observed in all cases.

[00292] Examples of "asthma-associated parameters," "asthma-associated with ABPA parameters" and "allergic asthma-associated parameters" include: (1) relative percent change from baseline (e.g., at week 12) in forced expiratory volume in 1 second (FEV_1); (2) a relative percent change from baseline (e.g., at week 12) as measured by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%); (3) annualized rate of loss of asthma control events during the treatment period; (4) annualized rate of severe exacerbation events during the treatment period; (5) time to loss of asthma control events during the treatment period; (6) time to severe exacerbation events during the treatment period; (7) time to loss of asthma control events during overall study period; (8) time to severe exacerbation events during overall study period; (9) health care resource utilization; (10) change from baseline (e.g., at week 12) in: i) morning and evening asthma symptom scores, ii) ACQ-5 score, iii) AQLQ score, iv) morning and evening PEF, v) number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief, vi) nocturnal awakenings; or (11) change from baseline (e.g., at week 12 or week 24) in: i) 22-item Sino Nasal Outcome Test (SNOT-22), ii) Hospital Anxiety and Depression Score (HADS), iii) EuroQual questionnaire (EQ-5D-3L or EQ-5D-5L). An "improvement in an asthma-associated parameter" means an increase from baseline of one or more of FEV_1, AM PEF or PM PEF, and/or a decrease from baseline of one or more of daily albuterol/levalbuterol use, ACQ5 score, average nighttime awakenings or SNOT-22 score. As used herein, the term "baseline," with regard to an asthma-associated parameter, means the numerical value of the asthma-associated parameter for a patient prior to or at the time of administration of a pharmaceutical composition comprising an IL-4R antagonist.

[00293] To determine whether an asthma-associated (e.g., an allergic asthma-associated) parameter or an asthma associated with ABPA parameter has "improved," the parameter is quantified at baseline and at a time point after administration of the pharmaceutical composition described herein. For example, an asthma-associated parameter may be measured at day 1, day 2, day 3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, day 14, or at week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, week 24, or longer, after the initial treatment with the pharmaceutical

composition. The difference between the value of the parameter at a particular time point following initiation of treatment and the value of the parameter at baseline is used to establish whether there has been an "improvement" in the asthma associated parameter (e.g., an increase or decrease, as the case may be, depending on the specific parameter being measured).

[00294] The terms "acquire" or "acquiring" as used herein, refer to obtaining possession of a physical entity, or a value, e.g., a numerical value, by "directly acquiring" or "indirectly acquiring" the physical entity or value, such as an asthma-associated parameter. "Directly acquiring" means performing a process (e.g., performing a synthetic or analytical method) to obtain the physical entity or value. "Indirectly acquiring" refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Directly acquiring a physical entity includes performing a process that includes a physical change in a physical substance, e.g., a starting material. Exemplary changes include making a physical entity from two or more starting materials, shearing or fragmenting a substance, separating or purifying a substance, combining two or more separate entities into a mixture, performing a chemical reaction that includes breaking or forming a covalent or non-covalent bond. Directly acquiring a value includes performing a process that includes a physical change in a sample or another substance, e.g., performing an analytical process which includes a physical change in a substance, e.g., a sample, analyte, or reagent (sometimes referred to herein as "physical analysis").

[00295] Information that is acquired indirectly can be provided in the form of a report, e.g., supplied in paper or electronic form, such as from an online database or application (an "App"). The report or information can be provided by, for example, a healthcare institution, such as a hospital or clinic; or a healthcare provider, such as a doctor or nurse.

[00296] Forced Expiratory Volume in 1 Second (FEV_1). According to certain embodiments, administration of an IL-4R antagonist to a patient results in an increase from baseline of forced expiratory volume in 1 second (FEV_1). Methods for measuring FEV_1 are known in the art. For example, a spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations can be used to measure FEV_1 in a patient. The ATS/ERS Standardization of Spirometry may be used as a guideline. Spirometry is generally performed between 6 and 10 AM after an albuterol withhold of at least 6 hours. Pulmonary function tests are generally measured in the sitting position, and the highest measure is recorded for FEV_1 (in liters).

[00297] Therapeutic methods that result in an increase of FEV_1 from baseline of at least 0.05 L at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist are provided. For example, administration of an IL-4R antagonist to a subject in need thereof causes an increase of FEV_1 from baseline of about 0.05 L, 0.10 L, 0.12 L, 0.14 L, 0.16 L, 0.18 L, 0.20 L, 0.22 L, 0.24 L, 0.26 L, 0.28 L, 0.30 L, 0.32 L, 0.34 L, 0.36 L, 0.38 L, 0.40 L, 0.42 L, 0.44 L, 0.46 L, 0.48 L, 0.50 L, or more at week 12.

[00298] FEF25–75%. According to certain embodiments, administration of an IL-4R antagonist to a patient results in an increase from baseline of FEF25-75%. Methods for measuring FEF are known in the art. For example, a spirometer that meets the 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations can be used to measure FEV_1 in a patient. The FEF25-75% (forced expiratory flow between 25% and 75%) is the speed (in liters per second) at which a person can empty the middle half of his or her air during a maximum expiration (i.e., Forced Vital Capacity or FVC). The parameter relates to the average flow from the point at which 25 percent of the FVC has been exhaled to the point at which 75 percent of the FVC has been exhaled. The FEF25-75% of a subject provides information regarding small airway function, such as the extent of small airway disease and/or inflammation. A change in FEF25-75% is an early indicator of obstructive lung disease. In certain embodiments, an improvement and/or increase in the FEF25-75% parameter is an improvement of at least 10%, 25%, 50% or more as compared to baseline. In certain embodiments, the methods described herein result in normal FEF25-75% values in a subject (e.g., values ranging from 50-60% and up to 130% of the average).

[00299] Morning and Evening Peak Expiratory Flow (AM PEF and PM PEF). According to certain embodiments, administration of an IL-4R antagonist to a patient results in an increase from baseline of morning (AM) and/or evening (PM) peak expiratory flow (AM PEF and/or PM PEF). Methods for measuring PEF are known in the art. For example, according to one method for measuring PEF, patients are issued an electronic PEF meter for recording morning (AM) and evening (PM) PEF (as well as daily albuterol use, morning and evening asthma symptom scores, and number of nighttime awakenings due to asthma symptoms that require rescue medications). Patients are instructed on the use of the device, and written instructions on the use of the electronic PEF meter are provided to the patients. In addition, a medical professional may instruct the patients on how to record pertinent variables in the electronic PEF meter. AM PEF is generally performed within 15 minutes after arising (between 6 am

and 10 am) prior to taking any albuterol. PM PEF is generally performed in the evening (between 6 pm and 10 pm) prior to taking any albuterol. Subjects should try to withhold albuterol for at least 6 hours prior to measuring their PEF. Three PEF efforts are performed by the patient and all 3 values are recorded by the electronic PEF meter. Usually the highest value is used for evaluation. Baseline AM PEF may be calculated as the mean AM measurement recorded for the 7 days prior to administration of the first dose of pharmaceutical composition comprising the IL-4R antagonist, and baseline PM PEF may be calculated as the mean PM measurement recorded for the 7 days prior to administration of the first dose of pharmaceutical composition comprising the IL-4R antagonist.

[00300] Therapeutic methods that result in an increase in AM PEF and/or PM PEF from baseline of at least 1.0 L/min at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist are provided. For example, according to exemplary embodiments, administration of an IL-4R antagonist to a subject in need thereof causes an increase in PEF from baseline of about 0.5 L/min, 1.0 L/min, 1.5 L/min, 2.0 L/min, 2.5 L/min, 3.0 L/min, 3.5 L/min, 4.0 L/min, 4.5 L/min, 5.0 L/min, 5.5 L/min, 6.0 L/min, 6.5 L/min, 7.0 L/min, 7.5 L/min, 8.0 L/min, 8.5 L/min, 9.0 L/min, 9.5 L/min, 10.0 L/min, 10.5 L/min, 11.0 L/min, 12.0 L/min, 15 L/min, 20 L/min, or more at week 12.

[00301] Albuterol/Levalbuterol Use. According to certain embodiments, administration of an IL-4R antagonist to a patient results in a decrease from baseline of daily albuterol or levalbuterol use. The number of albuterol/levalbuterol inhalations can be recorded daily by the patients in a diary, PEF meter, or other recording device. During treatment with the pharmaceutical composition described herein, use of albuterol/levalbuterol typically may be on an as-needed basis for symptoms, not on a regular basis or prophylactically. The baseline number of albuterol/levalbuterol inhalations/day may be calculated based on the mean for the 7 days prior to administration of the first dose of pharmaceutical composition comprising the IL-4R antagonist.

[00302] Therapeutic methods are provided that result in a decrease in albuterol/levalbuterol use from baseline of at least 0.25 puffs per day at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist. For example, administration of an IL-4R antagonist to a subject in need thereof causes a decrease in albuterol/levalbuterol use from baseline of about 0.25 puffs per day, 0.50 puffs per day, 0.75 puffs per day, 1.00 puff per day, 1.25 puffs per day, 1.5 puffs per day, 1.75 puffs per day, 2.00

puffs per day, 2.25 puffs per day, 2.5 puffs per day, 2.75 puffs per day, 3.00 puffs per day, or more at week 12.

[00303] OCS Use. According to certain embodiments, administration of an IL-4R antagonist to a patient can be used in conjunction with an OCS such as oral prednisone. The number of OCS administrations can be recorded daily by the patients in a diary, PEF meter, or other recording device. During treatment with the pharmaceutical composition described herein, occasional short-term use of prednisone typically can be used to control acute asthmatic episodes, e.g., episodes in which bronchodilators and other anti-inflammatory agents fail to control symptoms. In other aspects, prednisone is used concurrent with or as a substitution for ICS. Oral prednisone may be administered in dosages of about 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg. OCS can optionally be administered once a day or multiple times a day (e.g., twice a day, three times a day, four times a day, etc.)

[00304] In certain exemplary embodiments, methods for reducing or eliminating the dependency of the subject on OCS use are provided. The reduction or elimination of steroid dependency is highly advantageous and desirable. In certain embodiments, a reduction of 50% or greater (e.g., 50%, 60%, 70%, 80%, 90% or more) in the OCS dose is achieved after administration of IL-4R antibody therapy at a period of time (e.g., at week 24 In certain embodiments, the OCS is substantially eliminated after 40 weeks, 45 weeks, 50 weeks, 52 weeks, or greater after first dose following administration of the loading dose. In other embodiments, the level of OCS use is reduced to less than 5 mg per day (e.g., less than 5 mg, 4 mg, 3 mg, 2 mg or less per day). In other embodiments, the dependency on OCS use is substantially eliminated after 3 months, 6 months, 9 months or 1 year following treatment with IL4R antibody or fragment thereof.

[00305] 5-Item Asthma Control Questionnaire (ACQ) Score. According to certain embodiments, administration of an IL-4R antagonist to a patient results in a decrease from baseline of five-item Asthma Control Questionnaire (ACQ5) score. The ACQ5 is a validated questionnaire to evaluate asthma control.

[00306] Therapeutic methods are provided that result in a decrease in ACQ5 score from baseline of at least 0.10 points at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist. For example, administration of an IL-4R antagonist to a subject in need thereof causes a decrease in ACQ score from baseline of about 0.10 points, 0.15 points, 0.20 points, 0.25 points, 0.30 points, 0.35

points, 0.40 points, 0.45 points, 0.50 points, 0.55 points, 0.60 points, 0.65 points, 0.70 points, 0.75 points, 0.80 points, 0.85 points, or more at week 12.

[00307] Night-Time Awakenings. According to certain embodiments, administration of an IL-4R antagonist to a patient results in a decrease from baseline of average number of nighttime awakenings.

[00308] In certain embodiments, the methods decrease the average number of nighttime awakenings from baseline by at least about 0.10 times per night at week 12 following initiation of treatment. For example, administration of an IL-4R antagonist to a subject in need thereof can cause a decrease in average number of nighttime awakenings from baseline of about 0.10 times per night, 0.15 times per night, 0.20 times per night, 0.25 times per night, 0.30 times per night, 0.35 times per night, 0.40 times per night, 0.45 times per night, 0.50 times per night, 0.55 times per night, 0.60 times per night, 0.65 times per night, 0.70 times per night, 0.75 times per night, 0.80 times per night, 0.85 times per night, 0.90 times per night, 0.95 times per night, 1.0 times per night, 2.0 times per night, or more at week 12.

[00309] 22-Item Sinonasal Outcome Test (SNOT-22) Score. According to certain embodiments, administration of an IL-4R antagonist to a patient results in a decrease from baseline of 22-item Sinonasal Outcome Test (SNOT-22). The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life (Hopkins et al 2009, Clin. Otolaryngol. 34: 447-454).

[00310] Therapeutic methods are provided that result in a decrease in SNOT-22 score from baseline of at least 1 point at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist. For example, administration of an IL-4R antagonist to a subject in need thereof can cause a decrease in SNOT-22 score from baseline of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 points, or more at week 12.

[00311] Biomarkers. In certain embodiments, the subject experiences an improvement in lung function as measured by a biomarker, e.g., a biomarker associated with allergic asthma (e.g., severe uncontrolled allergic asthma) and/or a biomarker associated with ABPA. For example, the biomarker may be fractional exhaled nitric oxide (FeNO), eotaxin-3, total IgE, allergen-specific IgE (e.g., Af-associated IgE), periostin, eosinophil (Eos) level, or thymus and activation-regulated chemokine (TARC). In certain embodiments, an improvement in lung function is indicated by a reduction or an increase (as appropriate) at week 4, week 12 or week 24 following treatment.

Methods for Treating Asthma and/or ABPA

[00312] In some embodiments, methods are provided for treating asthma, including, e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe uncontrolled asthma or inadequately controlled asthma, as well as allergic forms of any of these, in a subject in need thereof, wherein the methods comprise administering a pharmaceutical composition comprising an IL-4R antagonist to the subject. In particular embodiments, the methods are useful for treating allergic asthma, e.g., moderate-to-severe uncontrolled allergic asthma, in a subject. In other particular embodiments, the methods are useful for treating asthma associated with ABPA in a subject.

[00313] In some embodiments, methods are provided for treating ABPA in a subject in need thereof, wherein the methods comprise administering a pharmaceutical composition comprising an IL-4R antagonist to the subject. In particular embodiments, the methods are useful for treating ABPA in a subject having comorbid asthma, e.g., moderate-to-severe uncontrolled asthma.

[00314] As used herein, the term "asthma" can be used interchangeably with "intermittent asthma," or "bronchial asthma." "Asthma," "bronchial asthma" and "intermittent asthma," and allergic forms of each of these, refer to asthma in which one or any combination of the following are true: symptoms occur 2 or fewer days per week; symptoms do not interfere with normal activities; nighttime symptoms occur fewer than 2 days per month; or one or more lung function tests (e.g., forced expiratory volume in one second (FEV_1) and/or peak expiratory flow (PEF) of greater than 80%) are normal when the subject is not suffering from an asthma attack.

[00315] As used herein, the term "allergic bronchopulmonary aspergillosis" or "ABPA" refers to a hypersensitive reaction to an *Aspergillus* antigen, typically, *Aspergillus fumigatus* in the lungs of a subject which may damage the airways and result in permanent lung damage. ABPA can be diagnosed by any combination of patient health history (including the presence of asthma and/or cystic fibrosis), X-ray and/or CT scans, allergy skin testing, and blood IgE levels (e.g., total IgE and/or *Aspergillus*-specific IgE, e.g., Af-specific IgE). In certain embodiments, ABPA is diagnosed by a combination of one or more of: (1) total serum IgE levels; (2) eosinophilia; (3) *Aspergillus*-specific IgE, e.g., Af-specific serum IgE; and (4) *Aspergillus*-specific IgE, e.g., Af-specific serum IgG. In particularly exemplary embodiments, a subject is diagnosed with ABPA is the subject exhibits one or more (e.g., one, two, or all three) of the following biomarkers: (1) a baseline serum IgE level of greater than 1000 IU/mL; (2) an Af-

specific baseline serum IgE level of greater than 0.35 kU/L; and (3) a baseline blood eosinophil level of greater than 500 cells/μL.

[00316] In certain embodiments, ABPA is diagnosed in a subject having an HLA-DR2 serotype (e.g., subtype HLA-DRB1*1501, subtype *HLA-DRB1*1503, or subtype *HLA-DRB1*1601) or an HLA-DR5 serotype (e.g., subtype HLA-DRB1*1101, subtype HLA-DRB1*1104, or subtype HLA-DRB1*1202).

[00317] As used herein, the term "asthma associated with ABPA" refers to a subject that has comorbid asthma and ABPA.

[00318] "IgE" refers to an antibody isotype that contains the ε heavy chain, and is a monomer having five domains in the immunoglobulin structure. IgE is typically present in plasma at a concentration of less than 1 μg/mL, and has a half-life of about 2 days in serum (Abbas and Lichtman (2004) Basic Immunology functions and disorders of the immune system. 2nd ed. Philadelphia: Saunders). The units kU/L or IU/mL (which units can be used interchangeably) are often used to express the level of IgE in peripheral blood, with one kU/L is equal to 2.4 ng/mL (Seagroatt and Anderson (1981) E. J. Biol Stand. 9:431).

[00319] IgE (e.g., total serum IgE and/or allergen specific IgE) can be determined using a variety of methods known in the art. For example, PRIST (paper radioimmunosorbent test) can be used, in which serum samples react with IgE that has been tagged with radioactive iodine. Bound radioactive iodine is detected, and is proportional to the amount of total IgE in the serum sample. In clinical immunology, levels of individual classes of immunoglobulins can be measured by nephelometry (or turbidimetry) to characterize the antibody profile of a subject. Other methods of measuring IgE levels include, but are not limited to, ELISA, immunofluorescence, Western blot, immunodiffusion, immunoelectrophoresis and the like. Measurement of a serum IgE concentration can be performed using a UniCAP 250® system (Pharmacia, Uppsala, Sweden) (See G. J. Gleich, A. K. Averbach and N. A. Swedlund, Measurement of IgE in normal and allergic serum by radioimmunoassay. *J. Lab. Clin. Med.* 77 (1971), p. 690.)

[00320] Allergic asthma refers to asthma that is triggered by allergens, e.g., inhaled allergens, such as dust mites, pet dander, pollen, fungi and the like. As used herein, the term "allergic asthma" refers to asthma in combination with one or more allergic markers, e.g., total serum IgE (e.g., a total serum IgE of ≥30 IU/mL, a total serum IgE of ≥700 IU/mL, or total serum IgE of ≥1000 IU/mL), and/or at least one positive allergen-specific IgE value (e.g., an allergen-

specific IgE value of ≥0.35 kU/L). In certain embodiments, the allergen is an airborne aeroallergen (e.g., an annual aeroallergen or a perennial aeroallergen).

[00321] In certain exemplary embodiments, a subject having allergic asthma has a total serum IgE level of about ≥5 IU/mL, about ≥10 IU/mL, about ≥20 IU/mL, about ≥30 IU/mL, about ≥40 IU/mL, about ≥50 IU/mL, about ≥60 IU/mL, about ≥70 IU/mL, about ≥80 IU/mL, about ≥90 IU/mL, about ≥100 IU/mL, about ≥110 IU/mL, about ≥120 IU/mL, about ≥130 IU/mL, about ≥140 IU/mL, about ≥150 IU/mL, about ≥160 IU/mL, about ≥170 IU/mL, about ≥180 IU/mL, about ≥190 IU/mL, about ≥200 IU/mL, about ≥250 IU/mL, about ≥300 IU/mL, about ≥350 IU/mL, about ≥400 IU/mL, about ≥450 IU/mL, about ≥500 IU/mL, about ≥550 IU/mL, about ≥600 IU/mL, about ≥650 IU/mL, about ≥700 IU/mL, about ≥750 IU/mL, about ≥800 IU/mL, about ≥850 IU/mL, about ≥900 IU/mL, about ≥950 IU/mL, about ≥1000 IU/mL or greater. In particularly exemplary embodiments, a subject having allergic asthma has a total serum IgE of greater than about 700 IU/mL (e.g., high total serum IgE). In other particularly exemplary embodiments, a subject having allergic asthma has a total serum IgE of greater than about 1000 IU/mL (e.g., very high total serum IgE). In certain exemplary embodiments, a subject has a total serum IgE level of at least 700 IU/mL as measured using an ImmunoCAP assay. In certain exemplary embodiments, a subject has a total serum IgE level of at least 1000 IU/mL as measured using an ImmunoCAP assay.

[00322] In certain exemplary embodiments, a subject having allergic asthma has at least one positive allergen-specific IgE value present in an amount of about ≥0.05 kU/L, about ≥0.10 kU/L, about ≥0.15 kU/L, about ≥0.20 kU/L, about ≥0.21 kU/L, about ≥0.22 kU/L, about ≥0.23 kU/L, about ≥0.24 kU/L, about ≥0.25 kU/L, about ≥0.26 kU/L, about ≥0.27 kU/L, about ≥0.28 kU/L, about ≥0.29 kU/L, about ≥0.30 kU/L, about ≥0.31 kU/L, about ≥0.32 kU/L, about ≥0.33 kU/L, about ≥0.34 kU/L, about ≥0.35 kU/L, about ≥0.36 kU/L, about ≥0.37 kU/L, about ≥0.38 kU/L, about ≥0.39 kU/L, about ≥0.40 kU/L, about ≥0.45 kU/L, about ≥0.50 kU/L, about ≥0.55 kU/L, about ≥0.60 kU/L, about ≥0.65 kU/L, about ≥0.70 kU/L or greater.

[00323] As used herein, a "perennial aeroallergen" refers to airborne allergens that can be present in the environment year-round, such as dust mites, fungi, dander and the like. Perennial aeroallergens include, but are not limited to, *Alternaria alternata*, *Aspergillus fumigatus*, *Aureobasidium pullulans*, *Candida albicans*, *Cladosporium herbarum*, *Dermatofagoides farinae*, *Dermatofagoides pteronyssinus*, *Mucor racemosus*, *Penicillium chrysogenum*, *Phoma betae*, *Setomelanomma rostrata*, *Stemphylium herbarum*, cat dander, dog dander, cow dander,

chicken feathers, goose feathers, duck feathers, cockroach (e.g., German cockroach, Oriental cockroach), mouse urine, peanut dust, tree nut dust, and the like.

[00324] As used herein, a "seasonal aeroallergen" refers to airborne allergens that are present in the environment seasonally, such as pollens and spores. Seasonal aeroallergens include, but are not limited to, tree pollen (e.g., birch, alder, cedar, hazel, hornbeam, horse chestnut, willow, poplar, linden, pine, maple, oak, olive and the like), grass pollen (e.g., ryegrass, cat's tail and the like), weed pollen (e.g., ragweed, plantain, nettles, mugwort, fat hen, sorrel and the like), fungal spores that increase during particular seasons, temperatures, etc. (e.g., molds), and the like.

[00325] As used herein, the term "persistent asthma" or "persistent bronchial asthma" refers to asthma that is more severe than (bronchial) asthma/intermittent (bronchial) asthma. A subject suffering from persistent asthma or persistent bronchial asthma experiences one or more of the following: symptoms more than 2 days per week; symptoms that interfere with normal activities; nighttime symptoms that occur more than 2 days per month; or one or more lung function tests (e.g., forced expiratory volume in one second (FEV_1) and/or peak expiratory flow (PEF) of less than 80%) that are not normal when the subject is not suffering from an asthma attack; the subject relies on daily asthma control medication; the subject has taken a systemic steroid more than once in the last year after a severe asthma flare-up; or use of a short-acting beta-2 agonist more than two days per week for relief of asthma symptoms.

[00326] Asthma/intermittent asthma, bronchial asthma/intermittent bronchial asthma, and persistent asthma/persistent bronchial asthma, and allergic forms of each of these, can be categorized as "mild," "moderate," "severe" or "moderate-to-severe." "Mild intermittent asthma" or "mild intermittent bronchial asthma" is defined as having symptoms less than once a week, and having forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) $\geq$80%. "Mild persistent asthma" or "mild persistent bronchial asthma" differs in that symptoms frequency is greater than once per week but less than once per day, and variability in FEV_1 or PEF is <20%–30%. "Moderate intermittent asthma" or "moderate intermittent bronchial asthma" is defined as having symptoms less than once a week, and having forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) of 60-80%. "Moderate persistent asthma" or "moderate persistent bronchial asthma," or an allergic form thereof, is defined as having daily symptoms, exacerbations that may affect activity and/or sleep, nocturnal symptoms more than once a week, daily use of inhaled short-acting beta-2 agonist

and having forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) of 60-80%. "Severe intermittent asthma" or "severe intermittent bronchial asthma," or an allergic form thereof, is defined as having symptoms less than once a week, and having forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) of 60%. "Severe persistent asthma" or "severe persistent bronchial asthma" is defined as having daily symptoms, frequent exacerbations that may affect activity and/or sleep, frequent nocturnal symptoms, limitation of physical activities, daily use of inhaled short-acting beta-2 agonist, and having forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) of 60%. "Moderate-to-severe intermittent asthma" or "moderate-to-severe intermittent bronchial asthma," or an allergic form thereof, is defined as having symptoms between those of moderate intermittent asthma/moderate intermittent bronchial asthma and severe intermittent asthma/severe intermittent bronchial asthma. "Moderate-to-severe persistent asthma" or "moderate-to-severe persistent bronchial asthma," or an allergic form thereof, is defined as having symptoms between those of moderate persistent asthma/moderate persistent bronchial asthma and severe persistent asthma/severe persistent bronchial asthma.

[00327] As used herein, the term "inadequately controlled asthma," or an allergic form thereof, refers to patients whose asthma is either "not well controlled" or "very poorly controlled" as defined by the "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma," National Heart, Blood and Lung Institute, NIH, Aug. 28, 2007. "Not well controlled asthma," or an allergic form thereof, is defined as having symptoms greater than two days per week, nighttime awakenings one to three times per week, some limitations on normal activity, short-acting $beta_2$-agonist use for symptom control greater than two days per week, FEV_1 of 60-80% of predicted and/or personal best, an ATAQ score of 1-2, an ACQ score of 1.5 or greater, and an ACT score of 16-19. "Very poorly controlled asthma," or an allergic form thereof, is defined as having symptoms throughout the day, nighttime awakenings four times or more per week, extreme limitations on normal activity, short-acting $beta_2$-agonist use for symptom control several times per day, FEV_1 of less than 60% of predicted and/or personal best, an ATAQ score of 3-4, an ACQ score of N/A, and an ACT score of less than or equal to 15.

[00328] In some embodiments, a subject is identified as having "moderate-to-severe uncontrolled" asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) if the subject receives such a diagnosis from a physician,

based on the Global Initiative for Asthma (GINA) 2009 Guidelines, and one or more of the following criteria: i) Existing treatment with moderate- or high-dose ICS/LABA (2 fluticasone propionate 250 μg twice daily or equipotent ICS daily dosage) with a stable dose of ICS/LABA for greater than or equal to 1 month prior to administration of the loading dose of IL-4R antagonist; ii) FEV_1 40 to 80% predicted normal prior to administration of the loading dose of IL-4R antagonist; iii) ACQ-5 score greater than or equal to 1.5 prior to administration of the loading dose of IL-4R antagonist; iv) reversibility of at least 12% and 200 mL in FEV_1 after 200 μg to 400 μg (2 to 4 inhalations) of salbutamol/albuterol prior to administration of the loading dose of IL-4R antagonist; or v) has experienced, within 1 year prior to administration of the loading dose of IL-4R antagonist, any of the following events: (a) treatment with greater than or equal to 1 systemic (oral or parenteral) steroid burst for worsening asthma, (b) hospitalization or an emergency/urgent medical care visit for worsening asthma.

[00329] "Severe asthma" or "severe allergic asthma" refers to asthma in which adequate control cannot be achieved by high-dose treatment with inhaled corticosteroids and additional controllers (e.g., long-acting inhaled beta 2 agonists, montelukast, and/or theophylline) or by oral corticosteroid treatment (e.g., for at least six months per year), or is lost when the treatment is reduced. In certain embodiments, severe asthma includes asthma that is treated with high-dose ICS and at least one additional controller (e.g., LABA, montelukast, or theophylline) or oral corticosteroids >6 months/year, wherein at least one of the following occurs or would occur if treatment is reduced: ACT <20 or ACQ >1.5; at least 2 exacerbations in the last 12 months; at least 1 exacerbation treated in hospital or requiring mechanical ventilation in the last 12 months; or FEV_1 <80% (if FEV_1/FVC below the lower limit of normal).

[00330] "Steroid-dependent asthma" or "steroid-dependent allergic asthma" refers to asthma which requires one or more of the following treatments: frequent, short term oral corticosteroid treatment bursts in the past 12 months; regular use of high dose inhaled corticosteroids in the past 12 months; regular use of injected long acting corticosteroids; daily use of oral corticosteroids; alternate-day oral corticosteroids; or prolonged use of oral corticosteroids in the past year.

[00331] "Oral corticosteroid-dependent asthma" of "oral corticosteroid-dependent allergic asthma" refers to a subject having ≥3 30-day oral corticosteroid (OCS) fills over a 12-month period and a primary asthma diagnosis within 12 months of the first OCS fill. Subjects with OCS-dependent asthma may also experience one or any combination of the following: have

received physician prescribed LABA and high dose ICS (total daily dose >500 μg fluticasone propionate dry powder formulation equivalent) for at least 3 months (the ICS and LABA can be parts of a combination product, or given by separate inhalers); have received additional maintenance asthma controller medications according to standard practice of care e.g., leukotriene receptor antagonists (LTRAs), theophylline, long-acting muscarinic antagonists (LAMAs), secondary ICS and cromones; received OCS for the treatment of asthma at a dose of between ≥ 7.5 to ≤ 30mg (prednisone or prednisolone equivalent); have received an OCS dose administered every other day (or different doses every other day); morning pre-bronchodilator (BD) FEV_1 of < 80% predicted normal; have evidence of asthma as documented by post-BD (albuterol/salbutatomol) reversibility of FEV_1 ≥12% and ≥200 mL (15-30 min after administration of 4 puffs of albuterol/salbutamol); or have a history of at least one asthma exacerbation event within 12 months.

[00332] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a blood eosinophil level of at least 300 cells per microliter; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00333] In another aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a blood eosinophil level of 200-299 cells per microliter; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00334] In another aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a blood eosinophil level of less than 200 cells per microliter; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00335] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a blood eosinophil level of at least 150 cells per microliter; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00336] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a blood eosinophil level of at least 300 cells per microliter; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00337] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline FeNO level of ≥20 ppb; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00338] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline FeNO level of ≥25 ppb; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00339] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline FeNO level of ≥50 ppb; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00340] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline total IgE level of ≥30 IU/mL; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00341] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline total IgE level of ≥700 IU/mL; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00342] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline total IgE level of ≥1000 IU/mL; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00343] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline allergen-specific IgE of ≥0.15 kU/L; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00344] In one aspect, methods for treating asthma are provided comprising: (a) selecting a patient that exhibits a baseline allergen-specific IgE of ≥0.35 kU/L; and (b) administering to the patient a pharmaceutical composition comprising an IL-4R antagonist.

[00345] In a related aspect, methods for treating asthma comprising an add-on therapy to background therapy are provided. In certain embodiments, an IL-4R antagonist is administered as an add-on therapy to an asthma patient who is on background therapy for a certain period of time (e.g., 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 5 months, 12 months, 18 months, 24 months, or longer) (also called the "stable phase"). In some embodiments, the background therapy comprises a ICS and/or a LABA.

[00346] In some embodiments, a method for reducing an asthma patient's dependence on ICS and/or LABA for the treatment of one or more asthma exacerbations comprising: (a) selecting a patient who has moderate-to-severe asthma that is uncontrolled with a background asthma therapy comprising an ICS, a LABA, or a combination thereof; and administering to the patient a pharmaceutical composition comprising an IL-4R antagonist, is provided.

[00347] In some embodiments methods to treat or alleviate conditions or complications associated with asthma or comorbid with asthma, such as chronic rhinosinusitis, allergic rhinitis, allergic fungal rhinosinusitis, chronic sinusitis, allergic bronchopulmonary aspergillosis (ABPA), unified airway disease, eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome), gastroesophageal reflux disease (GERD), atopic conjunctivitis, atopic dermatitis, vasculitis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), chronic eosinophilic pneumonia (CEP) and exercise induced bronchospasm, are provided.

[00348] Methods for treating persistent asthma (e.g., persistent allergic asthma) are also provided. As used herein, the term "persistent asthma" means that the subject has symptoms at least once a week at day and/or at night, with the symptoms lasting a few hours to a few days. In certain alternative embodiments, the persistent asthma is "mildly persistent" (e.g., more than twice a week but less than daily with symptoms severe enough to interfere with daily activities or sleep and/or where pulmonary function is normal or reversible with inhalation of a bronchodilator), "moderately persistent" (e.g., symptoms occurring daily with sleep interrupted at least weekly and/or with pulmonary function moderately abnormal), or "severely persistent" (e.g., continuous symptoms despite the correct use of approved medications and/or where pulmonary function is severely affected).

Interleukin-4 Receptor Antagonists

[00349] The methods featured herein comprise administering to a subject in need thereof a therapeutic composition comprising an IL-4R antagonist. As used herein, an "IL-4R antagonist" is any agent that binds to or interacts with IL-4R and inhibits the normal biological signaling function of IL-4R when IL-4R is expressed on a cell *in vitro* or *in vivo*. Non-limiting examples of categories of IL-4R antagonists include small molecule IL-4R antagonists, anti-IL-4R aptamers, peptide-based IL-4R antagonists (e.g., "peptibody" molecules), and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R. According to certain embodiments, the IL-4R antagonist comprises an anti-IL-4R antibody that can be used in the context of the methods described elsewhere herein. For example, in one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds to an IL-4R, and comprises the heavy chain and light chain (Complementarity Determining

Region) CDR sequences from the Heavy Chain Variable Region (HCVR) and Light Chain Variable Region (LCVR) of SEQ ID NOs:1 and 2, respectively.

[00350] The term "human IL4R" (hIL-4R) refers to a human cytokine receptor that specifically binds to interleukin-4 (IL-4), such as IL-4Rα.

[00351] The term "antibody" refers to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2, and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments, the FRs of the anti-IL-4R antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[00352] The term "antibody" also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds to an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques, such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[00353] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment."

[00354] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR that is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[00355] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody described herein include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids that result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule, typically the hinge region may consist of between 2 to 60 amino acids, typically between 5 to 50, or typically between 10 to 40 amino acids. Moreover, an antigen-binding fragment of an antibody described herein may comprise a homo-dimer or

hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[00356] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (*e.g.*, bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, may be adapted for use in the context of an antigen-binding fragment of an antibody described herein using routine techniques available in the art.

[00357] The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[00358] The term "human antibody" includes antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies described herein may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody" does not include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00359] The term "recombinant human antibody" includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is

used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[00360] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[00361] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) Molecular Immunology 30:105) to levels typically observed using a human IgG1 hinge. Antibodies having one or more mutations in the hinge, C_H2, or C_H3 region, which may be desirable, for example, in production, to improve the yield of the desired antibody form, are provided.

[00362] An "isolated antibody" means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody". An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[00363] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" IL-4R includes antibodies that bind IL-4R or portion thereof with a K_D of less than about 1000 nM, less than

about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM, or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human IL-4R may, however, have cross-reactivity to other antigens, such as IL-4R molecules from other (non-human) species.

[00364] The anti-IL-4R antibodies useful for the methods may comprise one or more amino acid substitutions, insertions, and/or deletions (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 substitutions and/or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 insertions and/or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 deletions) in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. Methods involving the use of antibodies, and antigen-binding fragments thereof, that are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) within one or more framework and/or one or more (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 with respect to the tetrameric antibody or 1, 2, 3, 4, 5 or 6 with respect to the HCVR and LCVR of an antibody) CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"), are provided. A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments that comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or

CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. The use of antibodies and antigen-binding fragments obtained in this general manner are encompassed within the invention.

[00365] Methods involving the use of anti-IL-4R antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the use of anti-IL-4R antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein, are provided.

[00366] The term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

[00367] The term "K_D" refers to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[00368] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope

may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

Preparation of Human Antibodies

[00369] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used to make human antibodies that specifically bind to human IL-4R.

[00370] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to IL-4R are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[00371] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[00372] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc., using standard procedures known to those skilled in the art. The mouse constant regions are replaced with a desired human constant region to generate a fully human antibody described herein, for example wild-type or

modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[00373] In general, the antibodies that can be used in the methods possess high affinities, as described above, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully-human antibodies described herein. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[00374] In one embodiment, human antibody or antigen-binding fragment thereof that specifically binds IL-4R that can be used in the context of the methods described herein comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 1. The antibody or antigen-binding fragment may comprise the three light chain CDRs (LCVR1, LCVR2, LCVR3) contained within a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 2. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[00375] In certain embodiments, the antibody or antigen-binding fragment thereof comprises the six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) from the heavy and light chain variable region amino acid sequence pairs (HCVR/LCVR) of SEQ ID NOs: 1 and 2.

[00376] In certain embodiments, the antibody or antigen-binding fragment thereof comprises six CDRs (HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3) having the amino acid sequences of SEQ ID NOs: 3/4/5/6/7/8.

[00377] In certain embodiments, the antibody or antigen-binding fragment thereof comprises HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 1 and 2.

[00378] In certain embodiments, the antibody is dupilumab, which comprises the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 1 and 2.

[00379] In certain embodiments, the antibody sequence is dupilumab, which comprises the heavy chain/light chain amino acid sequence pair of SEQ ID NOs: 9 and 10.

Dupilumab HCVR amino acid sequence:

[00380] EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSI SGSGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPR YYGLDVWGQGTTVTVS (SEQ ID NO: 1).

Dupilumab LCVR amino acid sequence:

[00381] DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIY LGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEI K (SEQ ID NO: 2).

Dupilumab HCDR1 amino acid sequence:

[00382] GFTFRDYA (SEQ ID NO: 3).

Dupilumab HCDR2 amino acid sequence:

[00383] ISGSGGNT (SEQ ID NO: 4).

Dupilumab HCDR3 amino acid sequence:

[00384] AKDRLSITIRPRYYGL (SEQ ID NO: 5).

Dupilumab LCDR1 amino acid sequence:

[00385] QSLLYSIGYNY (SEQ ID NO: 6).

Dupilumab LCDR2 amino acid sequence:

[00386] LGS (SEQ ID NO: 7).

Dupilumab LCDR3 amino acid sequence:

[00387] MQALQTPYT (SEQ ID NO: 8).

Dupilumab HC amino acid sequence:

[00388] EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLE WVSSISGSGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSI TIRPRYYGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLG (SEQ ID NO: 9) (amino acids 1-124 = HCVR; amino acids 125-451 = HC constant).

Dupilumab LC amino acid sequence:

[00389] DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIY LGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 10) (amino acids 1-112 = LCVR; amino acids 112-219 = LC constant).

Pharmaceutical Compositions

[00390] Methods that comprise administering an IL-4R antagonist to a patient, wherein the IL-4R antagonist is contained within a pharmaceutical composition are provided. The pharmaceutical compositions described herein are formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol. 52:238-311.

[00391] The dose of antibody administered to a patient may vary depending upon the age and the size of the patient, symptoms, conditions, route of administration, and the like. The dose

is typically calculated according to body weight or body surface area. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering pharmaceutical compositions comprising anti-IL-4R antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti *et al.*, 1991, *Pharmaceut. Res. 8*:1351).

[00392] Various delivery systems are known and can be used to administer the pharmaceutical compositions described herein, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262:4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intra-tracheal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[00393] A pharmaceutical composition described herein can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device (e.g., an autoinjector pen) readily has applications in delivering a pharmaceutical composition described herein. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[00394] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic

Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (Sanofi-Aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition described herein include, but are not limited to the SOLOSTAR™ pen (Sanofi-Aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few. Examples of large-volume delivery devices (e.g., large-volume injectors) include, but are not limited to, bolus injectors such as, e.g., BD Libertas West SmartDose, Enable Injections, SteadyMed PatchPump, Sensile SenseTrial, YPsomed YpsoDose, Bespak Lapas, and the like.

[00395] For direct administration to the sinuses, the pharmaceutical compositions described herein may be administered using, e.g., a microcatheter (e.g., an endoscope and microcatheter), an aerosolizer, a powder dispenser, a nebulizer or an inhaler. The methods include administration of an IL-4R antagonist to a subject in need thereof, in an aerosolized formulation. For example, aerosolized antibodies to IL-4R may be administered to treat asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA in a patient. Aerosolized antibodies can be prepared as described in, for example, US 8,178,098, incorporated herein by reference in its entirety.

[00396] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[00397] The injectable preparations may include dosage forms for intravenous, subcutaneous,

intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant (e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)), etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is typically filled in an appropriate ampoule.

[00398] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc.

[00399] Exemplary pharmaceutical compositions comprising an anti-IL-4R antibody that can be used as described herein are disclosed, e.g., in U.S. Patent Application Publication No. 2012/0097565.

Dosage

[00400] The amount of IL-4R antagonist (e.g., anti-IL-4R antibody) administered to a subject according to the methods described herein is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount of IL-4R antagonist that results in one or more of: (a) a reduction in the incidence of asthma exacerbations; (b) an improvement in one or more asthma-associated parameters (as defined elsewhere herein); and/or (c) a detectable improvement in one or more symptoms or indicia of an upper airway inflammatory condition. A "therapeutically effective amount" also includes an amount of IL-4R antagonist that inhibits, prevents, lessens, or delays the progression of asthma in a subject.

[00401] In the case of an anti-IL-4R antibody, a therapeutically effective amount can be from about 0.05 mg to about 700 mg, e.g., about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg,

about 2.0 mg, about 3.0 mg, about 5.0 mg, about 7.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, or about 700 mg of the anti-IL-4R antibody. In certain embodiments, 300 mg of an anti-IL-4R antibody is administered.

[00402] The amount of IL-4R antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (i.e., mg/kg). For example, the IL-4R antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight. For example, the IL-4R antagonist can be administered at a dose of 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg or 6 mg/kg.

[00403] In some embodiments, the dose of IL-4R antagonist may vary according to eosinophil count. For example, the subject may have a blood eosinophil count (i.e., a high blood eosinophil count) ≥300 cells/μL, or 300 – 499 cells/μL or ≥500 cells/μL (HEos); a blood eosinophil count of 200 to 299 cells/μL (moderate blood eosinophils); or a blood eosinophil count <200 cells/μL (low blood eosinophils).

[00404] In some embodiments, the dose of IL-4R antagonist may vary according to FeNO value. For example, the subject may have an FeNO value of ≥50 ppb (e.g., high FeNO); an FeNO value of ≥25 ppb; an FeNO value of between about 25 ppb and about 50 ppb; an FeNO value of <50 ppb; an FeNO value of <25 ppb (e.g., low FeNO); or an FeNO value of <20 ppb (e.g., low FeNO).

[00405] In some embodiments, the dose of IL-4R antagonist may vary according to total serum IgE value. For example, the subject may have a total serum IgE value of ≥30 IU/mL; a total serum IgE value of ≥700 IU/mL (e.g., high serum IgE); or a total serum IgE value of ≥1000 IU/mL (e.g., very high serum IgE).

[00406] In some embodiments, the dose of IL-4R antagonist may vary according to allergen-specific IgE value. In some embodiments, the dose of IL-4R antagonist may vary according to Af-specific IgE value. For example, the subject may have an allergen-specific IgE value of ≥0.15 kU/L; or an allergen-specific IgE value of ≥0.35 kU/L.

[00407] In certain embodiments, the methods comprise a loading dose of about 400 to about 600 mg of an IL-4R antagonist.

[00408] In certain embodiments, the methods comprise one or more maintenance doses of about 200 to about 300 mg of the IL-4R antagonist.

[00409] In certain embodiments, the ICS and LABA are administered for the duration of administration of the IL-4R antagonist.

[00410] In certain embodiments, the loading dose comprises 600 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00411] In certain embodiments, the loading dose comprises 400 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance dose comprises 200 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00412] In certain embodiments, the loading dose comprises 400 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance dose comprises 200 mg of the antibody or antigen-binding fragment thereof administered every other week, which may be increased to 300 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00413] In other embodiments, the loading dose comprises 600 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00414] In other embodiments, the loading dose comprises 400 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00415] In other embodiments, the loading dose comprises 600 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered once a week.

[00416] In other embodiments, the loading dose comprises 400 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered once a week.

[00417] In other embodiments, the loading dose comprises 600 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every third week.

[00418] In other embodiments, the loading dose comprises 400 mg of an anti-IL-4R antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every third week.

[00419] In one embodiment, the subject is 6 to <18 years old and the IL-4R antibody or antigen binding fragment thereof is administered at 2 mg/kg or 4 mg/kg.

[00420] In another embodiment, the subject is 12 to <18 years old and the IL-4R antibody or antigen binding fragment thereof is administered at 2 mg/kg or 4 mg/kg.

[00421] In another embodiment, the subject is 6 to <12 years old and the IL-4R antibody or antigen binding fragment thereof is administered at 2 mg/kg or 4 mg/kg.

[00422] In another embodiment, the subject is 2 to <6 years old and the IL-4R antibody or antigen binding fragment thereof is administered at 2 mg/kg or 4 mg/kg.

[00423] In yet another embodiment, the subject is <2 years old and the IL-4R antibody or antigen binding fragment thereof is administered at 2 mg/kg or 4 mg/kg.

Combination Therapies

[00424] Certain embodiments of the methods described herein comprise administering to the subject one or more additional therapeutic agents in combination with the IL-4R antagonist. As used herein, the expression "in combination with" means that the additional therapeutic agents are administered before, after, or concurrent with the pharmaceutical composition comprising the IL-4R antagonist. In some embodiments, the term "in combination with" includes sequential or concomitant administration of an IL-4R antagonist and a second therapeutic agent. Methods to treat asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) or an associated condition or complication or to reduce at least one exacerbation, comprising administration of an IL-4R antagonist in combination with a second therapeutic agent for additive or synergistic activity, are provided.

[00425] For example, when administered "before" the pharmaceutical composition comprising the IL-4R antagonist, the additional therapeutic agent may be administered about 72 hours, about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes, or about 10 minutes prior to the administration of the pharmaceutical composition comprising the IL-4R antagonist. When administered "after" the pharmaceutical composition comprising the IL-4R antagonist, the additional therapeutic agent may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, or about 72 hours after the administration of the pharmaceutical composition comprising the IL-4R antagonist. Administration "concurrent" with the pharmaceutical composition comprising the IL-4R antagonist means that the additional therapeutic agent is administered to the subject in a separate dosage form within less than 5 minutes (before, after, or at the same time) of administration of the pharmaceutical composition comprising the IL-4R antagonist, or administered to the subject as a single combined dosage formulation comprising both the additional therapeutic agent and the IL-4R antagonist.

[00426] The additional therapeutic agent may be, e.g., another IL-4R antagonist, an IL-1 antagonist (including, e.g., an IL-1 antagonist as set forth in US Patent No. 6,927,044), an IL-6 antagonist, an IL-6R antagonist (including, e.g., an anti-IL-6R antibody as set forth in US Patent No. 7,582,298), a TNF antagonist, an IL-8 antagonist, an IL-9 antagonist, an IL-17 antagonist, an IL-5 antagonist, an IgE antagonist, a CD48 antagonist, a leukotriene inhibitor, an anti-fungal agent, an NSAID, a long-acting $beta_2$ agonist (e.g., salmeterol or formoterol), an inhaled corticosteroid (e.g., fluticasone or budesonide), a systemic corticosteroid (e.g., oral or intravenous), methylxanthine, nedocromil sodium, cromolyn sodium, or combinations thereof. For example, in certain embodiments, the pharmaceutical composition comprising an IL-4R antagonist is administered in combination with a combination comprising a long-acting $beta_2$ agonist and an inhaled corticosteroid (e.g., fluticasone + salmeterol (e.g., Advair® (GlaxoSmithKline)); or budesonide + formoterol (e.g., SYMBICORT® (Astra Zeneca))).

[00427] In some embodiments, an additional therapeutic agent administered in combination with the IL-4R antagonist is a vaccine. In certain exemplary embodiments, the vaccine is a viral vaccine or a bacterial vaccine. In certain exemplary embodiments, the vaccine is a live

(e.g., live-attenuated) viral vaccine or a live (e.g., live-attenuated) bacterial vaccine.

[00428] Suitable vaccines include, but are not limited to adenovirus, anthrax (e.g., AVA vaccine (BioThrax)), cholera (e.g., Vaxchora), diphtheria (e.g., DTaP (Daptacel, Infanrix), Td (Tenivac, generic), DT (generic), Tdap (Adacel, Boostrix), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), hepatitis A (e.g., HepA (Havrix, Vaqta), HepA-HepB (Twinrix)), hepatitis B (e.g., HepB (Engerix-B, Recombivax HB, Heplisav-B), DTaP-HepB-IPV (Pediarix), HepA-HepB (Twinrix)), *Haemophilus influenzae* type b (Hib) (e.g., Hib (ActHIB, PedvaxHIB, Hiberix), DTaP-IPV/Hib (Pentacel)), human papillomavirus (HPV) (e.g., HPV9 (Gardasil 9)), influenza (flu) (e.g., IIV (also called IIV3, IIV4, RIV3, RIV4 and ccIIV4) (Afluria, Fluad, Flublok, Flucelvax, FluLaval, Fluarix, Fluvirin, Fluzone, Fluzone High-Dose, Fluzone Intradermal), LAIV (FluMist)), Japanese encephalitis (e.g., JE (Ixiaro)), measles (e.g., MMR (M-M-R II), MMRV (ProQuad)), meningococcus (e.g., MenACWY (Menactra, Menveo), MenB (Bexsero, Trumenba)), mumps (e.g., MMR (M-M-R II), MMRV (ProQuad)), pertussis (e.g., DTaP (Daptacel, Infanrix), Tdap (Adacel, Boostrix), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), pneumococcus (e.g., PCV13 (Prevnar13), PPSV23 (Pneumovax 23)), polio (e.g., Polio (Ipol), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), rabies (e.g., Rabies (Imovax Rabies, RabAvert)), rotavirus (e.g., RV1 (Rotarix), RV5 (RotaTeq)), rubella (e.g., MMR (M-M-R II), MMRV (ProQuad)), shingles (e.g., ZVL (Zostavax), RZV (Shingrix)), smallpox (e.g., Vaccinia (ACAM2000)), tetanus (e.g., DTaP (Daptacel, Infanrix), Td (Tenivac, generic), DT (generic), Tdap (Adacel, Boostrix), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), tuberculosis, typhoid fever (e.g., Typhoid Oral (Vivotif), Typhoid Polysaccharide (Typhim Vi)), varicella (e.g., VAR (Varivax), MMRV (ProQuad)), yellow fever (e.g., YF (YF-Vax)) and the like. Suitable vaccines are also listed at the US Centers for Disease Control vaccine list, incorporated herein in its entirety for all purposes (cdc.gov/vaccines/vpd/vaccines-list.html).

[00429] In some embodiments, the vaccine is an inactivated vaccine, a recombinant vaccine, a conjugate vaccine, a subunit vaccine, a polysaccharide vaccine, or a toxoid vaccine. In some embodiments, the vaccine is a yellow fever vaccine. In some embodiments, the subject treated with the vaccine is concurrently treated for a type 2 inflammatory disease with an IL-4R antagonist. In some embodiments, the subject treated with the vaccine is concurrently treated for asthma with an IL-4R antagonist.

[00430] In certain embodiments, treatment with an IL-4R antagonist is suspended or terminated prior to treatment with the vaccine. In certain embodiments, treatment with the IL-4R antagonist is suspended about 1 to about 9 (e.g., about 1, about 1½, about 2, about 2½, about 3, about 3½, about 4, about 4½, about 5, about 5½, about 6, about 6½, about 7, about 7½, about 8, about 8½, about 9, or more) weeks prior to administration of the vaccine. In some embodiments, treatment with the IL-4R antagonist is suspended about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, or about 60 days prior to administration of the vaccine.

[00431] In certain embodiments, treatment with the IL-4R antagonist is resumed subsequent to treatment with the vaccine. In certain embodiments, treatment with the IL-4R antagonist is resumed about 1 to about 14 (e.g., about 1, about 1½, about 2, about 2½, about 3, about 3½, about 4, about 4½, about 5, about 5½, about 6, about 6½, about 7, about 7½, about 8, about 8½, about 9, about 9½, about 10, about 10½, about 11, about 11½, about 12, about 12½, about 13, about 13½, about 14, about 14½, or more) weeks subsequent to administration of the vaccine. In some embodiments, treatment with the IL-4R antagonist is resumed about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, about 60, about 61, about 62, about 63, about 64, about 65, about 66, about 67, about 68, about 69, about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, or about 90 days subsequent to administration of the vaccine.

[00432] In certain embodiments, the effectiveness of the IL-4R antagonist is not decreased by administration in combination with the vaccine, or by subsequent administration of the vaccine.

In some embodiments, the subject's forced expiratory volume (FEV_1) is stable before and after administration of the vaccine.

[00433] In some embodiments, the effectiveness of the vaccine is not decreased by administration in combination with the IL-4R antagonist, or by previous and/or subsequent administration of the IL-4R antagonist. In some embodiments, the subject develops seroprotective neutralization titers to the vaccine when the vaccine is co-administered with the IL-4R antagonist.

[00434] In certain exemplary embodiments, a subject is administered a vaccine described herein, wherein before, during, or after administration of the vaccine, the subject is administered at least one dose of IL-4R antagonist.

[00435] In some embodiments, the subject administered the vaccine has a type 2 inflammatory disease. In certain exemplary embodiments, the type 2 inflammatory disease is one or any combination of asthma, allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSsNP), eosinophilic esophagitis (EoE), atopic dermatitis (AD), food and environmental allergies, aspirin exacerbated respiratory disease (AERD), or a respiratory disease exacerbated by non-steroidal anti-inflammatory drugs (NSAIDs).

Administration Regimens

[00436] According to certain embodiments, multiple doses of an IL-4R antagonist may be administered to a subject over a defined time course. Such methods comprise sequentially administering to a subject multiple doses of an IL-4R antagonist. As used herein, "sequentially administering" means that each dose of IL-4R antagonist is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks, or months). Methods that comprise sequentially administering to the patient a single initial dose of an IL-4R antagonist, followed by one or more secondary doses of the IL-4R antagonist, and optionally followed by one or more tertiary doses of the IL-4R antagonist, are provided.

[00437] Methods comprising administering to a subject a pharmaceutical composition comprising an IL-4R antagonist at a dosing frequency of about four times a week, twice a week, once a week (q1w), once every two weeks (every two weeks is used interchangeably with every other week, bi-weekly or q2w), once every three weeks (tri-weekly or q3w), once every four weeks (monthly or q4w), once every five weeks (q5w), once every six weeks (q6w), once every

eight weeks (q8w), once every twelve weeks (q12w), or less frequently so long as a therapeutic response is achieved, are provided. In certain embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once a week dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every two weeks dosing (every two weeks is used interchangeably with every other week, bi-weekly or q2w) of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every three weeks dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every four weeks dosing (monthly dosing) of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every five weeks dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every six weeks dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every eight weeks dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In other embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once every twelve weeks dosing of an amount of about 75 mg, 100 mg, 150 mg, 200 mg, or 300 mg, can be employed. In one embodiment, the route of administration is subcutaneous.

[00438] The term "week" or "weeks" refers to a period of (n x 7 days) ±2 days, e.g. (n x 7 days) ±1 day, or (n x 7 days), wherein "n" designates the number of weeks, e.g. 1, 2, 3, 4, 5, 6, 8, 12 or more.

[00439] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the IL-4R antagonist. Thus, the "initial dose" is the dose that is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses that are administered after the initial dose; and the "tertiary doses" are the doses that are administered after the secondary doses. The initial, secondary,

and tertiary doses may all contain the same amount of IL-4R antagonist, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of IL-4R antagonist contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (e.g., 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). In one embodiment, the maintenance dose may be lower than the loading dose. For example, one or more loading doses of 600mg of IL-4R antagonist may be administered followed by maintenance doses of about 75mg to about 300mg.

[00440] In certain embodiments, the loading dose is about 400 to about 600 mg of the IL-4R antagonist. In one embodiment, the loading dose is 400 mg of the IL-4R antagonist. In another embodiment, the loading dose is 600 mg of the IL-4R antagonist.

[00441] In certain embodiments, the maintenance dose is about 200 to about 300 mg of the IL-4R antagonist. In one embodiment, the maintenance dose is 200 mg of the IL-4R antagonist. In another embodiment, the maintenance dose is 300 mg of the IL-4R antagonist.

[00442] In certain embodiments, the loading dose is two times the maintenance dose.

[00443] In some embodiments, the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every other week (every other week is used interchangeably with every two weeks, bi-weekly or q2w).

[00444] In some embodiments, a subject has OCS-dependent asthma, and the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00445] In some embodiments, a subject has co-morbid moderate-to-severe atopic dermatitis, and the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00446] In some embodiments, the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance dose comprises 200 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00447] In some embodiments, a subject has OCS-dependent asthma, and the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00448] In some embodiments, a subject has co-morbid moderate-to-severe atopic dermatitis, and the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every other week.

[00449] In some embodiments, the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00450] In some embodiments, a subject has OCS-dependent asthma, and the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00451] In some embodiments, a subject has co-morbid moderate-to-severe atopic dermatitis, and the loading dose comprises 600 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 300 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00452] In some embodiments, the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00453] In some embodiments, a subject has OCS-dependent asthma, and the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00454] In some embodiments, a subject has co-morbid moderate-to-severe atopic dermatitis, and the loading dose comprises 400 mg of the antibody or antigen-binding fragment thereof, and the one or more maintenance doses comprises 200 mg of the antibody or antigen-binding fragment thereof administered every fourth week.

[00455] In one exemplary embodiment, each secondary and/or tertiary dose is administered 1 to 14 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12,

12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose" means, in a sequence of multiple administrations, the dose of IL-4R antagonist that is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[00456] The methods may include administering to a patient any number of secondary and/or tertiary doses of an IL-4R antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[00457] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

[00458] Methods comprising sequential administration of an IL-4R antagonist and a second therapeutic agent, to a patient to treat asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) or an associated condition are provided. In some embodiments, the methods comprise administering one or more doses of an IL-4R antagonist followed by one or more doses (e.g., 2, 3, 4, 5, 6, 7, 8, or more) of a second therapeutic agent. For example, one or more doses of about 75 mg to about 300 mg of the IL-4R antagonist may be administered after which one or more doses (e.g., 2, 3, 4, 5, 6, 7, 8, or more) of a second therapeutic agent (e.g., an inhaled corticosteroid or a beta2-agonist or any other therapeutic agent, as described elsewhere herein) may be administered to treat, alleviate, reduce or ameliorate one or more symptoms of asthma. In some embodiments, the IL-4R antagonist is administered at one or more doses (e.g., 2, 3, 4, 5, 6, 7, 8, or more) resulting in an improvement in one or more asthma-associated parameters followed by the

administration of a second therapeutic agent to prevent recurrence of at least one symptom of asthma. Alternative embodiments pertain to concomitant administration of an IL-4R antagonist and a second therapeutic agent. For example, one or more doses (e.g., 2, 3, 4, 5, 6, 7, 8, or more) of an IL-4R antagonist are administered and a second therapeutic agent is administered at a separate dosage at a similar or different frequency relative to the IL-4R antagonist. In some embodiments, the second therapeutic agent is administered before, after or concurrently with the IL-4R antagonist.

[00459] In certain embodiments, the IL-4R antagonist is administered every other week for 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 or more. In other embodiments, the IL-4R antagonist is administered every four weeks for 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, 36 weeks, 40 weeks, 44 weeks, 48 weeks or more. In specific embodiments, the IL-4R antagonist is administered for at least 24 weeks.

[00460] Methods for treating a subject having severe uncontrolled asthma (e.g., severe steroid-dependent asthma) comprising administering to the subject a loading dose of an antibody or an antigen-binding fragment thereof that specifically binds to IL-4R are provided. In certain embodiments, the methods comprise administering to the subject a plurality of maintenance doses of the antibody or the antigen-binding fragment thereof, wherein the plurality of maintenance doses are administered during a treatment phase. The treatment phase comprises an induction phase, an OCS reduction phase, and an OCS maintenance phase.

[00461] In certain exemplary embodiments, the induction phase comprises a period during which subjects continuously receive their OCS dose(s). In certain exemplary embodiments, the reduction phase comprises a period during which subjects receive a lower OCS dose relative to the dose received during the induction phase. In certain exemplary embodiments, the maintenance phase comprises a period during which a subject receives a certain stable amount or dose(s) of OCS. Alternatively, the maintenance phase comprises a period in which OCS therapy/administration is reduced or eliminated. In certain embodiments, OCS use by the patient is completely eliminated and the patient is steroid free within less than 1 year of treatment with the IL4R antibody or fragment thereof (e.g., within 1 year, 6 months, 3 months or 1 month of initial treatment).

[00462] In another aspect, a method for treating a subject having severe steroid-dependent asthma and/or severe uncontrolled asthma comprises administering to the subject a loading dose of about 600 mg of an antibody or an antigen-binding fragment thereof that specifically binds to interleukin-4 receptor (IL-4R), and administering to the subject a plurality of maintenance doses of the antibody or the antigen-binding fragment thereof. Each maintenance dose is about 300 mg of the antibody or antigen-binding fragment thereof, wherein the plurality of maintenance doses are administered during a treatment phase comprising an induction phase, an oral corticosteroid (OCS) reduction phase, and a maintenance phase, and wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR sequences from the HCVR/ LCVR sequence pair comprises SEQ ID NOs: 1 and 2.

Treatment Populations

[00463] The methods provided herein include administering to a subject in need thereof a therapeutic composition comprising an IL-4R antagonist. The expression "a subject in need thereof" means a human or non-human animal that exhibits one or more symptoms or indicia of asthma (e.g., allergic asthma, e.g., moderate-to-severe uncontrolled allergic asthma or asthma associated with ABPA) and/or ABPA, or who has been diagnosed with asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA. For example, "a subject in need thereof" may include, e.g., subjects who, prior to treatment, exhibit (or have exhibited) one or more asthma-associated (e.g., allergic asthma-associated) parameter, such as, e.g., impaired FEV_1 (e.g., less than 2.0 L), impaired FEF25-75%; impaired AM PEF (e.g., less than 400 L/min), impaired PM PEF (e.g., less than 400 L/min), an ACQ5 score of at least 2.5, at least 1 nighttime awakenings per night, and/or a SNOT-22 score of at least 20. In various embodiments, the methods may be used to treat mild, moderate-to-severe, and severe asthma (e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA in patients in need thereof. In certain embodiments, the methods may be used to treat mild, moderate-to-severe, and severe asthma e.g., allergic asthma, asthma associated with ABPA, moderate-to-severe asthma, persistent asthma or the like) and/or ABPA in patients in need thereof, wherein the patients further exhibit comorbid moderate-to-severe atopic dermatitis.

[00464] In certain embodiments, "a subject in need thereof" means a human or non-human animal that exhibits subject a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus*

fumigatus-specific IgE level of greater than 0.35 kU/L, or a baseline blood eosinophil count of at least about 500 cells/μl. In certain embodiments, "a subject in need thereof" means a human or non-human animal that exhibits at least two of a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl. In certain embodiments, "a subject in need thereof" means a human or non-human animal that exhibits a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl.

[00465] In a related embodiment, a "subject in need thereof" may be a subject who, prior to receiving an IL-4R antagonist, has been prescribed or is currently taking a combination of ICS/LABA. Examples of ICS include mometasone furoate, budesonide, and fluticasone propionate. Examples of LABA include formoterol and salmeterol. Examples of ICS/LABA therapies include fluticasone/salmeterol combination therapy and budesonide/formoterol combination therapy. For example, methods that comprise administering an IL-4R antagonist to a patient who has been taking a regular course of ICS/LABA for two or more weeks immediately preceding the administration of the IL-4R antagonist (such prior treatments are referred to herein as "background treatments") are provided. Therapeutic methods in which background treatments are continued in combination with administration of the IL-4R antagonist are provided. In yet other embodiments, the amount of the ICS component, the LABA component, or both, is gradually decreased prior to or after the start of IL-4R antagonist administration. In some embodiments, methods to treat patients with persistent asthma for at least $\geq$ 12 months are provided. In one embodiment, a patient with persistent asthma may be resistant to treatment by a therapeutic agent, such as a corticosteroid, and may be administered an IL-4R antagonist according to the present methods.

[00466] In some embodiments, a "subject in need thereof" may be a subject with elevated levels of an asthma-associated biomarker. Examples of asthma-associated and/or ABPA-associated biomarkers include, but are not limited to, IgE (e.g., total IgE and/or *A. fumigatus*-specific IgE), thymus and activation regulated chemokine (TARC), blood eosinophils, eotaxin-3, CEA, YKL-40, and periostin. In some embodiments, a "subject in need thereof" may be a subject with blood eosinophils $\geq$ 300 cells/μL, 200-299 cells/μL, or $<$ 200 cells/μL. In one embodiment, a "subject in need thereof" may be a subject with elevated level of bronchial or airway inflammation as measured by the fraction of exhaled nitric oxide (FeNO). In another

embodiment, a "subject in need thereof" may be a subject with elevated eotaxin levels. In another embodiment, a "subject in need thereof" may be a subject with elevated TARC levels. In another embodiment, a "subject in need thereof" may be a subject with elevated IgE levels (e.g., total IgE and/or *A. fumigatus*-specific IgE levels).

[00467] In some embodiments, a "subject in need thereof" is selected from the group consisting of: a subject age 18 years old or older, a subject 12 years or older, a subject age 12 to 17 years old (12 to <18 years old), a subject age 6 to 11 years old (6 to <12 years old), and a subject age 2 to 5 years old (2 to <6 years old). In some embodiments, a "subject in need thereof" is selected from the group consisting of: an adult, an adolescent, and a child. In some embodiments, a "subject in need thereof" is selected from the group consisting of: an adult age 18 years of age or older, an adolescent age 12 to 17 years old (12 to <18 years old), a child age 6 to 11 years old (6 to <12 years old), and a child age 2 to 5 years old (2 to <6 years old). The subject can be less than 2 years of age, e.g., 12 to 23 months, or 6 to 11 months.

[00468] In some embodiments, a "subject in need thereof" is a subject who is a current smoker. In some embodiments, the subject is a current smoker who smokes, e.g., cigarettes, cigars, pipes, water pipes, and/or vaporizers (i.e., "vapes"). In some embodiments, the subject is a current smoker who has a smoking history of smoking greater than or equal to 10 packs of cigarettes per year. In some embodiments, the subject is a current smoker and has a smoking history of smoking fewer than 10 packs of cigarettes per year. In some embodiments, the subject is a current smoker and has a smoking history of smoking more than 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 or more packs of cigarettes per year. In some embodiments, the subject is a current smoker who has a smoking history of smoking for 6 months, 1 year, 2 years, 3 years, 5 years, 10 years or longer.

[00469] In some embodiments, a "subject in need thereof" is a subject who is a former smoker. In some embodiments, the subject is a former smoker who has a history of smoking cigarettes, cigars, pipes, water pipes and/or vapes. In some embodiments, the subject is a former smoker who has a smoking history of smoking greater than or equal to 10 packs of cigarettes per year. In some embodiments, the subject is a former smoker who has a smoking history of smoking fewer than 10 packs per year. In some embodiments, the subject is a former smoker who has a smoking history of smoking more than 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 or more packs of cigarettes per year. In some embodiments, the subject is a former smoker who has a smoking history of smoking for 6 months, 1 year, 2 years, 3 years, 5 years, 10 years or longer. In some

embodiments, the subject is a former smoker who has ceased smoking for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. In some embodiments, the subject is a former smoker who has ceased smoking for at least 6 months. In some embodiments, the subject is a former smoker that intends to quit permanently.

[00470] In some embodiments, a "subject in need thereof" is a subject who is a non-smoker. In some embodiments, a subject is a non-smoker that does not have a history of smoking cigarettes, cigars, pipes, water pipes and/or vapes. In some embodiments, a subject is a non-smoker that does not have a history of smoking tobacco.

[00471] In some embodiments, a "subject in need thereof" is a subject who is treated with a vaccine, e.g., a viral vaccine or a bacterial vaccine. In some embodiments, the vaccine is a live vaccine, e.g., a live (e.g., live-attenuated) viral vaccine or a live (e.g., live-attenuated) bacterial vaccine.

[00472] Suitable vaccines include, but are not limited to adenovirus, anthrax (e.g., AVA vaccine (BioThrax)), cholera (e.g., Vaxchora), diphtheria (e.g., DTaP (Daptacel, Infanrix), Td (Tenivac, generic), DT (generic), Tdap (Adacel, Boostrix), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), hepatitis A (e.g., HepA (Havrix, Vaqta), HepA-HepB (Twinrix)), hepatitis B (e.g., HepB (Engerix-B, Recombivax HB, Heplisav-B), DTaP-HepB-IPV (Pediarix), HepA-HepB (Twinrix)), *Haemophilus influenzae* type b (Hib) (e.g., Hib (ActHIB, PedvaxHIB, Hiberix), DTaP-IPV/Hib (Pentacel)), human papillomavirus (HPV) (e.g., HPV9 (Gardasil 9)), influenza (flu) (e.g., IIV (also called IIV3, IIV4, RIV3, RIV4 and ccIIV4) (Afluria, Fluad, Flublok, Flucelvax, FluLaval, Fluarix, Fluvirin, Fluzone, Fluzone High-Dose, Fluzone Intradermal), LAIV (FluMist)), Japanese encephalitis (e.g., JE (Ixiaro)), measles (e.g., MMR (M-M-R II), MMRV (ProQuad)), meningococcus (e.g., MenACWY (Menactra, Menveo), MenB (Bexsero, Trumenba)), mumps (e.g., MMR (M-M-R II), MMRV (ProQuad)), pertussis (e.g., DTaP (Daptacel, Infanrix), Tdap (Adacel, Boostrix), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), pneumococcus (e.g., PCV13 (Prevnar13), PPSV23 (Pneumovax 23)), polio (e.g., Polio (Ipol), DTaP-IPV (Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), rabies (e.g., Rabies (Imovax Rabies, RabAvert)), rotavirus (e.g., RV1 (Rotarix), RV5 (RotaTeq)), rubella (e.g., MMR (M-M-R II), MMRV (ProQuad)), shingles (e.g., ZVL (Zostavax), RZV (Shingrix)), smallpox (e.g., Vaccinia (ACAM2000)), tetanus (e.g., DTaP (Daptacel, Infanrix), Td (Tenivac, generic), DT (generic), Tdap (Adacel, Boostrix), DTaP-IPV

(Kinrix, Quadracel), DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel)), tuberculosis, typhoid fever (e.g., Typhoid Oral (Vivotif), Typhoid Polysaccharide (Typhim Vi)), varicella (e.g., VAR (Varivax), MMRV (ProQuad)), yellow fever (e.g., YF (YF-Vax)) and the like. Suitable vaccines are also listed at the US Centers for Disease Control vaccine list, incorporated herein in its entirety for all purposes (cdc.gov/vaccines/vpd/vaccines-list.html).

[00473] In some embodiments, the vaccine is an inactivated vaccine, a recombinant vaccine, a conjugate vaccine, a subunit vaccine, a polysaccharide vaccine, or a toxoid vaccine. In some embodiments, the vaccine is a yellow fever vaccine. In some embodiments, the subject treated with the vaccine concurrently is treated for a type 2 inflammatory disease with an IL-4R antagonist. In some embodiments, the subject treated with the vaccine concurrently is treated for asthma with an IL-4R antagonist. In some embodiments, the subject suspends treatment with an IL-4R antagonist prior to administration of the vaccine.

[00474] In certain embodiments the subject suspends treatment with the IL-4R antagonist about 1 to about 9 (e.g., about 1, about 1½, about 2, about 2½, about 3, about 3½, about 4, about 4½, about 5, about 5½, about 6, about 6½, about 7, about 7½, about 8, about 8½, about 9, or more) weeks prior to administration of the vaccine. In certain embodiments, the subject suspends treatment with the IL-4R antagonist about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, or about 60 days prior to administration of the vaccine.

[00475] In certain embodiments, the subject resumes treatment with the IL-4R antagonist subsequent to treatment with the vaccine. In certain embodiments, the subject resumes treatment with the IL-4R antagonist 1 to 14 (e.g., about 1, about 1½, about 2, about 2½, about 3, about 3½, about 4, about 4½, about 5, about 5½, about 6, about 6½, about 7, about 7½, about 8, about 8½, about 9, about 9½, about 10, about 10½, about 11, about 11½, about 12, about 12½, about 13, about 13½, about 14, about 14½, or more) weeks subsequent to administration of the vaccine. In certain embodiments, the subject resumes treatment with the IL-4R antagonist about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about

10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, about 60, about 61, about 62, about 63, about 64, about 65, about 66, about 67, about 68, about 69, about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, or about 90 days subsequent to administration of the vaccine.

[00476] A normal IgE level in healthy subjects is typically less than about 100 IU/mL (e.g., as measured using the IMMUNOCAP® assay (Phadia, Inc. Portage, MI)). Thus, methods comprising selecting a subject who exhibits an elevated serum IgE level, which is a serum IgE level greater than about 100 IU/mL, greater than about 150 IU/mL, greater than about 500 IU/mL, greater than about 700 IU/mL, greater than about 1000 IU/mL, greater than about 1500 IU/mL, greater than about 2000 IU/mL, greater than about 2500 IU/mL, greater than about 3000 IU/mL, greater than about 3500 IU/mL, greater than about 4000 IU/mL, greater than about 4500 IU/mL, or greater than about 5000 IU/mL, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist, are provided.

[00477] A normal *Aspergillus fumigatus* (Af)-specific IgE level in healthy subjects is typically less than about 0.10 kU/L (e.g., as measured using the IMMUNOCAP® assay (Phadia, Inc. Portage, MI)). Thus, methods comprising selecting a subject who exhibits an elevated serum IgE level, which is a serum IgE level greater than or equal to about 0.1 kU/L, greater than about 0.35 kU/L, greater than about 0.70 kU/L, greater than about 3.50 kU/L, greater than about 17.50 kU/L, greater than about 50.00 kU/L, or greater than about 100.00 kU/L, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist, are provided.

[00478] In certain embodiments, IgE levels (e.g., total IgE levels and/or *A. Fumigatus*-specific IgE levels) are improved relative to baseline, e.g., an improvement of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100% or more from baseline.

[00479] TARC levels in healthy subjects are in the range of 106 ng/L to 431 ng/L, with a mean of about 239 ng/L. (An exemplary assay system for measuring TARC level is the TARC quantitative ELISA kit offered as Cat. No. DDN00 by R&D Systems, Minneapolis, MN.) Thus, methods comprising selecting a subject who exhibits an elevated TARC level, which is a serum TARC level greater than about 431 ng/L, greater than about 500 ng/L, greater than about 1000 ng/L, greater than about 1500 ng/L, greater than about 2000 ng/L, greater than about 2500 ng/L, greater than about 3000 ng/L, greater than about 3500 ng/L, greater than about 4000 ng/L, greater than about 4500 ng/L, or greater than about 5000 ng/L, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist, are provided. In certain embodiments, TARC levels are improved relative to baseline, e.g., an improvement of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100% or more from baseline.

[00480] Eotaxin-3 belongs to a group of chemokines released by airway epithelial cells, which is up-regulated by the Th2 cytokines IL-4 and IL-13 (Lilly et al 1999, J. Allergy Clin. Immunol. 104: 786-790). Methods comprising administering an IL-4R antagonist to treat patients with elevated levels of eotaxin-3, such as more than about 100 pg/ml, more than about 150 pg/ml, more than about 200 pg/ml, more than about 300 pg/ml, or more than about 350 pg/ml, are provided. Serum eotaxin-3 levels may be measured, for example, by ELISA. In certain embodiments, serum eotaxin-3 levels are improved relative to baseline, e.g., an improvement of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100% or more from baseline.

[00481] Periostin is an extracellular matrix protein involved in the Th2-mediated inflammatory processes. Periostin levels are found to be up-regulated in patients with asthma (Jia et al 2012 J Allergy Clin Immunol. 130:647-654.e10. doi: 10.1016/j.jaci.2012.06.025. Epub 2012 Aug 1). Methods comprising administering an IL-4R antagonist to treat patients with elevated levels of periostin are provided.

[00482] Fractional exhaled NO (FeNO) is a biomarker of bronchial or airway inflammation. FeNO is produced by airway epithelial cells in response to inflammatory cytokines including IL-4 and IL-13 (Alwing et al 1993, Eur. Respir. J. 6: 1368-1370). FeNO levels in healthy

adults range from 2 to 30 parts per billion (ppb). An exemplary assay for measuring FeNO is by using a NIOX instrument by Aerocrine AB, Solna, Sweden. The assessment may be conducted prior to spirometry and following a fast of at least an hour. Methods comprising administering an IL-4R antagonist to patients with elevated levels of exhaled NO (FeNO), such as more than about 30 ppb, more than about 31 ppb, more than about 32 ppb, more than about 33 ppb, more than about 34 ppb, or more than about 35 ppb, are provided.

[00483] Carcinoembryogenic antigen (CEA) (also known as CEA cell adhesion molecule 5 [CEACAM5]) is a tumor marker that is found correlated to non-neoplastic diseases of the lung (Marechal et al. 1988, Anticancer Res. 8: 677-680). CEA levels in serum may be measured by ELISA. Methods comprising administering an IL-4R antagonist to patients with elevated levels of CEA, such as more than about 1.0 ng/ml, more than about 1.5 ng/ml, more than about 2.0 ng/ml, more than about 2.5 ng/ml, more than about 3.0 ng/ml, more than about 4.0 ng/ml, or more than about 5.0 ng/ml, are provided.

[00484] YKL-40 (named for its N-terminal amino acids tyrosine(Y), lysine (K)and leucine (L) and its molecular mass of 40kD) is a chitinase-like protein found to be up regulated and correlated to asthma exacerbation, IgE, and eosinophils (Tang et al 2010 Eur. Respir. J. 35: 757-760). Serum YKL-40 levels are measured by, for example, ELISA. Methods comprising administering an IL-4R antagonist to patients with elevated levels of YKL-40, such as more than about 40 ng/ml, more than about 50 ng/ml, more than about 100 ng/ml, more than about 150 ng/ml, more than about 200 ng/ml, or more than about 250 ng/ml, are provided.

[00485] Periostin is a secreted matricellular protein associated with fibrosis, and its expression is upregulated by recombinant IL-4 and IL-13 in cultured bronchial epithelial cells and bronchial fibroblasts (Jia et al. (2012) J. Allergy Clin. Immunol.130:647). In human asthmatic patients periostin expression levels correlate with reticular basement membrane thickness, an indicator of subepithelial fibrosis. *Id.* Methods comprising administering an IL-4R antagonist to patients with elevated levels of periostin are provided.

[00486] Induced sputum eosinophils and neutrophils are well-established direct markers of airway inflammation (Djukanovic et al. 2002, Eur. Respire. J. 37: 1S-2S). Sputum is induced with inhalation of hypertonic saline solution and processed for cell counts according to methods known in the art, for example, the guidelines of European Respiratory Society.

[00487] In some embodiments, the subjects are stratified into the following groups: a blood eosinophil count (high blood eosinophils) ≥300 cells/μL (HEos) or 300 – 499 cells/μL or ≥500

cells/μL, a blood eosinophil count of 200 to 299 cells/μL (moderate blood eosinophils), or a blood eosinophil count <200 cells/μL (low blood eosinophils), and are administered an anti-IL-4R antibody or antigen binding fragment thereof at a dose or dosing regimen based upon the eosinophil level.

[00488] In some embodiments, the subjects are stratified into the following groups: a blood eosinophil count of ≥300 cells/μL, of 300 – 499 cells/μL, or of ≥500 cells/μL (high blood eosinophils); a blood eosinophil count of ≥150 cells/μL (moderate blood eosinophils); or a blood eosinophil count of < 150 cells/μL (low blood eosinophils), and are administered an anti-IL-4R antibody or antigen binding fragment thereof at a dose or dosing regimen based upon the eosinophil level.

[00489] In some embodiments, a subject has "eosinophilic phenotype" asthma defined by a blood eosinophil count of ≥150 cells/μL, a blood eosinophil count of ≥300 cells/μL, a blood eosinophil count of 300 – 499 cells/μL, or a blood eosinophil count of ≥500 cells/μL, and is administered an anti-IL-4R antibody or antigen binding fragment thereof.

[00490] In some embodiments, the subjects are stratified into the following groups: a total baseline serum IgE concentration of ≥30 IU/mL; a total baseline serum IgE concentration of ≥100 IU/mL; a total baseline serum IgE concentration of ≥200 IU/mL; a total baseline serum IgE concentration of ≥300 IU/mL; a total baseline serum IgE concentration of ≥400 IU/mL; a total baseline serum IgE concentration of ≥500 IU/mL; a total baseline serum IgE concentration of ≥600 IU/mL; a total baseline serum IgE concentration of ≥700 IU/mL (e.g., high serum IgE); a total baseline serum IgE concentration of ≥800 IU/mL; a total baseline serum IgE concentration of ≥900 IU/mL; or a total baseline serum IgE concentration of ≥1000 IU/mL (e.g., very high IgE), and are administered an anti-IL-4R antibody or antigen binding fragment thereof at a dose or dosing regimen based upon the IgG concentration.

[00491] In some embodiments, the subjects are stratified into the following groups: an allergen-specific IgE (e.g., an *A. Fumigatus*-specific) concentration of ≥0.05 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.10 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.15 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.20 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.25 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.30 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.35 kU/L; an allergen-specific (e.g., an *A.*

Fumigatus-specific) IgE concentration of ≥0.40 kU/L; an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.45 kU/L; or an allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration of ≥0.50 kU/L, and are administered an anti-IL-4R antibody or antigen binding fragment thereof at a dose or dosing regimen based upon the allergen-specific (e.g., an *A. Fumigatus*-specific) IgE concentration.

[00492] In some embodiments, the subjects are stratified into the following groups: a baseline FeNO value of ≥20 ppb; a baseline FeNO value of ≥25 ppb; a baseline FeNO value of ≥50 ppb (e.g., high FeNO); a baseline FeNO value of <25 ppb (e.g., low FeNO); a baseline FeNO value of <50 ppb; or a baseline FeNO value of between about 25 ppb and about 50 ppb, and are administered an anti-IL-4R antibody or antigen binding fragment thereof at a dose or dosing regimen based upon the FeNO value.

Methods for Assessing Pharmacodynamic Asthma-Associated Parameters and/or ABPA-Associated Parameters

[00493] Methods for assessing one or more pharmacodynamic asthma-associated parameters and/or one or more pharmacodynamic ABPA-associated parameters a subject in need thereof, caused by administration of a pharmaceutical composition comprising an IL-4R antagonist, are provided. A reduction in the incidence of an asthma exacerbation (as described above) or an improvement in one or more asthma-associated parameters (as described above) may correlate with an improvement in one or more pharmacodynamic asthma-associated parameters; however, such a correlation is not necessarily observed in all cases.

[00494] Examples of "pharmacodynamic asthma-associated parameters" or "pharmacodynamic ABPA-associated parameters" include, for example, the following: (a) biomarker expression levels; (b) serum protein and RNA analysis; (c) induced sputum eosinophils and neutrophil levels; (d) exhaled nitric oxide (FeNO); and (e) blood eosinophil count. An "improvement in a pharmacodynamic asthma-associated parameter" means, for example, a decrease from baseline of one or more biomarkers, such as TARC, eotaxin-3 or IgE, a decrease in sputum eosinophils or neutrophils, FeNO, periostin or blood eosinophil count. As used herein, the term "baseline," with regard to a pharmacodynamic asthma-associated parameter, means the numerical value of the pharmacodynamic asthma-associated parameter for a patient prior to or at the time of administration of a pharmaceutical composition described herein.

[00495] To assess a pharmacodynamic asthma-associated parameter or a pharmacodynamic ABPA-associated parameter, the parameter is quantified at baseline and at a time point after administration of the pharmaceutical composition. For example, a pharmacodynamic asthma-associated parameter or a pharmacodynamic ABPA-associated parameter may be measured at about day 1, about day 2, about day 3, day 4, about day 5, about day 6, about day 7, about day 8, about day 9, about day 10, about day 11, about day 12, about day 14, or at about week 3, about week 4, about week 5, about week 6, about week 7, about week 8, about week 9, about week 10, about week 11, about week 12, about week 13, about week 14, about week 15, about week 16, about week 17, about week 18, about week 19, about week 20, about week 21, about week 22, about week 23, about week 24, or longer, after the initial treatment with the pharmaceutical composition. The difference between the value of the parameter at a particular time point following initiation of treatment and the value of the parameter at baseline is used to establish whether there has been change, such as an "improvement," in the pharmacodynamic asthma-associated parameter (*e.g.*, an increase or decrease, as the case may be, depending on the specific parameter being measured).

[00496] In certain embodiments, administration of an IL-4R antagonist to a patient causes a change, such as a decrease or increase, in expression of a particular biomarker. Asthma-associated biomarkers and/or ABPA-associated biomarkers include, but are not limited to, the following: (a) total IgE; (b) Af-specific IgE; (c) thymus and activation-regulated chemokine (TARC); (d) YKL-40; (e) carcinoembryonic antigen in serum; (f) eotaxin-3 in plasma; (g) periostin in serum; and (h) eosinophil levels in serum. For example, administration of an IL-4R antagonist to an asthma patient and/or an ABPA patient can cause one or more of a decrease in TARC or eotaxin-3 levels, or a decrease in total serum IgE levels. The decrease can be detected at about week 1, about week 2, about week 3, about week 4, about week 5, or longer following administration of the IL-4R antagonist. Biomarker expression can be assayed by methods known in the art. For example, protein levels can be measured by ELISA (Enzyme Linked Immunosorbent Assay). RNA levels can be measured, for example, by reverse transcription coupled to polymerase chain reaction (RT-PCR).

[00497] Biomarker expression, as discussed above, can be assayed by detection of protein or RNA in serum. The serum samples can also be used to monitor additional protein or RNA biomarkers related to response to treatment with an IL-4R antagonist, IL-4/IL-13 signaling, asthma, atopy or eosinophilic diseases (e.g., by measuring soluble IL-4Rα, IL-4, IL-13,

periostin). In some embodiments, RNA samples are used to determine RNA levels (non-genetic analysis), e.g., RNA levels of biomarkers; and in other embodiments, RNA samples are used for transcriptome sequencing (e.g., genetic analysis).

Formulations

[00498] In some embodiments, the antibody or antigen binding fragment thereof is formulated in a composition comprising: i) about 150 mg/mL of antibody or an antigen-binding fragment thereof that specifically binds to IL-4R, ii) about 20 mM histidine, iii) about 12.5 mM acetate, iv) about 5% (w/v) sucrose, v) about 25 mM arginine hydrochloride, vi) about 0.2% (w/v) polysorbate 80, wherein the pH of the formulation is about 5.9, and wherein the viscosity of the formulation is about 8.5 cPoise.

[00499] In alternative embodiments, the antibody or antigen binding fragment thereof is formulated in a composition comprising: i) about 175 mg/mL of antibody or an antigen-binding fragment thereof that specifically binds to IL-4R, ii) about 20 mM histidine, iii) about 12.5 mM acetate, iv) about 5% (w/v) sucrose, v) about 50 mM arginine hydrochloride, and vi) about 0.2% (w/v) polysorbate 80, wherein the pH of the formulation is about 5.9, and wherein the viscosity of the formulation is about 8.5 cPoise.

[00500] In specific embodiments, the antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1 and an LCVR comprising the amino acid sequence of SEQ ID NO: 2.

[00501] Suitable stabilized formulations are also set forth in US 8,945,559, which is incorporated herein by reference in its entirety for all purposes.

[00502] The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of the figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference for all purposes.

[00503] Furthermore, in accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Green & Sambrook, *Molecular Cloning: A Laboratory Manual,* Fourth Edition (2012) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; *DNA Cloning: A Practical Approach,* Volumes I and II (D.N. Glover ed. 1985); *Oligonucleotide Synthesis* (M.J. Gait

ed. 1984); *Nucleic Acid Hybridization* [B.D. Hames & S.J. Higgins eds. (1985)]; *Transcription And Translation* [B.D. Hames & S.J. Higgins, eds. (1984)]; *Animal Cell Culture* [R.I. Freshney, ed. (1986)]; *Immobilized Cells And Enzymes* [IRL Press, (1986)]; B. Perbal, *A Practical Guide To Molecular Cloning* (1984); F.M. Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994).

EXAMPLES

[00504] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions featured in the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[00505] The exemplary IL-4R antagonist used in the following Examples is the human anti-IL-4R antibody named dupilumab (also referred to herein as "mAb1").

EXAMPLE 1: Methods – Allergic Asthma

Study Design

[00506] QUEST was a phase 3, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma. A total of 1902 patients aged ≥12 years were randomized in a 2:2:1:1 ratio to add-on subcutaneous dupilumab 200 mg (loading dose 400 mg) or 300 mg (loading dose 600 mg) every 2 weeks (q2w) or matched-volume placebos for 52 weeks. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

[00507] The effect of dupilumab on key asthma outcome measures in subgroups of patients with and without evidence of allergic asthma at baseline in the QUEST study was compared.

Allergic asthma was defined using the most common criteria in clinical practice in the US for determining eligibility for biologic therapy with omalizumab (i.e., total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline) (US Food and Drug Administration, available at the website: accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf). Because dupilumab treatment is not limited by weight or serum levels of total IgE, no upper threshold for serum total IgE was specified.

[00508] The study enrolled adults and adolescents (aged ≥12 years) with physician-diagnosed asthma for at least 12 months (based on Global Initiative for Asthma (GINA) 2014 guidelines) that were receiving treatment with a medium-to-high dose inhaled glucocorticoid and up to two additional controllers. Eligible patients fulfilled the following criteria: forced expiratory volume in 1 second (FEV_1) before bronchodilator use ≤80% of predicted normal value for adults and ≤90% of predicted normal value for adolescents; FEV_1 reversibility of ≥12% and 200 mL; a score of ≥1.5 on the 5-item Asthma Control Questionnaire (ACQ-5); and worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for 3 days or more. Complete inclusion and exclusion criteria are published at Clinical Trials.gov (LIBERTY ASTHMA QUEST (NCT02414854)), which study is incorporated herein by reference in its entirety.

Patients

[00509] Patients were classified by whether or not they met the criteria for allergic asthma based on the following: a total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline. The perennial allergens used were *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, Oriental cockroach and *Aspergillus fumigatus*. Percutaneous allergy skin testing was not performed. The baseline demographics for the study are summarized in Table 1.

[00510] A total of 1083 patients (57% of the QUEST study ITT population) met the criteria used to define allergic asthma: a total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline. The remaining patients (n=819; 43% of ITT population) did not meet the criteria for allergic asthma. Of these 819 patients, 7% (n=55) had ≥1 positive perennial aeroallergen-specific IgE at baseline but a total serum IgE of <30 IU/mL, 14% (n=114) had ≥1 positive seasonal allergen but tested negative for all perennial allergens,

38% (n=314) had a history of allergic rhinitis but tested negative for all perennial and seasonal allergens, and 41% (n=336) did not have a history of allergic rhinitis and also tested negative for all perennial and seasonal allergens.

[00511] Patients who met the criteria for allergic asthma were generally younger (mean 44.5 years vs. 52.5 years), had asthma onset at an earlier age (mean 21.6 years vs 34.2 years), and a higher proportion had comorbid atopic conditions (96% vs 64%) compared with the subgroup that did not meet the criteria for allergic asthma (Table 1). Furthermore, the allergic asthma subgroup had fewer mean severe exacerbations in the previous year (1.94 vs 2.30) and a higher mean prebronchodilator FEV_1 (1.85 L vs 1.67 L). These patients, compared with patients who did not meet the criteria for allergic asthma, also had higher serum TARC concentrations (median 327 pg/mL vs 277 pg/mL) and similar levels of FeNO (median 26 ppb vs 23 ppb) and blood eosinophil counts (median 250 cells/μL vs 260 cells/μL).

Endpoints

[00512] Endpoints analyzed were annualized severe exacerbation rates, change from baseline in prebronchodilator FEV_1 (L), and change from baseline in ACQ-5 score over the 52-week treatment period in the subgroups of patients that met and did not meet the allergic asthma criteria. Within each subgroup, severe exacerbations during the 52-week treatment period and changes from baseline in prebronchodilator FEV_1 (L) at week 12 were also analyzed in populations of patients with baseline blood eosinophils ≥150 cells/μL, ≥300 cells/μL, and baseline fractional exhaled nitric oxide (FeNO) ≥25 ppb. An additional analysis was performed on the subset of allergic asthma patients with baseline serum total IgE >700 IU/mL, patients for whom omalizumab therapy is not indicated in the US.

[00513] The effect of dupilumab treatment on the following biomarkers of type 2 inflammation was also assessed in the allergic asthma vs. the non-allergic asthma subgroups: serum total IgE levels; FeNO levels; and serum thymus and activation-regulated chemokine (TARC) levels. The effect of dupilumab treatment on serum-specific IgE levels for each of the perennial aeroallergens tested during the 52-week treatment period was also examined in those patients who tested positive (≥0.35 kU/L) at baseline.

Table 1. Baseline demographic and disease characteristics

	Allergic asthma (n=1083)				Did not meet the criteria for allergic asthma (n=819)			
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (n=183)	Dupilumab (n=360)	Placebo (n=179)	Dupilumab (n=361)	Placebo (n=134)	Dupilumab (n=271)	Placebo (n=142)	Dupilumab (n=272)
Age, mean (SD), years	44.0 (16.8)	45.5 (16.0)	44.1 (14.9)	43.9 (15.8)	54.0 (11.8)	51.0 (13.7)	53.2 (12.8)	52.7 (13.6)
Female, n (%)	101 (55.2)	196 (54.4)	114 (63.7)	216 (59.8)	97 (72.4)	191 (70.5)	104 (73.2)	178 (65.4)
BMI, mean (SD), kg/m^2	29.3 (7.35)	28.47 (6.35)	28.78 (6.88)	28.91 (6.91)	30.39 (7.09)	29.82 (6.67)	29.76 (7.02)	29.27 (6.37)
Age at asthma onset, mean (SD), years	20.9 (17.9)	23.0 (19.5)	20.9 (16.9)	20.8 (17.8)	35.9 (17.3)	32.5 (17.3)	35.7 (17.4)	34.2 (18.8)
With ongoing atopic medical condition,* n (%)	176 (96.2)	337 (93.6)	173 (96.6)	354 (98.1)	90 (67.2)	172 (63.5)	93 (65.5)	170 (62.5)
Atopic dermatitis	21 (11.5)	48 (13.3)	32 (17.9)	42 (11.6)	14 (10.4)	13 (4.8)	6 (4.2)	20 (7.4)
Allergic rhinitis	142 (77.6)	265 (73.6)	140 (78.2)	284 (78.7)	79 (59)	156 (57.6)	85 (59.9)	154 (56.6)
Food allergy	21 (11.5)	35 (9.7)	25 (14.0)	32 (8.9)	7 (5.2)	13 (4.8)	11 (7.7)	15 (5.5)
Hives	13 (7.1)	16 (4.4)	9 (5.0)	22 (6.1)	6 (4.5)	14 (5.2)	6 (4.2)	8 (2.9)
Former smokers, n (%)	27 (14.8)	75 (20.8)	38 (21.2)	67 (18.6)	32 (23.9)	51 (18.8)	29 (20.4)	49 (18.0)
Severe asthma exacerbations in the past year, mean (SD), n	1.89 (1.48)	1.98 (2.99)	2.22 (1.99)	1.79 (1.33)	2.32 (1.68)	2.18 (2.16)	2.43 (2.17)	2.33 (2.35)
Prebronchodilator FEV_1, mean (SD), L	1.84 (0.64)	1.85 (0.64)	1.84 (0.61)	1.88 (0.58)	1.66 (0.55)	1.70 (0.58)	1.64 (0.49)	1.66 (0.61)
ACQ-5 score,† mean (SD)	2.69 (0.69)	2.73 (0.82)	2.73 (0.76)	2.74 (0.78)	2.75 (0.77)	2.80 (0.77)	2.81 (0.79)	2.80 (0.74)
Total serum IgE, median (IQR), IU/mL; n	337.0 (147.0–	304.0 (137.0– 835.5); 360	315.0 (142.0–	326.0 (152.0– 762.0); 361	60.0 (24.0–	63.0 (24.0– 135.0); 264	67.0 (24.0–	64.0 (24.0– 150.0); 265

	Allergic asthma (n=1083)				Did not meet the criteria for allergic asthma (n=819)			
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (n=183)	Dupilumab (n=360)	Placebo (n=179)	Dupilumab (n=361)	Placebo (n=134)	Dupilumab (n=271)	Placebo (n=142)	Dupilumab (n=272)
	629.0); 183		763.0); 179		147.0); 131		154.0); 139	
FeNO, median (IQR), ppb; n	27.0 (15.0–50.0); 180	25.0 (16.0–45.0); 358	30.0 (17.5–53.0); 176	24.0 (14.0–42.0); 358	24.0 (14.0–42.0); 131	22.0 (13.0–36.0); 266	22.5 (13.5–39.5); 140	24.0 (14.0–43.0); 269
Serum TARC, median (IQR), pg/mL; n	307.0 (218.0–508.0); 179	351.0 (224.5–478.5); 360	313.0 (206.0–525.0); 179	317.0 (198.0–456.0); 357	284.0 (196.0–421.0); 130	265.0 (187.5–402.5); 264	281.5 (186.0–449.0); 140	276.0 (178.0–386.0); 265
Blood eosinophil count, median (IQR), cells/μL; n	290.0 (150.0–490.0); 183	240.0 (120.0–470.0); 359	260.0 (160.0–440.0); 179	240.0 (140.0–430.0); 361	250.0 (130.0–470.0); 134	250.0 (120.00–460.0); 271	270.0 (120.0–470.0); 141	270.0 (130.0–510.0); 272

Statistical analyses

[00514] Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all randomized patients, separated by subgroups (i.e., with or without total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline). Data were analyzed for each subgroup according to the four assigned treatment groups (dupilumab vs placebo) regardless of whether an intervention was received (Castro et al. (2018) New Engl. J. Med. 378:2486-96). Annualized rates of severe exacerbations over the 52-week treatment period were analyzed using a negative binomial regression model, which included as covariates the assigned intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and number of severe exacerbations in the previous year. All severe exacerbations that occurred during the 52-week treatment period were included regardless of whether the patient remained on treatment.

[00515] The change from baseline in prebronchodilator FEV_1 (L) and ACQ-5 scores during the 52-week treatment period were analyzed using mixed-effect models with repeated measures,

which included as covariates the four assigned intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, visit, visit-by-intervention interaction, corresponding baseline value, and baseline-by-visit interaction. In addition, sex and baseline height were also included as covariates for FEV_1 analyses. If treatment was discontinued, any measurements recorded after discontinuation were included throughout the 52-week treatment period.

[00516] Biomarker analyses were performed in the exposed population, defined as all patients exposed to study medication. For both patient subgroups, differences between dupilumab and matched placebo in the change from baseline in levels of eosinophils and FeNO, considered as key biomarkers of type 2 inflammation, were analyzed using a rank analysis of covariance model including the 4 assigned intervention groups, age, sex, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and corresponding baseline value as covariates. For the analysis of specific IgEs, the analyses were restricted to patients who were positive (≥0.35 kU/L) for the specific IgEs at baseline.

[00517] A nominal P value of <0.05 for the comparison between each dupilumab dose and matched placebo (within each subgroup) was considered statistically significant.

[00518] The residuals from the linear mixed model for the allergic subgroup with baseline serum IgE >700 IU/mL were examined to ensure normally distributed population. The histogram of the residuals as well as the q-q plot are shown in **Fig. 6**.

EXAMPLE 2: Annualized Rate of Severe Asthma Exacerbations – Allergic Asthma

[00519] In the allergic asthma subgroup, dupilumab reduced the adjusted annualized rate of severe exacerbations compared with matched placebo by 36.9% with 200 mg q2w (95% confidence interval (CI) 13.4%-54.0%; nominal P=.004) and 45.5% with 300 mg q2w (95% CI 26.0% to 59.9%; nominal P<.001; **Fig. 1A**). In patients who did not meet the criteria for allergic asthma, the adjusted annualized rate of severe exacerbation events was also significantly reduced by 60.0% with dupilumab 200 mg q2w (95% CI 42.7% to 72.1%; nominal P<.001), and by 44.6% with 300 mg q2w (95% CI 21.5% to 60.9%; nominal P<.001) compared with placebo (**Fig. 1A**). In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, dupilumab 200 mg and 300 mg q2w significantly (all nominal P<.01) reduced the rate of severe exacerbations in patients with baseline blood eosinophils ≥150 cells/μL and ≥300 cells/μL, and in those with baseline FeNO ≥25 ppb. The

magnitude of effect was numerically greater compared with the respective overall subgroup (**Fig. 1B-1D**). Among patients in the allergic asthma subgroup with baseline serum total IgE >700 IU/mL, both dupilumab doses significantly (nominal P<.001) reduced severe exacerbation rates during the 52-week treatment period compared with matched placebo, and the magnitude of effect was numerically greater versus the overall allergic asthma subgroup (**Fig. 1E**).

EXAMPLE 3: Prebronchodilator FEV_1 – Allergic Asthma

[00520] At week 12, dupilumab 200 mg and 300 mg q2w treatment significantly improved prebronchodilator FEV_1 vs placebo by least squares (LS) mean 0.13 L (95% CI 0.05 to 0.20; nominal P<.001) and 0.16 L (95% CI 0.09 to 0.23; nominal P<.001), respectively, in the allergic asthma subgroup, and by 0.14 L (95% CI 0.07 to 0.22; nominal P<.001) and 0.09 L (95% CI 0.01 to 0.16; nominal P=.02) vs placebo, respectively, in those patients who did not meet the criteria (**Fig. 2A**). As observed for severe exacerbations, the magnitude of improvement versus placebo in prebronchodilator FEV_1 at week 12 was equal to or greater than in patients with baseline blood eosinophils ≥150 cells/μL and ≥300 cells/μL and those with baseline FeNO ≥25 ppb than in the respective overall subgroups (all nominal P<.05; **Fig. 2B**). Among patients in the allergic asthma subgroup with baseline serum total IgE >700 IU/mL, dupilumab 300 mg q2w showed a similar magnitude of effect on prebronchodilator FEV_1 at week 12 compared with the overall subgroup (LS mean difference vs placebo 0.12 L (95% CI -0.03 to 0.26; nominal P=.11)), whereas a greater magnitude of effect was observed in patients treated with dupilumab 200 mg q2w (LS mean difference vs placebo 0.27 L (95% CI 0.13 to 0.42); nominal P<.001).

[00521] In both the allergic and non-allergic subgroups, improvements in prebronchodilator FEV_1, were observed as early as the first evaluation at week 2 and persisted through week 52 (**Fig. 2A**).

EXAMPLE 4: Asthma Control – Allergic Asthma

[00522] In the allergic asthma subgroup, the LS mean change from baseline in ACQ-5 score was improved by -1.39 (standard error [SE] 0.05) with a difference vs placebo of -0.28 (95% CI -0.46 to -0.11; nominal P<.01) in dupilumab 200 mg q2w-treated patients and by -1.42 (SE 0.05) with a difference vs placebo of -0.26 (95% CI -0.44 to -0.08; nominal P<.01) at week 24

(**Fig. 3**) in dupilumab 300 mg q2w-treated patients. In the subgroup that did not meet the allergic asthma criteria, the improvement in ACQ-5 score from baseline at week 24 was -1.51 (SE 0.06) with a difference vs. placebo of -0.44 (95% CI -0.65 to -0.22; nominal P<.0001) in dupilumab 200 mg q2w-treated patients, and -1.35 (SE 0.06) with a difference vs placebo of -0.08 (95% CI -0.29 to 0.12; nominal P=.43) observed in patients treated with dupilumab 300 mg q2w (**Fig. 3**).

EXAMPLE 5: Serum total IgE and Aeroallergen-Specific IgE – Allergic Asthma

[00523] In the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, both dupilumab 200 mg and 300 mg q2w dose regimens significantly reduced total serum IgE compared with matched placebo at week 12 (the earliest assessed time point; nominal P<.001; **Fig. 4A**). Reductions in total serum IgE occurred gradually throughout the treatment period (nominal P<.001 vs placebo at all time points).

[00524] In patients with allergic asthma who tested positive at baseline (≥0.35 kU/L) for the respective perennial aeroallergen, significant reductions from baseline in percentage of antigen-specific serum IgE levels were observed over time for each of the 8 perennial aeroallergens that were assessed (**Fig. 5A-H**). These reductions were statistically significant at week 12 (the earliest assessed time point) compared with matched placebo (nominal P<.05) and continued over the 52-week treatment period. Too few patients tested positive for oriental cockroach allergens at baseline to allow for a meaningful analysis.

EXAMPLE 6: FeNO and Serum TARC – Allergic Asthma

[00525] In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, dupilumab 200 mg and 300 mg q2w dose regimens vs. placebo were associated with a marked decrease in FeNO by the first evaluation, after 2 weeks of treatment. The decrease in FeNO was sustained throughout the 52-week treatment period (nominal P<.001 at all time points) (**Fig. 4B**). By week 52, median FeNO values for the dupilumab 200 mg and 300 mg q2w doses in both subgroups were similar to the published median value for healthy volunteers (16 ppb).

[00526] In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, serum TARC concentrations were significantly reduced vs. matched placebo at week 12 (the earliest assessed time point) in patients treated with dupilumab 200 mg or 300 mg q2w. These reductions were sustained throughout the 52-week treatment period (nominal *P*<.001 at all time points) (**Fig. 4C**).

EXAMPLE 7: Discussion – Allergic Asthma

[00527] Dupilumab significantly reduced severe exacerbation rates and improved FEV_1 and asthma control (as measured by ACQ-5) in patients with allergic asthma. Improvements in FEV_1 and asthma control were evident by the first evaluation at week 2, and sustained throughout the 52-week treatment period. Some variability in the magnitude of exacerbation rates and asthma control was observed between the two dupilumab doses vs. their respective placebo. Without intending to be bound by scientific theory, this was likely related to the need to use two different matched-volume placebos. Reductions in severe exacerbation rates and improvements in FEV_1 were greater in patients with higher baseline levels of type 2 inflammatory biomarkers. The proportion of patients who met the criteria for allergic asthma (57%) in this study was significantly lower than patients who reported a history of ≥1 atopic condition in the overall QUEST population (Castro et al. (2018) New Engl. J. Med. 378:2486-96). This difference is primarily due to the exclusion of patients who had a history of allergic rhinitis but did not have evidence of hypersensitivity to aeroallergens, the exclusion of patients who had hypersensitivity only to seasonal allergens (to a lesser extent), and the exclusion of patients with perennial allergen sensitivity but whose total serum IgE was <30 IU/mL. It

should be acknowledged that the timing of specific IgE measurements in this global study was not designed to coincide with peak seasonal allergen exposure in each country/region.

[00528] Dupilumab was shown to be effective in patients with allergic asthma as well as those who did not meet the criteria for allergic asthma. These findings support the critical roles of IL-4 and IL-13 in driving IgE-mediated and non–IgE-mediated type 2 inflammation in asthma. The clinical benefits observed in this study extended to those patients with allergic asthma whose serum total IgE exceeded 700 IU/mL at baseline. This is a clinically relevant subset of allergic asthma patients for whom anti-IgE therapy with omalizumab is not indicated in the US. (See USDA website: accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf, accessed April 2, 2019). This subgroup was included in the analysis because dosing of dupilumab, unlike omalizumab, is not limited by body weight and serum total serum IgE in adolescent and adult patients with uncontrolled, moderate-to-severe asthma.

[00529] Consistent with the mechanism of action of dupilumab in suppressing IgE production, dupilumab significantly reduced serum total IgE and aeroallergen-specific IgE in patients with allergic asthma, and reduced serum total IgE in those who did not meet the criteria for allergic asthma.

[00530] Similarly, dupilumab significantly reduced levels of other type 2 inflammatory biomarkers including FeNO and serum TARC in both patient subgroups. The decline in total and specific IgE is slower relative to other biomarkers such as FeNO. The decline in IgE concentrations did not plateau during the 52-week treatment period.

[00531] In summary, this is the first demonstration of the clinical and pharmacodynamic effects of dual IL-4 and IL-13 inhibition with dupilumab in patients with allergic asthma defined by the presence of total serum IgE $\geq$30 IU/mL and $\geq$1 perennial aeroallergen-specific IgE $\geq$0.35 kU/L at baseline. Dupilumab significantly reduced the rate of severe exacerbations, improved FEV_1, and demonstrated clinically meaningful improvements in asthma control (ACQ-5) during the 52-week treatment period regardless of subgroup, and treatment was generally well tolerated in the overall study population. Markers of type 2 inflammation, including FeNO, total IgE, and TARC, were also significantly reduced with dupilumab treatment in both subgroups. The findings from this study support the roles of IL-4 and IL-13 in IgE- and non–IgE-mediated inflammatory pathways in asthma. IL-4/IL-13 inhibition by dupilumab therapy is beneficial for both allergic and non-allergic asthma phenotypes.

EXAMPLE 8: Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Asthma and Serologic Evidence of Allergic Bronchopulmonary Aspergillosis (ABPA)

[00532] Allergic bronchopulmonary aspergillosis (ABPA) is a severe allergic pulmonary disease caused by hypersensitivity to *Aspergillus fumigatus* (Af) antigen. Not all patients with asthma develop ABPA when exposed to the fungus. However, individuals with a genetic predisposition (HLA-DR2 (HLA-DRB1*1501 and *HLA-DRB1*1503) & HLA-DR5) are susceptible to develop ABPA when exposed to Af antigen. SNPs of IL-4Rα and IL-13 also are involved in genetic susceptibility, and these individuals mount profound type 2 immune response with very high IgE, eosinophilia, elevated FeNO, etc.

[00533] The mainstay of ABPA treatment is systemic steroids. However, not all patients respond to systemic steroids, and the disease may progress to bronchiectasis and fibrosis. Accordingly, there is a high unmet need to treat subjects having ABPA.

Study

[00534] Phase 3 LIBERTY ASTHMA QUEST study (NCT02414854). Patients with serologic evidence of ABPA (baseline serum total IgE >1000IU/mL, positive serum IgE-Af >0.35IU/mL, blood eosinophils >500 cells/μL) receiving add-on dupilumab (200mg or 300mg) every 2 weeks vs. placebo were assessed.

Population

[00535] Of 1902 patients with moderate-to-severe asthma enrolled in QUEST, 30 patients with serologic evidence of ABPA (ABPA-S) were identified (1.6%). The baseline characteristics of these and the remaining intention-to-treat (ITT) population of QUEST (n = 1872) are shown in **Table 2**. At baseline, no meaningful differences in mean age, FEV_1, ACQ-5, or Asthma Quality of Life Questionnaire (AQLQ) were observed in patients with and without ABPA-S, although ABPA-S patients had higher baseline levels of the type 2 biomarkers eosinophils, IgE, and FeNO compared with asthma patients without ABPA-S.

Endpoints/Visit

[00536] The annualized event rate of severe exacerbations (defined as a deterioration of asthma symptoms requiring treatment for ≥3 days with systemic corticosteroids, or hospitalization or an emergency room visit requiring systemic corticosteroids), and the change from baseline in pre-bronchodilator FEV1 (L) and patient-reported 5-item Asthma Control Questionnaire (ACQ-5) score, assessed at baseline and at regular intervals throughout the 52-week treatment period (**Fig. 7**). The LS mean change from baseline in pre-bronchodilator

FEV1 (L) was determined at weeks 24 and 52 in an ITT population (**Fig. 8**). Total (absolute) serum IgE was determined at week 52 in an exposed population (**Fig. 9**). Total (absolute) Af-specific serum IgE was determined at week 52 in an exposed population (**Fig. 10**). Total (absolute) FeNO levels were determined at week 52 in an expose population (**Fig. 11**).

Treatment Arms

[00537] Dupilumab 200 mg q2w, dupilumab 300 mg q2w, and matched placebo, pooled.

Results

[00538] Annualized severe exacerbation rates during the 52-week treatment period were analyzed using negative binomial regression models. LS mean change in FEV_1 from baseline to weeks 24 and 52 was determined using mixed-effect models with repeated measures. Total IgE, IgE-Af, and FeNO at week 52 were assessed using Wilcoxon rank-sum test.

[00539] In patients with ABPA-S, dupilumab significantly reduced the adjusted annualized rate of severe exacerbations compared with placebo by 81.1% (95% confidence interval [CI] 0.052–0.693; P = .01) (**Fig. 12**).

Pre-bronchodilator FEV1

[00540] Numerical improvements in pre-bronchodilator FEV1 were observed in dupilumab-treated versus placebo-treated patients with ABPA-S. Improvements were observed as early as week 2, the first time point at which patients were assessed, and were maintained throughout the 52-week treatment period (**Fig. 13**). Dupilumab versus placebo improved pre-bronchodilator FEV_1 in patients with ABPA-S by a least squares (LS) mean difference of 0.21 L (95% CI −0.18 to 0.60; P = .28) at week 12, and by 0.33 L (−0.02 to 0.68; P = .07) at week 52.

Asthma Control

[00541] In patients with ABPA-S, dupilumab improved ACQ-5 score as early as 2 weeks after treatment commenced, with an LS mean difference of –0.56 (95% CI –1.09 to –0.02; P < .05) versus placebo. This continued over the 52-week treatment period, with numerical improvements in ACQ-5 score at each time point except for weeks 12 and 16. At week 52, dupilumab improved ACQ-5 score by an LS mean difference of –0.20 (–0.86 to 0.46; P = .54) versus placebo (**Fig. 14**).

Serum Total IgE and A. fumigatus-Specific IgE

[00542] Baseline serum total IgE was markedly elevated in ABPA-S patients compared with asthma patients without ABPA-S (median values: 2148–3383 IU/mL vs 159–165 IU/mL).

During treatment, substantial reductions in serum total IgE were observed in dupilumab-treated ABPA-S patients compared with placebo-treated ABPA-S patients from the earliest assessed time point at Week 12 (**Fig. 15A**). These reductions continued to decline progressively throughout the treatment period, and by week 52 the median serum total IgE concentration was 691.5 IU/mL (95% CI 323.0–2617.0) with a median percentage change from baseline of −75.6% (−81.6 to −44.6). In placebo-treated patients, the concentration at week 52 was 1714.0 IU/mL (95% CI 727.0–3048.0) with a median percentage change from baseline of −19.6% (95% CI −56.3 to 102.6; P < .01) (**Fig. 15A**). This was similar to the median percentage change from baseline in serum total IgE observed in the overall ITT population of the QUEST study (dupilumab –69.5% [95% CI –79.0 to –56.9] versus placebo –3.6% [95% CI –22.7 to 20.8]), demonstrating that the median percentage change of serum total IgE from baseline with dupilumab was similar, irrespective of baseline IgE values.

[00543] Dupilumab treatment in patients with ABPA-S also suppressed levels of *A. fumigatus*-specific IgE from a baseline median value of 2.4 IU/mL (95% CI 0.6–11.2) (placebo group baseline median value 3.0 IU/mL [95% CI 0.5–28.8]). These reductions were evident by week 12. After further gradual reductions, the median *A. fumigatus*-specific IgE concentration at week 52 was 0.8 IU/mL (95% CI 0.1–2.6), with a median percentage change from baseline of −74.8% (95% CI −83.5 to −56.2) in dupilumab-treated patients. Corresponding values in placebo-treated patients were 4.6 IU/mL (95% CI 0.6–21.5) and −40.4% (95% CI −71.2 to 208.9; P < .05) (**Fig. 15B**).

Other Type 2 Biomarkers

[00544] In patients with ABPA-S, median baseline concentrations of FeNO were 49.0 ppb (95% CI 24.0–68.0) and 31.0 ppb (95% CI 19.0–63.0) in dupilumab and placebo groups, respectively. Dupilumab decreased FeNO concentration from baseline as early as week 2 of treatment, with a median concentration of 18.0 ppb (95% CI 12.0–26.0) and median percentage change of –50.8% (95% CI –62.5 to –41.9) in the dupilumab group versus 38.0 ppb (95% CI 23.0–50.0), percentage change –5.0% (95% CI –25.4 to 50.0) in the placebo group (P < .01). Reduction in FeNO was sustained up to week 52 with a median of 18.0 ppb (95% CI 12.0–26.0) and median percentage change of –60.0% (95% CI –75.0 to –32.7) in dupilumab-treated patients versus a median 25.0 ppb (95% CI 10.0–56.0) and median percentage change of –24.3% (95% CI –52.2 to 57.1) in placebo-treated patients (P < .05) (**Fig. 16A**). Dupilumab

treatment reduced FeNO to levels similar to the published median value of 16 ppb for healthy volunteers.

[00545] Serum concentrations of TARC were also reduced by dupilumab treatment in patients with ABPA-S. Baseline median serum TARC concentrations were 553.0 pg/mL (95% CI 442.0–1510.0) and 646.0 pg/mL (385.0–894.0) in the dupilumab and placebo groups, respectively. At week 12, dupilumab reduced serum TARC concentrations to a median of 257.0 pg/mL (193.0–438.0) with a median percentage change from baseline of −62.0% (−76.0 to −35.3) versus a median value of 674.0 pg/mL (462.0–900.0) and median percentage change of −10.1% (−17.9 to 15.1) in patients treated with placebo ($P < .01$). These significant reductions were sustained throughout the 52-week treatment period, with a median value 234.0 pg/mL (182.0–336.0) and median percentage change from baseline of −66.1% (−79.6 to −51.0) at week 52 in patients treated with dupilumab versus 580.0 pg/mL (451.0–1020.0) and −17.4% (−35.7 to 25.8) with placebo ($P < .01$) (**Fig. 16B**).

[00546] Treatment with dupilumab also reduced serum concentrations of eotaxin-3 in patients with ABPA-S. Reductions were observed from week 12, with a median value of 24.5 pg/mL (95% CI 18.0–41.7) and median percentage change from baseline of –64.9% (–83.3 to -44.7) in dupilumab-treated patients versus 53.1 pg/mL (23.0–125.0) and –5.4% (–40.6 to 34.8) in the placebo-treated group ($P < .01$). These reductions were sustained up to week 52, with a median value of 23.2 pg/mL (16.1–32.1) and percentage change of –73.1% (–85.0 to –48.6) in the dupilumab group versus 35.7 pg/mL (19.3–78.7) and –29.3% (–80.2 to 27.2) in the placebo group ($P < .05$) (**Fig. 16C**).

[00547] Median blood eosinophil counts at baseline were elevated (825–1075 eosinophils/μL) in ABPA-S patients. At week 52, patients treated with dupilumab had a median blood eosinophil count of 595.0 cells/μL (95% CI 360.0–1160.0) and a median percentage change from baseline of −31.3% (−55.2 to 0) versus 590.0 cells/μL (340.0–1080.0) and −45.5% (−55.5 to 0) in placebo-treated patients ($P = .69$) (**Fig. 16D**).

Safety in Patients with ABPA-S

[00548] The incidence of treatment-emergent adverse events (TEAEs) in patients with ABPA-S was similar irrespective of treatment received (94.4% in combined dupilumab and 100% in combined placebo) (Table 3). The most frequent TEAE, occurring at a higher rate among patients who received dupilumab than in those who received placebo, was upper respiratory tract infection (27.8% of patients receiving dupilumab vs. 25.0% of patients receiving placebo).

Injection-site reactions (Medical Dictionary for Regulatory Activities High Level Term) occurred in 16.7% of dupilumab-treated patients versus 0% of placebo-treated patients. Per the trial protocol, all cases of an eosinophil count > 3000/mm3 during the 52-week intervention period were reported as adverse events. 1 ABPA-S patient (5.6%) treated with dupilumab 200 mg every 2 weeks (q2w) reported moderate eosinophilia. This was a laboratory finding with no associated symptoms, and the patient completed the 52-week treatment period. No patient treated with dupilumab 300 mg or placebo reported eosinophilia. Serious TEAEs were reported in 1 (5.6%) dupilumab-treated patient and 2 (16.7%) placebo-treated patients. No TEAEs leading to death were reported in this population.

Discussion

[00549] In the LIBERTY ASTHMA QUEST study, dupilumab demonstrated beneficial effects in a subgroup of patients identified post hoc as meeting the diagnostic criteria for ABPA-S. Treatment with dupilumab markedly reduced severe exacerbation rates and demonstrated a trend towards improved lung function. Although the improvement in FEV_1 did not meet statistical significance, probably due to the small sample size, the mean change from baseline of 510 mL at week 52 in dupilumab-treated patients was clinically meaningful. FEV_1 improvement occurred rapidly, as early as 2 weeks after treatment commenced, and was sustained throughout the 52-week treatment period. Dupilumab treatment also improved asthma control (ACQ-5 score) in this subgroup of patients with typically difficult to control symptoms.

[00550] Consistent with the pathophysiology of ABPA, this subgroup of patients had evidence of robust type 2 inflammation, with markedly elevated baseline levels of the type 2 biomarkers, including FeNO, blood eosinophils, TARC, serum total IgE, and *A. fumigatus*-specific IgE, compared with asthma patients without serologic evidence of ABPA. Without intending to be bound by scientific theory, the increased FeNO concentration in ABPA patients likely represents concomitant airway inflammation, not driven by the allergic response, further underscoring the utility of FeNO as a marker for type 2 inflammation. Two of the defining diagnostic features of ABPA are very high serum concentrations of total IgE and *A. fumigatus*-specific IgE. Studies have shown that B cells from patients with ABPA have higher sensitivity to IL-4, and spontaneously produce large amounts of IgE, IgG, and IgA antibodies against *A. fumigatus* antigens. Indeed, serum total IgE concentrations are routinely monitored in the management of ABPA to assess disease activity, with reductions to near normal levels

considered a marker of disease remission. Treatment with dupilumab markedly suppressed both total and specific IgE, consistent with the mechanism of action of dupilumab, which, by blocking IL-4 and IL-13 signaling, inhibits isotype switching of B cells and therefore the production of IgE. In addition, biomarkers of type 2 inflammation, both in blood (TARC and eotaxin-3) and in local airways (FeNO), were also rapidly suppressed in dupilumab-treated ABPA-S patients, indicating that through its dual blockade of IL-4 and IL-13, dupilumab was able to rapidly control the underlying pathogenic type 2 inflammation common to ABPA patients.

[00551] Dupilumab was generally well tolerated in ABPA patients, with similar occurrences of TEAEs in dupilumab- and placebo-treated patients. The most frequent TEAE observed in dupilumab-treated patients was upper respiratory tract infection. Unlike the transient eosinophilia that has been observed in patients with asthma, only 1 (5.6%) dupilumab-treated ABPA patient reported eosinophilia during the treatment period in this analysis, despite these patients being hypereosinophilic at baseline (median concentration 925.0 cells/μL). Furthermore, unlike in asthma studies where eosinophil counts at week 52 are unchanged, in this analysis ABPA-S patients showed an overall reduction in median blood eosinophil counts during the 52-week treatment period.

[00552] Clinically, asthma patients with ABPA have poor symptom control and more frequent exacerbations compared with those who do not have ABPA. Unlike asthma, if ABPA diagnosis is delayed or the disease is undertreated, it progresses to lung function decline and fibrotic end-stage lung disease. These data indicate the utility of dupilumab as a novel treatment for patients with ABPA, improving symptoms and lung function by controlling the underlying pathogenic type 2 inflammation.

Table 2. Baseline demographics and clinical characteristics of overall ITT patient population with and without serologic evidence of ABPA.

	With ABPA		Without ABPA	
	Placebo combined q2w (n = 12)	Dupilumab 200/300 mg q2w combined	Placebo combined q2w (n = 626)	Dupilumab 200/300 mg q2w combined (n
Age, mean (SD), y	48.5 (19.4)	40.0 (19.7)	48.2 (15.1)	47.9 (15.3)
Female, n (%)	8 (66.7)	7 (38.9)	408 (65.2)	774 (62.1)
BMI, mean (SD), kg/m^2	30.66 (6.61)	24.04 (4.70)	29.46 (7.11)	29.13 (6.59)

Pre-bronchodilator FEV_1, mean (SD), L	1.59 (0.49)	2.00 (0.68)	1.76 (0.59)	1.78 (0.61)
Pre-bronchodilator FEV_1, mean (SD), % predicted	58.33 (13.98)	60.94 (15.30)	58.39 (13.54)	58.41 (13.49)
FEV_1 reversibility, mean (SD), %	13.64 (8.44)	23.43 (12.73)	25.99 (18.27)	26.60 (23.42)
Exacerbations in past year, mean (SD), n	2.50 (1.68)	2.28 (1.53)	2.19 (1.85)	2.04 (2.30)
High-dose ICS/LABA use, n (%)	10 (83.3)	9 (50.0)	329 (52.6)	631 (50.6)
ACQ-5 score, mean (SD)	2.82 (0.83)	2.70 (0.67)	2.74 (0.75)	2.76 (0.78)
AQLQ global score, mean (SD)	4.36 (0.73)	4.53 (1.05)	4.28 (1.03)	4.29 (1.07)
Blood eosinophil count, cells/μL				
Median (IQR, Q1–Q3)	1075.00 (645.00–1365.00)	825.00 (670.00–1100.00)	260.00 (140.00–450.00)	250.00 (130.00–440.00)
Mean (SD)	1075.00 (438.96)	936.11 (379.60)	367.52 (367.49)	341.61 (350.04)
ECP, ng/mL				
Median (IQR Q1–Q3),	37.00 (21.00–54.00)	38.50 (23.00–59.00)	17.00 (9.00–31.00)	16.00 (8.00–32.00)
Mean (SD)	40.36 (24.27)	56.22 (57.12)	26.33 (29.44)	24.79 (27.76)
FeNO, ppb				
Median (IQR, Q1–Q3)	31.00 (19.50–53.00)	49.00 (24.00–68.00)	26.00 (15.00–47.00)	24.00 (14.00–42.00)
Mean (SD)	39.08 (27.17)	50.33 (30.06)	36.39 (33.81)	33.99 (32.40)
Total IgE, IU/mL				
Median (IQR, Q1–Q3)	2148.00 (1445.50–2734.00)	3383.00 (1480.00–5000.00)	165.00 (59.00–423.00)	159.00 (61.00–432.50)
Mean (SD)	2128.58 (878.16)	3335.67 (1687.73)	388.31 (672.17)	395.65 (651.79)

A. fumigatus-specific IgE, IU/mL				
Median (IQR, Q1–Q3)	2.96 (0.52–28.80)	2.44 (0.64–11.20)	0.05 (0.05–0.05)	0.05 (0.05–0.05)
Mean (SD)	11.58 (17.03)	7.27 (10.34)	0.50 (2.66)	0.36 (1.66)
Periostin, ng/mL				
Median (IQR, Q1–Q3)	88.10 (58.10–115.35)	108.30 (84.70–151.60)	71.00 (54.10–94.30)	69.70 (54.30–92.70)
Mean (SD)	86.72 (33.51)	136.78 (78.09)	80.16 (38.81)	78.34 (37.06)
Eotaxin-3, pg/mL				
Median (IQR, Q1–Q3)	46.50 (29.40–165.00)	66.95 (51.50–153.00)	36.70 (22.80–62.20)	38.50 (25.10–59.20)
Mean (SD)	95.30 (96.82)	123.33 (136.33)	50.72 (72.68)	73.17 (419.78)
TARC, pg/mL				
Median (IQR, Q1–Q3)	646.00 (470.50–891.50)	553.00 (442.00–1510.00)	296.00 (202.00–460.50)	301.00 (197.00–443.00)
Mean (SD)	670.00 (321.41)	1387.35 (2065.80)	382.61 (315.47)	365.31 (284.44)

ABPA, allergic bronchopulmonary aspergillosis; *ACQ-5*, 5-item Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *ECP*, eosinophil cationic protein; *ICS*, inhaled corticosteroids; *IQR*, interquartile range; *ITT*, intention-to-treat; *FeNO*, fractional exhaled nitric oxide; *FEV1*, forced expiratory volume in 1 second; *LABA*, long-acting β2-agonist; *ppb*, parts per billion; *q2w*, every 2 weeks; *SD*, standard deviation; *TARC*, thymus and activation-regulated chemokine.

Table 3. Treatment-emergent adverse events in patients with serologic evidence of ABPA that emerged during the intervention period – safety population

Event, n (%)	Matched placebo combined q2w (n = 12)	Dupilumab 200/300 mg q2w combined (n = 18)
Any TEAE	12 (100)	17 (94.4)
Any serious TEAE[†]	2 (16.7)	1 (5.6)

Any TEAE leading to death	0	0
TEAEs occurring in ≥10% of patients (MedDRA PT)‡		
Upper respiratory tract infection	3 (25.0)	5 (27.8)
Viral upper respiratory tract infection	6 (50.0)	3 (16.7)
Conjunctivitis, allergic	0	2 (11.1)
Arthralgia	2 (16.7)	3 (16.7)
Musculoskeletal chest pain	0	2 (11.1)
Accidental overdose	0	2 (11.1)
Injection-site reactions§	0	3 (16.7)

ABPA, allergic bronchopulmonary aspergillosis; *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, Preferred Term; *q2w*, every 2 weeks; *TEAE*, treatment-emergent adverse event. One ABPA-S patient in the dupilumab-treated group reported eosinophilia versus none in the placebo-treated group. †Serious TEAEs included gastroenteritis and asthma in placebo-treated patients and musculoskeletal chest pain and osteoarthritis in dupilumab-treated patients. ‡Adverse events in this category were reported according to the PTs in the MedDRA, version 20.0, unless otherwise indicated. §Injection-site reaction is a high level term in MedDRA.

EXAMPLE 9: Yellow fever vaccine post-hoc analysis: open–label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study

Study Design

[00553] The LTS12551 (TRAVERSE) study was a multinational, multicenter, single-arm, open-label, extension study to evaluate the long-term safety and tolerability of dupilumab 300 mg q2w in patients with asthma, who completed the treatment and follow-up periods in Study DRI12544, or who completed the treatment period in Studies EFC13579, EFC13691, or PDY14192. DRI12544 (N=776) was a phase 2b, randomized, double-blind, placebo-controlled, dose ranging, parallel group study comparing different doses and regimens of dupilumab subcutaneous (SC) for 24 weeks in adult patients with moderate to severe, uncontrolled asthma. PDY14192 (N=42) was a phase 2a, exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab 300 mg q2w SC for 12 weeks on airway inflammation of adults with uncontrolled persistent asthma. EFC13579 (N=1902) was a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab 200 mg and 300 mg q2w SC for 52 weeks in adult and adolescent patients with uncontrolled persistent asthma. EFC13691 (N=210) was a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab 300 mg q2w SC for 24 weeks in adult and adolescent patients with severe OCS dependent asthma.

[00554] While the study LTS12551 was ongoing, a yellow fever outbreak in Brazil required yellow fever vaccine (YFV) administration for all non-vaccinated individuals located in regions at risk. The sponsor implemented the regional protocol amendment 5 which permitted the administration of YFV (a live attenuated vaccine) to all patients requiring YFV in the outbreak affected area. All affected patients were required to discontinue dupilumab, and vaccination administration could occur after dupilumab discontinuation. Patients were allowed to re-start dupilumab at investigator discretion following demonstration of adequate yellow fever neutralization titers (i.e., plaque-reduction neutralization titers; PRNT). Patients who were not vaccinated were eligible to restart study treatment after the outbreak had subsided.

[00555] All patients continued to be followed until the end-of-study, regardless of whether dupilumab treatment was re-established. For those patients where yellow fever vaccination was planned, samples for drug pharmacokinetics (PK) and immunogenicity assessments, along with pre- and post- vaccination antibody titers, were to be collected both before and 4-6 weeks and might be extended up to 8 weeks after vaccination, upon patient consent. Overall, thirty-seven patients discontinued treatment with dupilumab, and were subsequently vaccinated with YFV. Although patients were allowed to resume dupilumab treatment after demonstration of neutralizing titers at the discretion of the treating physician, none of the patients resumed dupilumab due to delay of the results.

[00556] A post-hoc YFV analysis was conducted to evaluate the humoral immune response, and safety/tolerability of YFV in this subset of 37 patients who participated in the LTS12551 study and received YFV.

Study Objectives

[00557] The objective of this study was to evaluate the humoral immune response, safety and tolerability of YFV, a live attenuated vaccine, in patients with moderate to severe asthma who participated in the study LTS12551 and were treated with dupilumab.

Patients

[00558] A total of 37 patients who participated in the LTS12551 study (an open label asthma study) and received YFV were included in this analysis. Of these, 33 were rolled over from EFC13579 study, and four were rolled over from EFC13691 study. Of the patients enrolled from EFC13579, 11 were previously treated with placebo in the parent study and then received dupilumab in the LTS12551 study (placebo/dupilumab category), and 22 were previously treated with dupilumab in the parent study and continued dupilumab in the LTS12551 study (dupilumab/dupilumab category). Of the patients enrolled from EFC13691 study, three patients were previously treated with placebo in the parent study and then received dupilumab in the LTS12551 study (placebo/dupilumab category) and one was previously treated with dupilumab in the parent study and continued dupilumab in the LTS12551 study (dupilumab/dupilumab category).

Demographics and Other Baseline Characteristics

[00559] The baseline demographic and patient characteristics for the 37 patients who received YFV were generally similar among patients who previously received placebo or dupilumab within each parent study (see Table 4, below). The mean age of the population was 46.5 years with a range of 24 to 68 years, 5 (13.5%) patients were aged ≥ 65 years, and 12 (32.4%) patients were male. The mean (SD) BMI (body mass index) was 30.1 (5.7) kg/m^2.

Table 4. Demographics and patient characteristics as of yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Age (years)					
Number	11	22	3	1	37
Mean (SD)	48.1 (11.3)	44.9 (11.8)	47.0 (17.1)	63.0 (NC)	46.5 (12.0)
Median	51.0	44.5	42.0	63.0	46.0
Min : Max	30 : 65	24 : 68	33 : 66	63 : 63	24 : 68
Age group (years) [n (%)]					
Number	11	22	3	1	37
<18	0	0	0	0	0
18 - 64	9 (81.8%)	20 (90.9%)	2 (66.7%)	1 (100%)	32 (86.5%)
65 - 74	2 (18.2%)	2 (9.1%)	1 (33.3%)	0	5 (13.5%)
75 - 84	0	0	0	0	0
Sex [n (%)]					
Number	11	22	3	1	37
Male	5 (45.5%)	5 (22.7%)	1 (33.3%)	1 (100%)	12 (32.4%)
Female	6 (54.5%)	17 (77.3%)	2 (66.7%)	0	25 (67.6%)
Race [n (%)]					
Number	11	22	3	1	37
Caucasian/White	5 (45.5%)	14 (63.6%)	2 (66.7%)	0	21 (56.8%)
Black/of African descent	3 (27.3%)	5 (22.7%)	1 (33.3%)	1 (100%)	10 (27.0%)
Asian/Oriental	1 (9.1%)	0	0	0	1 (2.7%)
Other	2 (18.2%)	3 (13.6%)	0	0	5 (13.5%)

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Ethnicity [n (%)]					
Number	11	22	3	1	37
Hispanic	7 (63.6%)	17 (77.3%)	0	0	24 (64.9%)
Not Hispanic	4 (36.4%)	5 (22.7%)	3 (100%)	1 (100%)	13 (35.1%)
Height (cm)					
Number	11	22	3	1	37
Mean (SD)	160.09 (8.03)	162.02 (11.44)	161.67 (7.23)	171.00 (NC)	161.66 (10.02)
Median	161.00	158.25	158.00	171.00	159.50
Min : Max	149.0 : 174.0	145.0 : 190.0	157.0 : 170.0	171.0 : 171.0	145.0 : 190.0
Weight (kg)					
Number	11	22	3	1	37
Mean (SD)	80.80 (14.77)	77.32 (16.39)	75.37 (18.38)	88.40 (NC)	78.50 (15.56)
Median	81.00	75.05	81.50	88.40	79.50
Min : Max	56.5 : 110.2	54.5 : 111.0	54.7 : 89.9	88.4 : 88.4	54.5 : 111.0
Weight group (kg) [n (%)]					
Number	11	22	3	1	37
<50	0	0	0	0	0
≥50 - <100	10 (90.9%)	20 (90.9%)	3 (100%)	1 (100%)	34 (91.9%)
≥100	1 (9.1%)	2 (9.1%)	0	0	3 (8.1%)
Body mass index (BMI)(kg/m^2)					
Number	11	22	3	1	37
Mean (SD)	31.52 (5.27)	29.52 (6.21)	28.65 (5.64)	30.23 (NC)	30.06 (5.74)

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Median	31.14	29.31	31.11	30.23	30.23
Min : Max	23.5 : 42.0	21.1 : 49.3	22.2 : 32.6	30.2 : 30.2	21.1 : 49.3
BMI group (kg/m^2) [n (%)]					
Number	11	22	3	1	37
<25	1 (9.1%)	6 (27.3%)	1 (33.3%)	0	8 (21.6%)
≥25 - <30	3 (27.3%)	6 (27.3%)	0	0	9 (24.3%)
≥30	7 (63.6%)	10 (45.5%)	2 (66.7%)	1 (100%)	20 (54.1%)
Region[a] [n(%)]					
Number	11	22	3	1	37
Latin America	11 (100%)	22 (100%)	3 (100%)	1 (100%)	37 (100%)
Territory[b] [n(%)]					
Number	11	22	3	1	37
Rest of World	11 (100%)	22 (100%)	3 (100%)	1 (100%)	37 (100%)

Note: The age, weight, height and BMI summarize the last available asssessments before yellow fever vaccination; and, the other demographics are from the baseline of parent studies. Percentages are calculated using number of patients assessed as denominator.

[a] Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia, Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA

[b] North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine

Medical History

[00560] Patients' comorbidity history is presented in Table 5. The majority of patients (91.9%) had a history of comorbid disease, with allergic rhinitis being the most frequent (86.5%).

Table 5. Comorbidity history of parent study - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Any comorbidity medical history[a] [n (%)]					
Number	11	22	3	1	37
Yes	9 (81.8%)	21 (95.5%)	3 (100%)	1 (100%)	34 (91.9%)
No	2 (18.2%)	1 (4.5%)	0	0	3 (8.1%)
Ongoing condition	9 (81.8%)	21 (95.5%)	3 (100%)	1 (100%)	34 (91.9%)
Atopic dermatitis history [n (%)]					
Number	11	22	3	1	37
Yes	1 (9.1%)	2 (9.1%)	0	0	3 (8.1%)
No	10 (90.9%)	20 (90.9%)	3 (100%)	1 (100%)	34 (91.9%)
Ongoing condition	1 (9.1%)	2 (9.1%)	0	0	3 (8.1%)
Allergic conjunctivitis and allergic rhinitis history [n (%)]					
Number	11	22	3	1	37
Yes	0	0	0	0	0
No	11 (100%)	22 (100%)	3 (100%)	1 (100%)	37 (100%)
Ongoing condition[b]	0	0	0	0	0
Allergic conjunctivitis history [n (%)]					
Number	11	22	3	1	37
Yes	0	0	0	0	0
No	11 (100%)	22 (100%)	3 (100%)	1 (100%)	37 (100%)
Ongoing condition	0	0	0	0	0

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Allergic rhinitis history [n (%)]					
Number	11	22	3	1	37
Yes	7 (63.6%)	21 (95.5%)	3 (100%)	1 (100%)	32 (86.5%)
No	4 (36.4%)	1 (4.5%)	0	0	5 (13.5%)
Ongoing condition	7 (63.6%)	21 (95.5%)	3 (100%)	1 (100%)	32 (86.5%)
Chronic rhinosinusitis [n (%)]					
Number	11	22	3	1	37
Yes	2 (18.2%)	1 (4.5%)	0	0	3 (8.1%)
No	9 (81.8%)	21 (95.5%)	3 (100%)	1 (100%)	34 (91.9%)
Ongoing condition	2 (18.2%)	1 (4.5%)	0	0	3 (8.1%)
Nasal polyposis history [n (%)]					
Number	11	22	3	1	37
Yes	0	1 (4.5%)	1 (33.3%)	0	2 (5.4%)
No	11 (100%)	21 (95.5%)	2 (66.7%)	1 (100%)	35 (94.6%)
Ongoing condition	0	1 (4.5%)	1 (33.3%)	0	2 (5.4%)
Eosinophilic esophagitis history [n (%)]					
Number	11	22	3	1	37
Yes	0	0	0	0	0
No	11 (100%)	22 (100%)	3 (100%)	1 (100%)	37 (100%)
Ongoing condition	0	0	0	0	0
Food allergy history [n (%)]					
Number	11	22	3	1	37
Yes	1 (9.1%)	0	0	0	1 (2.7%)

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
No	10 (90.9%)	22 (100%)	3 (100%)	1 (100%)	36 (97.3%)
Ongoing condition	1 (9.1%)	0	0	0	1 (2.7%)
Hives history [n (%)]					
Number	11	22	3	1	37
Yes	2 (18.2%)	1 (4.5%)	1 (33.3%)	0	4 (10.8%)
No	9 (81.8%)	21 (95.5%)	2 (66.7%)	1 (100%)	33 (89.2%)
Ongoing condition	1 (9.1%)	1 (4.5%)	1 (33.3%)	0	3 (8.1%)

Note: the comorbidity history is from the baseline of the parent studies.

[a] A patient will be considered with comorbidity history or ongoing comorbidity disease if the patient had or has any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, food allergy and hives history.

[b] Both allergic conjunctivitis and allergic rhinitis are ongoing.

Safety Evaluation

Extent of Exposure

[00561] The extent of exposure to investigational medicinal product in the exposed population in LTS12551 before yellow fever vaccination is summarized in Table 6. The mean (SD) duration of treatment with dupilumab in study LTS12551 was of 242.2 (34.4) days and was similar across all patients who received YFV. In patients who rolled over from EFC13579 study, the mean treatment duration was similar between the placebo/dupilumab and the dupilumab/dupilumab categories (255.0 and 230.1 days, respectively). In patients who rolled over from EFC13691 study, the mean treatment duration was similar between the placebo/dupilumab and the dupilumab/dupilumab categories (274.7 and 268.0 days, respectively).

Table 6. Exposure to investigational product before yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Cumulative exposure to study treatment (in year)	7.7	13.9	2.3	0.7	24.5
Average exposure per patient (in year)	0.7	0.6	0.8	0.7	0.7
Duration of study treatment (Day)					
Number	11	22	3	1	37
Mean (SD)	255.0 (29.0)	230.1 (28.2)	274.7 (66.2)	268.0 (NC)	242.2 (34.4)
Median	253.0	224.5	303.0	268.0	237.0
Min : Max	214 : 294	184 : 291	199 : 322	268 : 268	184 : 322

[00562] As shown in Table 7, the time between the last dose of dupilumab and yellow fever vaccination varied from 7 to 51 days, with a mean (SD) of 22.3 (±11.9) days.

Table 7. Summary of duration between the last IMP injection and yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Duration between the last IMP injection and yellow fever vaccination (Day)					
Number	11	22	3	1	37
Mean (SD)	23.8 (11.2)	23.3 (12.7)	11.0 (2.0)	18.0 (NC)	22.3 (11.9)
Median	24.0	23.0	11.0	18.0	18.0
Min : Max	11 : 42	7 : 51	9 : 13	18 : 18	7 : 51

Note: the duration is between the date of last IMP injection before the yellow fever vaccination and the date of yellow fever vaccination.

[00563] As shown in Table 8, the mean (SD) follow-up period for all patients after yellow fever vaccination was 186.6 (±72.3) days and ranged between 98 to 553 days.

Table 8. Summary of follow-up duration post yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

Table 5 - Summary of follow-up duration post yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Duration of post-vaccination follow-up (Day)					
Number	11	22	3	1	37
Mean (SD)	164.4 (33.1)	205.0 (84.3)	146.0 (66.6)	149.0 (NC)	186.6 (72.3)
Median	168.0	209.0	118.0	149.0	185.0
Min : Max	126 : 205	121 : 553	98 : 222	149 : 149	98 : 553

Adverse Events

[00564] A total of 37 patients received YFV. The vaccine was administered 7 to 51 days after the last dose of dupilumab. One out of 37 patients experienced a non-serious adverse event of body pain, feeling of malaise and dizziness after receiving the vaccine, reported as "vaccination complication." This occurred in a 45 year old female patient with a history of atopic dermatitis (AD), allergic conjunctivitis, and chronic rhinosinusitis. The event occurred 7 days after the yellow fever vaccination and resolved within 2 weeks. The remaining 36 patients tolerated the vaccine and did not report any adverse event which could be related to yellow fever vaccination. There were no reports of hypersensitivity reactions to vaccine. None of the patients resumed dupilumab due to delay of the results. There were no deaths, treatment-emergent SAEs (serious adverse events), or other significant AEs (adverse events) reported among the 37 patients who received yellow fever vaccination in LTS12551 study.

Safety Conclusions

[00565] YFV administered 7 to 51 days after discontinuation of dupilumab was well-tolerated in a group of 37 patients with asthma. Thirty-six out of 37 of these patients did not report any adverse reaction to YFV. One patient reported a transitory non-serious adverse event that was fully resolved, and is a common reaction to yellow fever vaccination (Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg. 2002;66(5):533-541.). Therefore, patients with therapeutic or sub therapeutic levels of dupilumab in this trial tolerated YFV.

Pharmacokinetic, Immune Response, and Immunogenicity Evaluations

Humoral Immune Response to Vaccine

[00566] The humoral immune response to YFV was determined using a standard plaque reduction neutralization titer (PRNT) assay (Q Squared solutions, LLC), where the reciprocal dilution in which 50% of the virus was neutralized (PRNT50) was calculated. Post-vaccine neutralization titers were obtained for all 37 patients, and pre- and post-vaccine PRNT titers were obtained for 23 of 37 patients (Table 9). Prior history of yellow fever vaccination and/or infection of the patients was unknown. As shown in Figs. 17A and 17B, of the 23 patients who provided serum pre-vaccination, 13 had PRNT <1:10 (defined as 'seronegative'), while the other 10 patients had titers in the 1:10 to 1:160 range (defined as 'seropositive').

[00567] All 37 patients showed seroprotective titers post-vaccination, defined as a PRNT titer >1:10, with an average post-vaccination titer of 1:7699 (± 10951 SD; median 2560, range 80 to 40960). As shown in Fig. 17A and 17B, while two of 23 patients had pre-vaccination titers that were not boosted post-vaccination, both patients already had seroprotective titers before YFV. Thus, all 37 vaccinated patients had seroprotective yellow fever neutralization titers post vaccination, including 13 patients with pre- and post-vaccine titers who demonstrated seroconversion.

Table 9. PK sample collection and vaccinated patients with PRNT titers

	N with post-vaccine seroprotective titer (>1:10)	N with pre-vaccine sample on the same day of YF Vaccine	N with pre-vaccine sample 1-25 days before YF vaccination	N without pre-vaccine sample
PK population (N=37)	37	19	16	2
ADA population (N=37)	37	18	16	3
Pre- and post- YF vaccine PRNT titers obtained (N=23*)	23	15	18	2
Post-YF vaccine PRNT titer only (N=14)	14	4	8	2

*13 seronegative at baseline

Pharmacokinetics and Immunogenicity Evaluations

[00568] Pre-vaccination and post-vaccination PK and ADA (anti-drug antibody) samples were collected. Functional dupilumab concentrations in serum were measured pre-vaccination and post- vaccination. Among the 37 patients, 35 and 34 patients had pre-vaccination PK samples and pre-vaccination ADA samples collected, respectively. All 37 patients had a post-vaccination PK and ADA sample collected. Nineteen patients had PK samples obtained on the day of vaccination. Sixteen patients had pre-vaccine PK obtained before the YFV administration (Table 9).

[00569] The duration between the last dupilumab dose to administration of yellow fever vaccination, duration between pre-vaccination PK sampling and administration of yellow fever vaccination, as well as duration between administration of yellow fever vaccination and post-vaccination PK sampling are summarized in Table 10.

Dupilumab concentration before and after yellow fever vaccination

[00570] At the time of yellow fever vaccination, patients had been exposed to dupilumab 300 mg q2w in LTS12551 for at least 24 weeks, and reached steady state with mean trough concentration of 73.3 mg/L at week 24. On average, the duration between the last dupilumab dose to administration of YFV was approximately 3 weeks (median duration of 18 days, Table 7). Pre-vaccination PK samples were collected in 35/37 patients. The mean concentration of all pre-vaccination PK samples was 59.5 mg/L with the limitation that not all PK samples were collected at the same day of yellow fever vaccination administration (Table 11). Pre-vaccination PK samples were collected on the same day as YFV administration in 19 patients. The mean dupilumab concentration in serum in those patients was 72.5 mg/L, which was similar to the mean steady state trough dupilumab concentration observed in patients treated with dupilumab 300 mg q2w in clinical studies of dupilumab in asthma and AD. For 16 patients, pre-vaccination PK samples were collected 1 to 25 days before YFV administration, and for these patients, the mean concentration was 44.0 mg/L.

[00571] Post-vaccine PK samples were collected approximately 5 weeks (ranged 28-54 days) after YFV administration and approximately 8 weeks (39 to 79 days) after the last dupilumab dose (Table 10). The observed mean concentration of post-vaccination PK samples was 13.7 mg/L (N=37), in the range of expected dupilumab concentrations with an approximately 8 weeks washout period after the last steady-state dose of 300 mg q2w (Table 11).

Table 10. Summary of PK serum sample time before and after yellow fever vaccination - PK population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Last visit before yellow fever vaccination					
Duration between the last IMP injection and PK sampling (day)					
Number	11	20	3	1	35
Mean (SD)	20.18 (8.65)	18.50 (8.90)	11.00 (2.00)	18.00 (NC)	18.37 (8.51)
Median	17.00	16.00	11.00	18.00	15.00
Min : Max	11.0 : 35.0	7.0 : 44.0	9.0 : 13.0	18.0 : 18.0	7.0 : 44.0
Duration between PK sampling and yellow fever vaccination (day)					
Number	11	20	3	1	35
Mean (SD)	3.64 (4.80)	5.45 (8.04)	0.00 (0.00)	0.00 (NC)	4.26 (6.78)
Median	3.00	0.50	0.00	0.00	0.00
Min : Max	0.0 : 15.0	0.0 : 25.0	0.0 : 0.0	0.0 : 0.0	0.0 : 25.0
First visit after yellow fever vaccination					
Duration between the last IMP injection and PK sampling (day)					
Number	11	22	3	1	37
Mean (SD)	58.36 (8.55)	57.95 (9.33)	50.00 (2.65)	60.00 (NC)	57.49 (8.75)
Median	56.00	55.50	49.00	60.00	55.00
Min : Max	46.0 : 74.0	39.0 : 79.0	48.0 : 53.0	60.0 : 60.0	39.0 : 79.0

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Duration between PK sampling and yellow fever vaccination (day)					
Number	11	22	3	1	37
Mean (SD)	34.55 (5.68)	34.64 (7.12)	39.00 (1.00)	42.00 (NC)	35.16 (6.43)
Median	33.00	34.00	39.00	42.00	35.00
Min : Max	28.0 : 44.0	28.0 : 54.0	38.0 : 40.0	42.0 : 42.0	28.0 : 54.0
Follow-up visit					
Duration between the last IMP injection and PK sampling (day)					
Number	11	22	3	1	37
Mean (SD)	184.36 (28.66)	203.36 (29.21)	157.00 (66.30)	167.00 (NC)	192.97 (34.43)
Median	196.00	208.50	127.00	167.00	197.00
Min : Max	139.0 : 219.0	145.0 : 259.0	111.0 : 233.0	167.0 : 167.0	111.0 : 259.0
Duration between PK sampling and yellow fever vaccination (day)					
Number	11	22	3	1	37
Mean (SD)	160.55 (29.11)	180.05 (30.86)	146.00 (66.57)	149.00 (NC)	170.65 (34.44)
Median	168.00	184.00	118.00	149.00	175.00
Min : Max	126.0 : 204.0	121.0 : 241.0	98.0 : 222.0	149.0 : 149.0	98.0 : 241.0

Note: the PK sampling time on the visit before or after yellow fever vaccination were for the unscheduled serum samples particularly collected for the yellow fever vaccination.
When concentration values are below the lower limit of quantification (LLOQ) of 78 ng/mL, one-half (39 ng/mL) of the LLOQ is used in the statistical summary.

Table 11. Summary of serum concentrations of dupilumab before and after yellow fever vaccination - PK population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
PK CONCENTRATION (ng/mL)					
Baseline of the parent study					
Number	0	20	0	1	21
Mean (SD)		18.35 (82.06)		0.00 (NC)	17.48 (80.09)
SEM		18.350		NC	17.476
CV		447.214		NC	458.258
Geometric Mean		0.00		0.00	0.00
Median		0.00		0.00	0.00
Min : Max		0.0 : 367.0		0.0 : 0.0	0.0 : 367.0
Last visit before yellow fever vaccination					
Number	11	20	3	1	35
Mean (SD)	56400.82 (40990.68)	57981.95 (35838.83)	55600.00 (33246.35)	45200.00 (NC)	59487.09 (36709.06)
SEM	12359.155	8013.806	19194.791	NC	6204.963
CV	72.677	61.816	38.839	NC	61.709
Geometric Mean	23339.51	35832.85	81612.15	45200.00	33828.82
Median	59200.00	53850.00	74400.00	45200.00	57700.00
Min : Max	39.0 : 112000.0	39.0 : 127000.0	59400.0 : 123000.0	45200.0 : 45200.0	39.0 : 127000.0

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
First visit after yellow fever vaccination					
Number	11	22	3	1	37
Mean (SD)	14472.45 (13841.78)	11802.68 (13963.92)	26896.67 (29653.68)	6810.00 (NC)	13685.30 (15298.02)
SEM	4173.453	2977.117	17120.563	NC	2514.968
CV	95.642	118.311	110.250	NC	111.785
Geometric Mean	3027.38	2428.14	17058.22	6810.00	3122.53
Median	14400.00	7430.00	14100.00	6810.00	7780.00
Min : Max	39.0 : 36700.0	39.0 : 50100.0	5790.0 : 60800.0	6810.0 : 6810.0	39.0 : 60800.0
Follow-up visit					
Number	11	22	3	1	37
Mean (SD)	39.00 (0.00)	39.00 (0.00)	39.00 (0.00)	39.00 (NC)	39.00 (0.00)
SEM	0.000	0.000	0.000	NC	0.000
CV	0.000	0.000	0.000	NC	0.000
Geometric Mean	39.00	39.00	39.00	39.00	39.00
Median	39.00	39.00	39.00	39.00	39.00
Min : Max	39.0 : 39.0	39.0 : 39.0	39.0 : 39.0	39.0 : 39.0	39.0 : 39.0

SEM: standard error of the mean, CV: coefficient of variation

Note: Serum samples are collected prior to the administration of IMP.

The PK concentrations on the visit before or after yellow fever vaccination were from the unscheduled serum samples particularly collected for the yellow fever vaccination.

When concentration values are below the lower limit of quantification (LLOQ) of 78 ng/mL, one-half (39 ng/mL) of the LLOQ is used in the statistical summary.

[00572] Pre-vaccination PK samples were collected on the same day of YFV administration in 15 out of 23 patients. The mean concentration of dupilumab in these 15 patients was 76.4 mg/L. Thirteen out of 15 patients had dupilumab concentrations higher than the mean trough concentration of 37.4 mg/L. Concentrations in serum above this level were assumed to be therapeutic and consistent with saturating levels of IL-4Rα blockade since 37.4 mg/L was the steady state mean trough concentration observed for asthma patients at 200 mg q2w in the parent Phase 3 study (EFC13579).

[00573] All 13 patients with serum dupilumab concentrations > 37.4 mg/L had seroprotective PRNT titers after YFV. Twelve of these patients demonstrated an increase in post-vaccination titers, while one of these 13 patients did not demonstrate an increase in titer, but was already within a seroprotective threshold at baseline. The fold change in PRNT titer level for these patients is demonstrated in Fig. 18. The neutralization titer of all 13 patients post-vaccination ranged from 1:80 to 1:40960 which is comparable to the post-vaccination titers in the patients who had dupilumab concentrations <37.4 mg/L (1:160 to 1:40960).

[00574] In summary, in this subset of 23 patients with pre- and post-vaccine PK and PRNT titers, there did not appear to be any relation between serum dupilumab levels and PRNT titer.

ADA incidence and titer before and after yellow fever vaccination

[00575] The ADA incidence before and after YFV administration and ADA titer category observed in patients is summarized in table 12. Positive ADA assay responses were observed in three patients both before and after the yellow fever vaccination. Among patients with a positive ADA assay response, one patient had low ADA titers (<1000), and two patients had high ADA titers (>10000). The number of patients in each ADA titer category did not change before and after yellow fever vaccination, suggesting no apparent impact of yellow fever vaccination on ADA responses. At the end of study, in addition to three patients who were positive before and after the yellow fever vaccination, positive ADA assay response was observed in one more patient in the follow up visit. Thus, among the total of four patients with positive ADA assay responses, two patients had low ADA titers (<1000), and two patients had high ADA titers (>10 000) in the follow up visit.

Table 12. Summary of ADA titer before and after yellow fever vaccination - ADA population - Patients with yellow fever vaccination in LTS12551

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Baseline of the parent study					
Number	11	21	3	1	36
Patients with ADA negative sample	11/11 (100%)	20/21 (95.2%)	3/3 (100%)	1/1 (100%)	35/36 (97.2%)
Patients with ADA positive sample	0/11	1/21 (4.8%)	0/3	0/1	1/36 (2.8%)
Titer					
Number	0	1	0	0	1
Median		30.0			30.0
Q1 : Q3		30.0 : 30.0			30.0 : 30.0
Min : Max		30 : 30			30 : 30
Low (<1000)	0/11	1/21 (4.8%)	0/3	0/1	1/36 (2.8%)
Moderate (1000-10000)	0/11	0/21	0/3	0/1	0/36
High (>10000)	0/11	0/21	0/3	0/1	0/36
Last visit before yellow fever vaccination					
Number	11	19	3	1	34
Patients with ADA negative sample	10/11 (90.9%)	17/19 (89.5%)	3/3 (100%)	1/1 (100%)	31/34 (91.2%)
Patients with ADA positive sample	1/11 (9.1%)	2/19 (10.5%)	0/3	0/1	3/34 (8.8%)
Titer					
Number	1	2	0	0	3
	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Median	61440.0	245880.0			61440.0
Q1 : Q3	61440.0 : 61440.0	240.0 : 491520.0			240.0 : 491520.0
Min : Max	61440 : 61440	240 : 491520			240 : 491520
Low (<1000)	0/11	1/19 (5.3%)	0/3	0/1	1/34 (2.9%)
Moderate (1000-10000)	0/11	0/19	0/3	0/1	0/34
High (>10000)	1/11 (9.1%)	1/19 (5.3%)	0/3	0/1	2/34 (5.9%)
First visit after yellow fever vaccination					
Number	11	22	3	1	37
Patients with ADA negative sample	10/11 (90.9%)	20/22 (90.9%)	3/3 (100%)	1/1 (100%)	34/37 (91.9%)
Patients with ADA positive sample	1/11 (9.1%)	2/22 (9.1%)	0/3	0/1	3/37 (8.1%)
Titer					
Number	1	2	0	0	3
Median	61440.0	123000.0			61440.0
Q1 : Q3	61440.0 : 61440.0	240.0 : 245760.0			240.0 : 245760.0
Min : Max	61440 : 61440	240 : 245760			240 : 245760
Low (<1000)	0/11	1/22 (4.5%)	0/3	0/1	1/37 (2.7%)
Moderate (1000-10000)	0/11	0/22	0/3	0/1	0/37
High (>10000)	1/11 (9.1%)	1/22 (4.5%)	0/3	0/1	2/37 (5.4%)
Follow-up visit					
Number	11	22	3	1	37
Patients with ADA negative sample	10/11 (90.9%)	19/22 (86.4%)	3/3 (100%)	1/1 (100%)	33/37 (89.2%)

	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Patients with ADA positive sample	1/11 (9.1%)	3/22 (13.6%)	0/3	0/1	4/37 (10.8%)
Titer					
Number	1	3	0	0	4
Median	15360.0	960.0			8160.0
Q1 : Q3	15360.0 : 15360.0	60.0 : 15360.0			510.0 : 15360.0
Min : Max	15360 : 15360	60 : 15360			60 : 15360
Low (<1000)	0/11	2/22 (9.1%)	0/3	0/1	2/37 (5.4%)
Moderate (1000-10000)	0/11	0/22	0/3	0/1	0/37
High (>10000)	1/11 (9.1%)	1/22 (4.5%)	0/3	0/1	2/37 (5.4%)

Note: Percentages are calculated using the denominator as the number of patients in the ADA population with reportable ADA status at the visit and with yellow fever vaccination in LTS12551 study.
The ADA titers on the visit before or after yellow fever vaccination were from the unscheduled ADA samples particularly collected for the yellow fever vaccination.

Conclusions based on Immune Response and Dupilumab PK

[00576] Immune response and dupilumab PK data suggest that therapeutic serum levels of dupilumab do not inhibit the protective immune responses to yellow fever vaccination, a live attenuated vaccine. Since dupilumab was not restarted after vaccination, serum levels continued to decline until the post-vaccination titer assessment.

Impact of Immune Response to Vaccine on Efficacy of Dupilumab

[00577] The potential impact of yellow fever vaccination on dupilumab efficacy was evaluated by examining the change in FEV_1 before and after vaccine administration. All patients that discontinued treatment with dupilumab due to yellow fever vaccination had been exposed to dupilumab in LTS12551 for an average 0.7 years and achieved a stable improvement in lung function prior to discontinuation of dupilumab (Table 6). The FEV_1 was stable between the visit before the YFV was administered and at the first visit after YFV (Fig. 19, Fig. 20). The mean (SD) FEV_1 was 2.08 (0.83) L and 1.98 (0.79) L, respectively (Table 13). In general, based on observed data in EFC13579 and DRI12544, FEV_1 levels may be anticipated to fall around 12 weeks after discontinuation of dupilumab.

Table 13. Analysis of change from baseline in FEV_1 (L) before and after yellow fever vaccination - Exposed population - Patients with yellow fever vaccination in LTS12551 study

	Patients from EFC13579 study		Patients from EFC13691 study		
FEV1 (L)	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Baseline of the parent study					
Value					
Number	11	22	3	1	37
Mean (SD)	1.70 (0.28)	1.86 (0.59)	1.61 (0.31)	1.61 (NC)	1.79 (0.49)
Median	1.71	1.80	1.54	1.61	1.71
Q1 : Q3	1.52 : 1.87	1.39 : 2.28	1.34 : 1.95	1.61 : 1.61	1.47 : 2.08
Min : Max	1.3 : 2.2	1.0 : 3.5	1.3 : 2.0	1.6 : 1.6	1.0 : 3.5
Last visit before yellow fever vaccination					
Value					
Number	11	22	3	1	37
Mean (SD)	1.85 (0.54)	2.20 (0.99)	2.11 (0.43)	1.91 (NC)	2.08 (0.83)
Median	1.72	1.96	1.92	1.91	1.92
Q1 : Q3	1.42 : 2.40	1.62 : 2.53	1.81 : 2.69	1.91 : 1.91	1.58 : 2.42
Min : Max	1.2 : 2.9	1.0 : 4.7	1.8 : 2.6	1.9 : 1.9	1.0 : 4.7
Change from baseline					
Number	11	22	3	1	37
Mean (SD)	0.15 (0.45)	0.34 (0.65)	0.50 (0.71)	0.30 (NC)	0.29 (0.58)
Median	0.01	0.17	0.38	0.30	0.15
Q1 : Q3	-0.13 : 0.29	-0.11 : 0.52	-0.14 : 1.26	0.30 : 0.30	-0.11 : 0.49
Min : Max	-0.3 : 1.3	-0.3 : 2.7	-0.1 : 1.3	0.3 : 0.3	-0.3 : 2.7

FEV1 (L)	Patients from EFC13579 study		Patients from EFC13691 study		
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	All (N=37)
Percent change from baseline					
Number	11	22	3	1	37
Mean (SD)	8.74 (27.24)	16.92 (32.36)	37.18 (51.75)	18.63 (NC)	16.18 (31.94)
Median	0.58	12.90	24.68	18.63	8.40
Q1 : Q3	-7.05 : 16.96	-5.00 : 26.78	-7.18 : 94.03	18.63 : 18.63	-6.25 : 24.68
Min : Max	-15.5 : 79.6	-23.1 : 136.2	-7.2 : 94.0	18.6 : 18.6	-23.1 : 136.2
First visit after yellow fever vaccination					
Value					
Number	11	22	3	1	37
Mean (SD)	1.79 (0.56)	2.07 (0.94)	1.90 (0.29)	2.18 (NC)	1.98 (0.79)
Median	1.68	1.92	1.89	2.18	1.89
Q1 : Q3	1.34 : 2.41	1.38 : 2.58	1.62 : 2.20	2.18 : 2.18	1.53 : 2.26
Min : Max	0.9 : 2.6	0.9 : 4.5	1.6 : 2.2	2.2 : 2.2	0.9 : 4.5
Change from baseline					
Number	11	22	3	1	37
Mean (SD)	0.10 (0.43)	0.21 (0.61)	0.29 (0.50)	0.57 (NC)	0.19 (0.54)
Median	0.20	0.15	0.08	0.57	0.15
Q1 : Q3	-0.35 : 0.25	-0.14 : 0.42	-0.06 : 0.86	0.57 : 0.57	-0.14 : 0.42
Min : Max	-0.4 : 1.0	-0.4 : 2.5	-0.1 : 0.9	0.6 : 0.6	-0.4 : 2.5
Percent change from baseline					
Number	11	22	3	1	37
Mean (SD)	5.08 (26.72)	9.53 (31.24)	22.10 (36.68)	35.40 (NC)	9.93 (29.66)
Median	10.70	10.51	5.19	35.40	10.70

FEV1 (L)	Patients from EFC13579 study		Patients from EFC13691 study		All
	Placebo/Dupilumab (N=11)	Dupilumab/Dupilumab (N=22)	Placebo/Dupilumab (N=3)	Dupilumab/Dupilumab (N=1)	(N=37)
Q1 : Q3	-21.64 : 18.32	-8.77 : 19.38	-3.08 : 64.18	35.40 : 35.40	-8.77 : 19.38
Min : Max	-27.3 : 59.9	-27.3 : 126.6	-3.1 : 64.2	35.4 : 35.4	-27.3 : 126.6
Follow-up visit					
Value					
Number	11	22	3	1	37
Mean (SD)	1.73 (0.45)	2.07 (0.88)	1.68 (0.38)	1.51 (NC)	1.92 (0.74)
Median	1.51	1.77	1.76	1.51	1.69
Q1 : Q3	1.31 : 2.21	1.39 : 2.39	1.27 : 2.01	1.51 : 1.51	1.39 : 2.14
Min : Max	1.3 : 2.4	1.1 : 4.4	1.3 : 2.0	1.5 : 1.5	1.1 : 4.4
Change from baseline					
Number	11	22	3	1	37
Mean (SD)	0.03 (0.40)	0.21 (0.61)	0.07 (0.52)	-0.10 (NC)	0.14 (0.53)
Median	0.00	0.12	-0.19	-0.10	0.03
Q1 : Q3	-0.37 : 0.28	-0.10 : 0.39	-0.27 : 0.67	-0.10 : -0.10	-0.17 : 0.31
Min : Max	-0.5 : 0.8	-0.7 : 2.4	-0.3 : 0.7	-0.1 : -0.1	-0.7 : 2.4
Percent change from baseline					
Number	11	22	3	1	37
Mean (SD)	2.34 (23.48)	11.20 (30.22)	7.57 (36.95)	-6.21 (NC)	7.80 (27.99)
Median	0.00	6.75	-9.74	-6.21	1.92
Q1 : Q3	-19.79 : 15.27	-6.03 : 17.48	-17.53 : 50.00	-6.21 : -6.21	-7.46 : 16.81
Min : Max	-23.7 : 49.4	-29.0 : 122.6	-17.5 : 50.0	-6.2 : -6.2	-29.0 : 122.6

Conclusions

[00578] In response to a regional yellow fever outbreak, 37 patients enrolled in LTS12551 discontinued dupilumab treatment and subsequently received YFV. Dupilumab did not decrease efficacy of a live-attenuated yellow fever virus vaccine. All 37 patients who were provided YFV demonstrated post-vaccine yellow fever virus antibody titers consistent with seroprotection. Pre- and post-vaccination neutralizing titers were obtained for 23 patients, with 15 of these patients having pre-vaccination serum obtained on the day of YFV administration. Of these 23 patients, 10 had pre-vaccine PRNT titers > 1:10, indicating potential prior exposure to virus or previous vaccination. The remaining 13 patients had PRNT titers < 1:10 (i.e., "seronegative"), suggesting no prior exposure or waning antibody response over time. Mean post-vaccination titer levels obtained between 28-42 days after vaccination were 1:7699 (± 10951 SD; median 2560, range 80 to 40960), with all but 2 patients showing increased titers post-vaccination, and all 23 patients showing neutralizing titers at levels consistent with seroprotection against yellow fever.

[00579] Therapeutic levels of dupilumab did not appear to inhibit seroprotective immune responses to dupilumab. In 15 patients who had both pre- and post-vaccine yellow fever titers, PK measurements were also obtained on the same day as vaccination. At the time of vaccination, 13

out of 15 patients had concentrations of dupilumab in serum higher than the mean concentration of 37.4 mg/L, a serum level considered sufficient to saturate the IL-4Rα in asthma (based on the indicated 200 mg q2w regimen). All 13 patients demonstrated seroprotective immune responses. While 12 of the 13 patients demonstrated an increase in neutralization titers post-vaccination, one patient's serum sample had the same neutralization titer pre- and post-vaccination. These data are supportive that therapeutic dupilumab concentrations in serum at the time of vaccination did not inhibit seroprotective immune responses, and all but one of these 13 patients showed a boosting of neutralizing antibody titers to yellow fever.

[00580] YFV was well-tolerated for all exposed patients. Of the 37 patients that received YFV, one patient reported a non-serious adverse event reported as a "vaccination complication" (i.e., body pain, feeling of malaise and dizziness), which is a common reaction to YFV, and has been reported in up to 30% of patients (Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg. 2002;66(5):533-541.). The patient's symptoms were reported as non-serious, and the patient was fully recovered within 2 weeks.

[00581] Yellow fever virus vaccination did not appear to impact dupilumab efficacy. All patients that were vaccinated had achieved a stable improvement in their lung function as measured by FEV_1. The FEV_1 remained stable both before and after yellow fever virus vaccination.

[00582] Taken as a whole, these data support the overall safety and tolerability of yellow fever vaccination in asthma patients who recently discontinued dupilumab. Without intending to be bound by scientific theory, the similar increase in neutralizing antibody titers post-vaccination between asthma patients who had therapeutic serum levels of dupilumab and those that had sub-therapeutic serum levels indicate suggest that, in the setting of dupilumab, immunocompetence of the humoral arm of the adaptive immune system is maintained to a live attenuated YFV.

CLAIMS

What is claimed is:

1. A method for treating a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

2. The method of claim 1, wherein the subject has a baseline blood eosinophil count of at least about 150 cells/μl.

3. The method of claim 1, wherein the subject has a baseline blood eosinophil count of at least about 300 cells/μl.

4. The method of claim 1, wherein the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 20 ppb.

5. The method of claim 1, wherein the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

6. The method of claim 5, wherein the allergen is selected from the group consisting of animal, fungus and plant.

7. The method of claim 6, wherein animal is selected from the group consisting of dust mite, cockroach, cat and dog.

8. The method of claim 7, wherein the dust mite is *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*.

9. The method of claim 6, wherein the fungus is selected from the group consisting of *Alternaria alternata*, *Cladosporium herbarum* and *Aspergillus fumigatus*.

10. The method of claim 5, wherein the allergen is selected from the group consisting of cat dander, dog dander, German cockroach and Oriental cockroach.

11. The method of claim 1, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

12. The method of claim 11, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

13. The method of claim 11, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

14. The method of claim 11, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

15. The method of claim 11, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

16. The method of claim 11, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

17. The method of claim 11, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

18. The method of claim 11, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

19. The method of claim 11, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

20. The method of claim 1, wherein treatment results in a reduction in annualized severe asthma exacerbations.

21. The method of claim 1, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

22. The method of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

23. The method of claim 1, wherein the antibody is dupilumab.

24. The method of claim 1, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

25. A method for treating a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil level of at least about 300 cells/μl.

26. The method of claim 25, wherein the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 20 ppb.

27. The method of claim 25, wherein the subject has a total serum IgE level of at least about 700 IU/mL.

28. The method of claim 25, wherein the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

29. The method of claim 28, wherein the allergen is selected from the group consisting of dust mite, cockroach, cat dander, dog dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, German cockroach and Oriental cockroach.

30. The method of claim 25, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

31. The method of claim 30, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

32. The method of claim 30, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

33. The method of claim 30, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

34. The method of claim 30, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

35. The method of claim 30, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

36. The method of claim 30, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

37. The method of claim 30, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

38. The method of claim 30, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

39. The method of claim 25, wherein treatment results in a reduction in annualized severe asthma exacerbations.

40. The method of claim 25, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

41. The method of claim 25, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

42. The method of claim 25, wherein the antibody is dupilumab.

43. The method of claim 25, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

44. A method for treating a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain

CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline fractional exhaled nitric oxide (FeNO) level of at least about 20 ppb.

45. The method of claim 44, wherein the subject has a baseline FeNO) level of at least about 25 ppb.

46. The method of claim 44, wherein the subject has a baseline blood eosinophil count of at least about 150 cells/µl or at least about 300 cells/µl.

47. The method of claim 44, wherein the subject has a total serum IgE level of at least about 700 IU/mL.

48. The method of claim 44, wherein the subject has an allergen-specific IgE level of at least about 0.35 kU/L.

49. The method of claim 48, wherein the allergen is selected from the group consisting of dust mite, cockroach, cat dander, dog dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, German cockroach and Oriental cockroach.

50. The method of claim 44, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

51. The method of claim 50, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

52. The method of claim 50, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

53. The method of claim 50, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

54. The method of claim 50, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

55. The method of claim 50, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

56. The method of claim 50, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

57. The method of claim 50, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

58. The method of claim 50, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

59. The method of claim 44, wherein treatment results in a reduction in annualized severe asthma exacerbations.

60. The method of claim 44, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

61. The method of claim 44, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

62. The method of claim 44, wherein the antibody is dupilumab.

63. The method of claim 44, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

64. A method of improving lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%) in a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

65. The method of claim 64, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

66. The method of claim 64, wherein the antibody is dupilumab.

67. The method of claim 64, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

68. A method of reducing annualized severe asthma exacerbations in a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

69. The method of claim 68, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

70. The method of claim 68, wherein the antibody is dupilumab.

71. The method of claim 68, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

72. A method of improving Asthma Control Questionnaire (ACQ-5) score in a subject having allergic asthma comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 700 IU/mL.

73. The method of claim 72, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

74. The method of claim 72, wherein the antibody is dupilumab.

75. The method of claim 72, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

76. A method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and

5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

77. The method of claim 76, wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

78. The method of claim 76, wherein the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L.

79. The method of claim 78, wherein the allergen is *Aspergillus fumigatus*.

80. The method of claim 76, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

81. The method of claim 80, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

82. The method of claim 80, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

83. The method of claim 80, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

84. The method of claim 80, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

85. The method of claim 80, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

86. The method of claim 80, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

87. The method of claim 80, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

88. The method of claim 80, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

89. The method of claim 76, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

90. The method of claim 76, wherein treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels.

91. The method of claim 79, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

92. The method of claim 76, wherein FeNO (ppb) is reduced.

93. The method of claim 76, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

94. The method of claim 76, wherein the antibody is dupilumab.

95. The method of claim 76, wherein the subject has moderate-to-severe uncontrolled asthma.

96. The method of claim 95, wherein treatment results in a reduction in annualized severe asthma exacerbations.

97. A method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L.

98. The method of claim 97, wherein the subject has a baseline blood eosinophil count of at least about 300 cells/μl.

99. The method of claim 97, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

100. The method of claim 97, wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

101. The method of claim 97, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

102. The method of claim 101, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

103. The method of claim 101, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

104. The method of claim 101, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

105. The method of claim 101, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

106. The method of claim 101, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

107. The method of claim 101, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

108. The method of claim 101, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

109. The method of claim 101, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

110. The method of claim 97, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

111. The method of claim 97, wherein treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels.

112. The method of claim 97, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

113. The method of claim 97, wherein FeNO (ppb) is reduced.

114. The method of claim 97, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

115. The method of claim 97, wherein the antibody is dupilumab.

116. The method of claim 97, wherein the subject has moderate-to-severe uncontrolled asthma.

117. The method of claim 116, wherein treatment results in a reduction in annualized severe asthma exacerbations.

118. A method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

119. The method of claim 118, wherein the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L.

120. The method of claim 119, wherein the allergen is *Aspergillus fumigatus*.

121. The method of claim 118, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

122. The method of claim 118, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

123. The method of claim 122, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

124. The method of claim 122, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

125. The method of claim 122, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

126. The method of claim 122, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

127. The method of claim 122, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

128. The method of claim 122, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

129. The method of claim 122, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

130. The method of claim 122, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

131. The method of claim 118, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

132. The method of claim 118, wherein treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels.

133. The method of claim 118, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

134. The method of claim 118, wherein FeNO (ppb) is reduced.

135. The method of claim 118, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

136. The method of claim 118, wherein the antibody is dupilumab.

137. The method of claim 118, wherein the subject has moderate-to-severe uncontrolled asthma.

138. The method of claim 137, wherein treatment results in a reduction in annualized severe asthma exacerbations.

139. A method of improving lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%) in a subject having asthma associated with allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

140. The method of claim 139, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

141. The method of claim 139, wherein the antibody is dupilumab.

142. The method of claim 139, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

143. A method of reducing annualized severe asthma exacerbations in a subject having asthma associated with allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

144. The method of claim 143, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

145. The method of claim 143, wherein the antibody is dupilumab.

146. The method of claim 143, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

147. A method of improving Asthma Control Questionnaire (ACQ-5) score in a subject having asthma associated with allergic bronchopulmonary aspergillosis (ABPA) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively,

and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

148. The method of claim 147, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

149. The method of claim 147, wherein the antibody is dupilumab.

150. The method of claim 147, wherein the subject has moderate-to-severe uncontrolled allergic asthma.

151. A method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

152. The method of claim 151, wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

153. The method of claim 151, wherein the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L.

154. The method of claim 153, wherein the allergen is Aspergillus fumigatus.

155. The method of claim 151, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

156. The method of claim 155, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

157. The method of claim 155, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

158. The method of claim 155, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

159. The method of claim 155, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

160. The method of claim 155, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

161. The method of claim 155, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

162. The method of claim 155, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

163. The method of claim 155, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

164. The method of claim 151, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

165. The method of claim 151, wherein treatment results in a decrease in one or both of total serum IgE levels and serum Aspergillus fumigatus-specific IgE levels.

166. The method of claim 154, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

167. The method of claim 151, wherein FeNO (ppb) is reduced.

168. The method of claim 151, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

169. The method of claim 151, wherein the antibody is dupilumab.

170. The method of claim 151, wherein the subject has asthma.

171. The method of claim 170, wherein treatment results in a reduction in annualized asthma exacerbations.

172. A method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has an Aspergillus fumigatus-specific IgE level of greater than 0.35 kU/L.

173. The method of claim 172, wherein the subject has a baseline blood eosinophil count of at least about 300 cells/μl.

174. The method of claim 172, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

175. The method of claim 172, wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

176. The method of claim 172, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

177. The method of claim 176, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

178. The method of claim 176, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

179. The method of claim 176, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

180. The method of claim 176, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

181. The method of claim 176, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

182. The method of claim 176, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

183. The method of claim 176, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

184. The method of claim 176, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

185. The method of claim 172, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

186. The method of claim 172, wherein treatment results in a decrease in one or both of total serum IgE levels and serum Aspergillus fumigatus-specific IgE levels.

187. The method of claim 172, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

188. The method of claim 172, wherein FeNO (ppb) is reduced.

189. The method of claim 172, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

190. The method of claim 172, wherein the antibody is dupilumab.

191. The method of claim 172, wherein the subject has asthma.

192. The method of claim 191, wherein treatment results in a reduction in annualized asthma exacerbations.

193. A method for treating a subject having comorbid allergic bronchopulmonary aspergillosis (ABPA) and cystic fibrosis (CF) comprising administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the

antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject has a baseline blood eosinophil count of at least about 500 cells/μl.

194. The method of claim 193, wherein the subject has an allergen-specific serum IgE level of at least about 0.35 kU/L.

195. The method of claim 194, wherein the allergen is *Aspergillus fumigatus*.

196. The method of claim 193, wherein the subject has a total serum IgE level of at least about 1000 IU/mL.

197. The method of claim 193, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

198. The method of claim 197, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

199. The method of claim 197, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

200. The method of claim 197, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

201. The method of claim 197, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

202. The method of claim 197, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

203. The method of claim 197, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

204. The method of claim 197, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

205. The method of claim 197, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

206. The method of claim 193, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

207. The method of claim 193, wherein treatment results in a decrease in one or both of total serum IgE levels and serum Aspergillus fumigatus-specific IgE levels.

208. The method of claim 193, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

209. The method of claim 193, wherein FeNO (ppb) is reduced.

210. The method of claim 193, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

211. The method of claim 193, wherein the antibody is dupilumab.

212. The method of claim 193, wherein the subject has asthma.

213. The method of claim 212, wherein treatment results in a reduction in annualized asthma exacerbations.

214. A method for treating a subject having allergic bronchopulmonary aspergillosis (ABPA) comprising

administering to the subject an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively,

wherein the subject has a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, or a baseline blood eosinophil count of at least about 500 cells/μl.

215. The method of claim 214, wherein the subject has at least two of a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl.

216. The method of claim 214, wherein the subject has a total serum IgE level of at least about 1000 IU/mL, an *Aspergillus fumigatus*-specific IgE level of greater than 0.35 kU/L, and a baseline blood eosinophil count of at least about 500 cells/μl.

217. The method of claim 214, wherein the antibody or antigen-binding fragment thereof is administered to the subject as a loading dose followed by a plurality maintenance doses.

218. The method of claim 217, wherein the antibody or antigen-binding fragment thereof is administered using an autoinjector, a needle and syringe, or a pen.

219. The method of claim 217, wherein a maintenance dose of antibody or antigen-binding fragment thereof is administered once every other week (q2w).

220. The method of claim 217, wherein the loading dose is about 600 mg of the antibody or the antigen-binding fragment thereof.

221. The method of claim 217, wherein each maintenance dose of antibody or antigen-binding fragment thereof is about 300 mg of the antibody or the antigen-binding fragment thereof.

222. The method of claim 217, wherein the loading dose is about 400 mg of the antibody or the antigen-binding fragment thereof.

223. The method of claim 217, wherein each maintenance dose of the antibody or antigen-binding fragment thereof is about 200 mg of the antibody or the antigen-binding fragment thereof.

224. The method of claim 217, wherein the maintenance doses of the antibody or antigen-binding fragment thereof are administered for at least 24 weeks.

225. The method of claim 217, wherein a first maintenance dose of antibody or antigen-binding fragment thereof is administered two weeks after the loading dose of antibody or antigen-binding fragment thereof.

226. The method of claim 214, wherein treatment results in an improvement in lung function as measured by forced expiratory volume (FEV_1) or by forced expiratory flow at 25-75% of the pulmonary volume (FEF25-75%).

227. The method of claim 214, wherein treatment results in a decrease in one or both of total serum IgE levels and serum *Aspergillus fumigatus*-specific IgE levels.

228. The method of claim 214, wherein treatment results in a decrease in one or more of TARC levels, eotaxin-3 levels and peripheral blood eosinophil levels.

229. The method of claim 214, wherein FeNO (ppb) is reduced.

230. The method of claim 214, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) sequence of SEQ ID NO: 2.

231. The method of claim 214, wherein the antibody is dupilumab.

232. The method of claim 214, wherein the subject has moderate-to-severe uncontrolled asthma.

233. The method of claim 232, wherein treatment results in a reduction in annualized severe asthma exacerbations.

234. The method of claim 214, wherein the subject exhibits comorbid asthma.

235. The method of claim 214, wherein the subject exhibits comorbid cystic fibrosis.

236. The method of claim 214, wherein the subject exhibits comorbid asthma and comorbid cystic fibrosis.

237. A method for treating a subject having asthma comprising administering to the subject two or more doses of an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively, and wherein the subject is further administered a vaccine.

238. The method of claim 237, wherein administration of the antibody or antigen-binding fragment thereof is temporarily suspended prior to administering the vaccine.

239. The method of claim 238, wherein the vaccine is administered at least 7 days after the antibody or antigen-binding fragment thereof was last administered to the subject.

240. The method of claim 239, wherein the vaccine is administered between about 7 days and about 60 days after the antibody or antigen-binding fragment thereof was last administered to the subject.

241. The method of any one of claims 238-240, wherein administration of the antibody or antigen-binding fragment thereof is resumed following administration of the vaccine.

242. The method of claim 241, wherein the antibody or antigen-binding fragment thereof is administered between about 1 day and about 90 days after administration of the vaccine.

243. The method of claim 242, wherein the antibody or antigen-binding fragment thereof is administered about 7 days after administration of the vaccine.

244. The method of claim 242, wherein the antibody or antigen-binding fragment thereof is administered about 14 days after administration of the vaccine.

245. The method of claim 242, wherein the antibody or an antigen-binding fragment thereof is administered about 21 days after administration of the vaccine.

246. The method of any one of claims 237-245, wherein efficacy of the antibody or antigen-binding fragment thereof is not decreased by administration of the vaccine.

247. The method of claim 246, wherein forced expiratory volume (FEV_1) of the subject is approximately the same before and after administration of the vaccine.

248. The method of any one of claims 237-247, wherein vaccine efficacy in the subject is not decreased by administration of the antibody or antigen-binding fragment thereof.

249. The method of claim 248, wherein the subject develops a seroprotective neutralization titer after administration of the vaccine.

250. The method of any one of claims 237-249, wherein the vaccine is a live vaccine.

251. The method of claim 250, where the vaccine comprises a live-attenuated yellow fever virus.

252. The method of any one of claims 237-251, wherein the vaccine is specific against yellow fever virus.

253. A method for administrating a vaccine to a subject, wherein before, during, or after administration of the vaccine, the subject is administered at least one dose of an antibody or an antigen-binding fragment thereof that specifically binds interleukin-4 receptor (IL-4R), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDR sequences comprising SEQ ID NOs: 3, 4, and 5, respectively, and three light chain CDR sequences comprising SEQ ID NOs: 6, 7, and 8, respectively.

254. The method of claim 253, wherein the subject has a type 2 inflammatory disease.

255. The method of claim 254, wherein the type 2 inflammatory disease is selected from the group consisting of one or any combination of asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSsNP), eosinophilic esophagitis (EoE), atopic dermatitis (AD), food and environmental allergies, aspirin exacerbated respiratory disease (AERD), and respiratory disease exacerbated by non-steroidal anti-inflammatory drugs (NSAIDs).

256. The method of claim 253, wherein the vaccine is administered to the subject about 1 day to about 90 days after the last dose of the antibody or an antigen-binding fragment thereof.

Fig. 1A

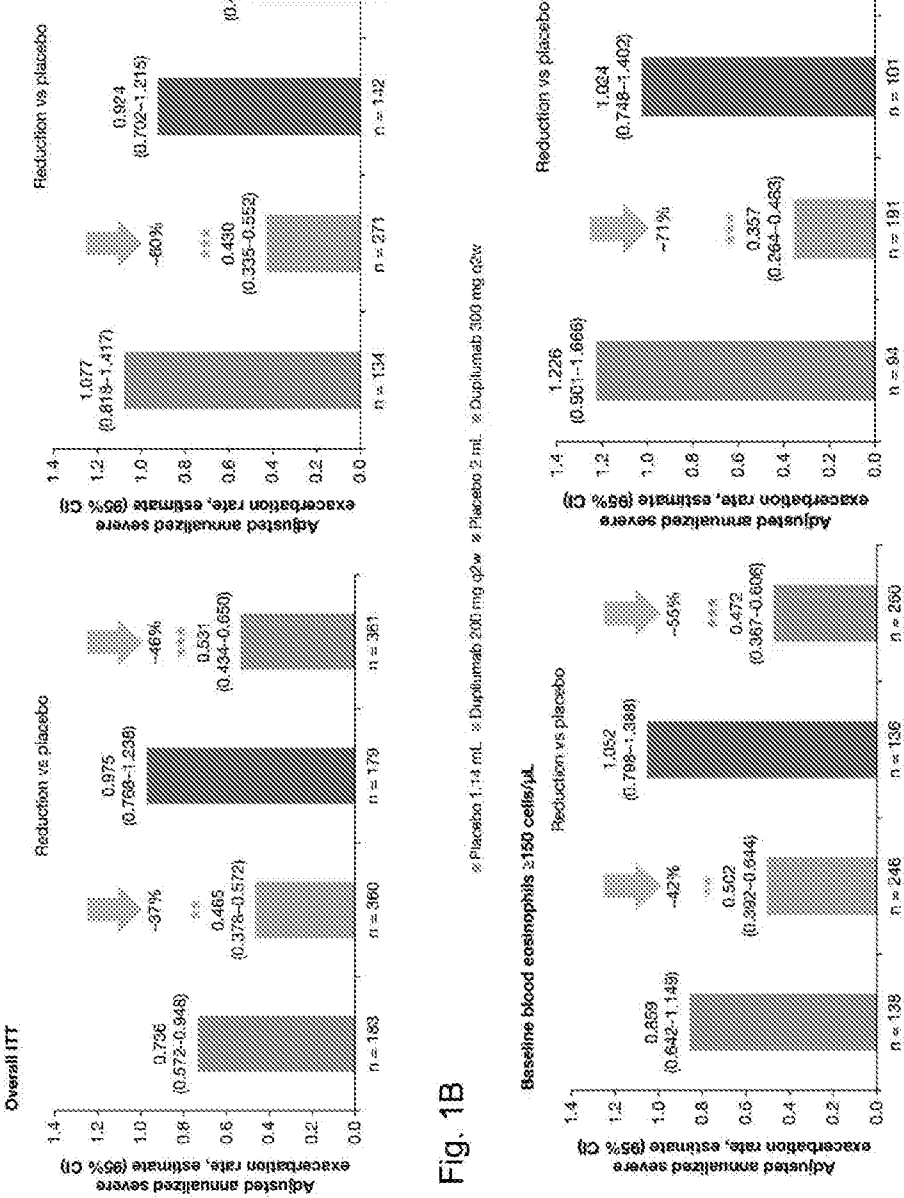

Placebo 1.14 mL
Dupilumab 200 mg q2w
Placebo 2 mL
Dupilumab 300 mg q2w
Allergic asthma
Overall ITT
Reduction vs placebo
Adjusted annualized severe exacerbation rate, estimate (95% CI)
0.736 (0.572–0.948)
0.465 (0.378–0.572)
0.875 (0.768–1.238)
0.531 (0.434–0.650)
1.077 (0.819–1.417)
0.430 (0.335–0.552)
0.924 (0.702–1.215)
0.511 (0.404–0.647)
-37%
-46%
-60%
-45%
n = 183
n = 360
n = 179
n = 361
n = 134
n = 271
n = 142
n = 272
Did not meet the criteria for allergic asthma

Fig. 1B

Placebo 1.14 mL
Dupilumab 200 mg q2w
Placebo 2 mL
Dupilumab 300 mg q2w
Baseline blood eosinophils ≥150 cells/µL
Reduction vs placebo
Adjusted annualized severe exacerbation rate, estimate (95% CI)
0.859 (0.642–1.149)
0.502 (0.382–0.644)
1.052 (0.798–1.388)
0.472 (0.367–0.606)
1.226 (0.901–1.666)
0.357 (0.264–0.483)
1.024 (0.748–1.402)
0.376 (0.280–0.505)
-42%
-55%
-71%
-63%
n = 138
n = 248
n = 136
n = 260
n = 84
n = 191
n = 101
n = 192

Fig. 1C

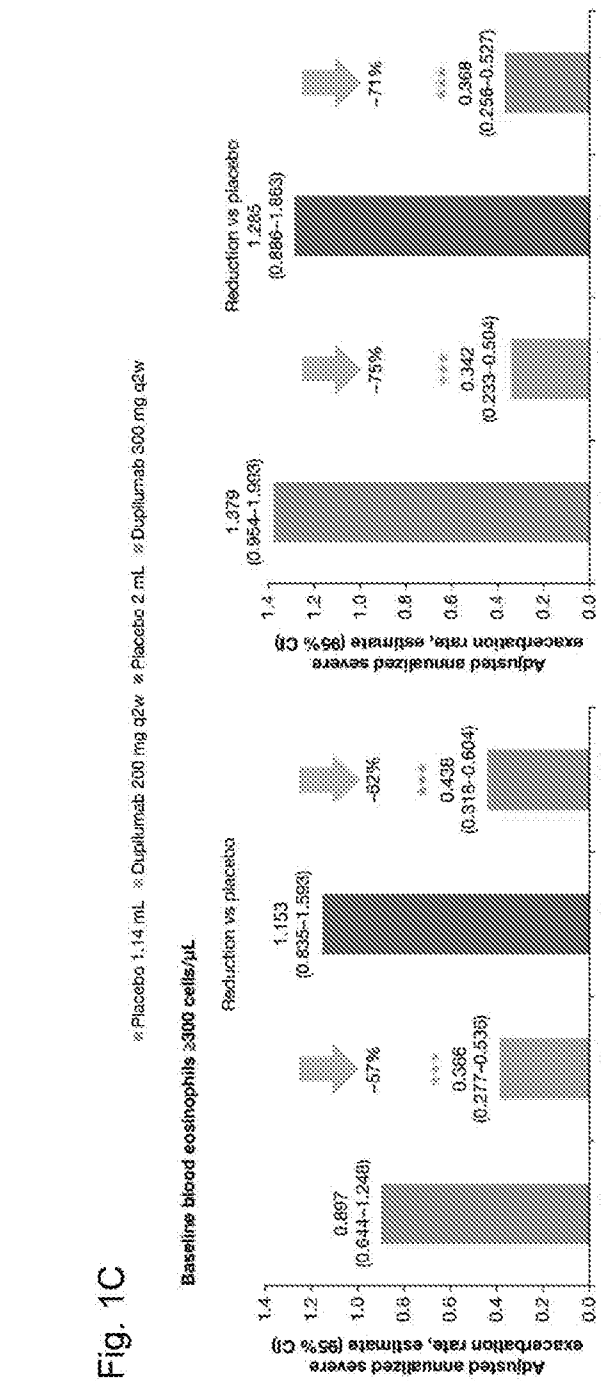

≈ Placebo 1.14 mL ≈ Dupilumab 200 mg q2w ≈ Placebo 2 mL ≈ Dupilumab 300 mg q2w
Baseline blood eosinophils ≥300 cells/µL
Reduction vs placebo
Adjusted annualized severe exacerbation rate, estimate (95% CI)
0.897 (0.644–1.248)
-57%
1.153 (0.835–1.593)
-82%
1.379 (0.954–1.993)
-75%
1.285 (0.886–1.863)
-71%
0.686 (0.277–0.536)
0.438 (0.318–0.604)
0.342 (0.233–0.504)
0.368 (0.256–0.527)
n = 89
n = 148
n = 80
n = 153
n = 59
n = 116
n = 62
n = 124

Fig. 1D

≈ Placebo 1.14 mL ≈ Dupilumab 200 mg q2w ≈ Placebo 2 mL ≈ Dupilumab 300 mg q2w
Baseline FeNO levels ≥25 ppb
Reduction vs placebo
Adjusted annualized severe exacerbation rate, estimate (95% CI)
0.883 (0.639–1.219)
-63%
1.128 (0.839–1.517)
-58%
1.191 (0.774–1.835)
-71%
1.029 (0.675–1.570)
-63%
0.350 (0.242–0.450)
0.475 (0.356–0.635)
0.351 (0.231–0.534)
0.381 (0.263–0.553)
n = 99
n = 185
n = 105
n = 176
n = 63
n = 114
n = 67
n = 134

Fig. 1E

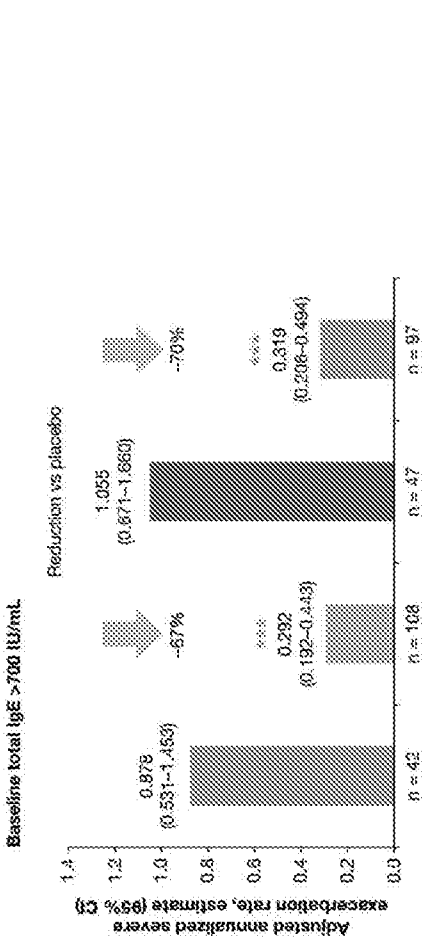
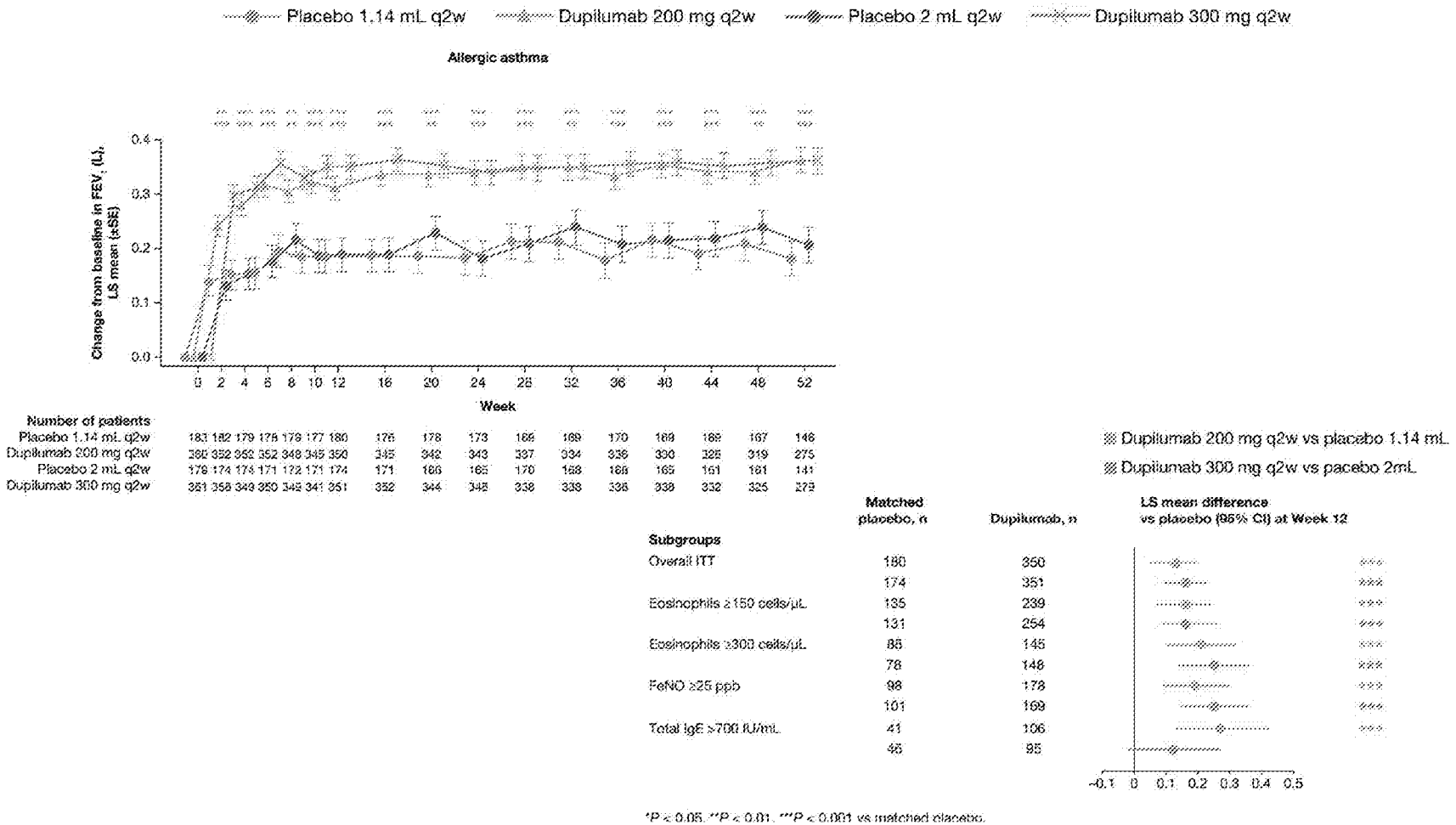

Placebo 1:14 mL
Dupilumab 200 mg q2w
Placebo 2 mL
Dupilumab 300 mg q2w
Baseline total IgE >700 IU/mL
Reduction vs placebo
Adjusted annualized severe exacerbation rate, estimate (95% CI)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.878
(0.531–1.453)
n = 42
-67%
1.055
(0.671–1.660)
n = 108
-70%
0.292
(0.192–0.443)
n = 47
0.319
(0.208–0.494)
n = 97
**P < 0.01, ***P < 0.001 vs matched placebo.

Fig. 2A



*P < 0.05, **P < 0.01, ***P < 0.001 vs matched placebo.

Fig. 2B

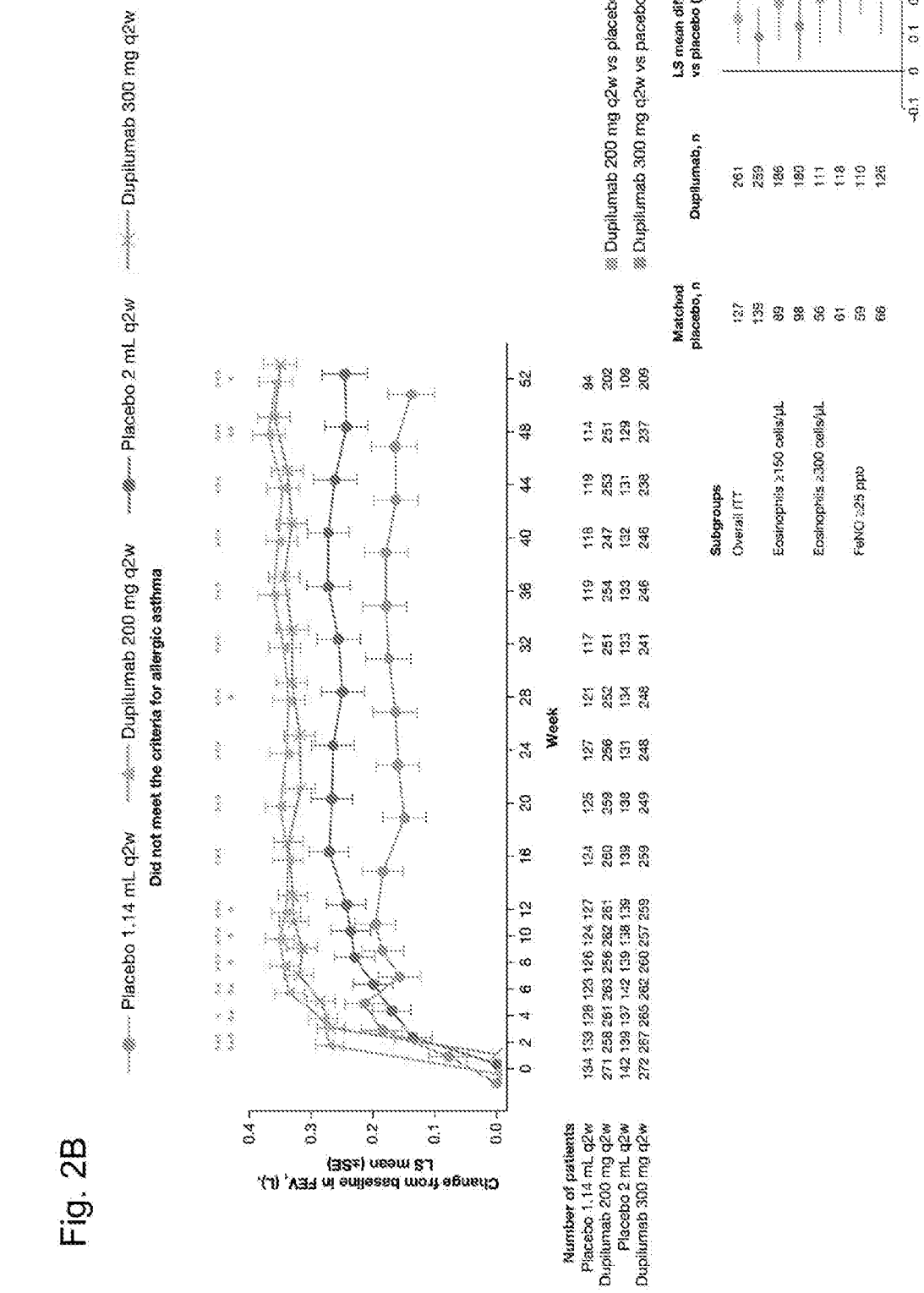

Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
Did not meet the criteria for allergic asthma
Change from baseline in FEV1 (L)
LS mean (±SE)
Week
Number of patients
Placebo 1.14 mL q2w 134 133 128 128 126 124 127 124 126 127 121 117 119 118 119 114 84
Dupilumab 200 mg q2w 271 258 261 263 256 262 261 260 259 252 251 254 247 253 251 202
Placebo 2 mL q2w 142 138 137 142 139 138 139 139 138 134 133 133 132 131 129 108
Dupilumab 300 mg q2w 272 267 265 262 260 257 259 259 249 248 248 241 246 248 238 237 209
Dupilumab 200 mg q2w vs placebo 1.14 mL
Dupilumab 300 mg q2w vs placebo 2mL
Subgroups
Matched placebo, n
Dupilumab, n
LS mean difference vs placebo (95% CI) at Week 12
Overall ITT 127 261
135 259
Eosinophils ≥150 cells/µL 89 186
98 193
Eosinophils ≥300 cells/µL 66 111
61 118
FeNO ≥25 ppb 89 119
66 126
-0.1 0 0.1 0.2 0.3 0.4

Fig. 3

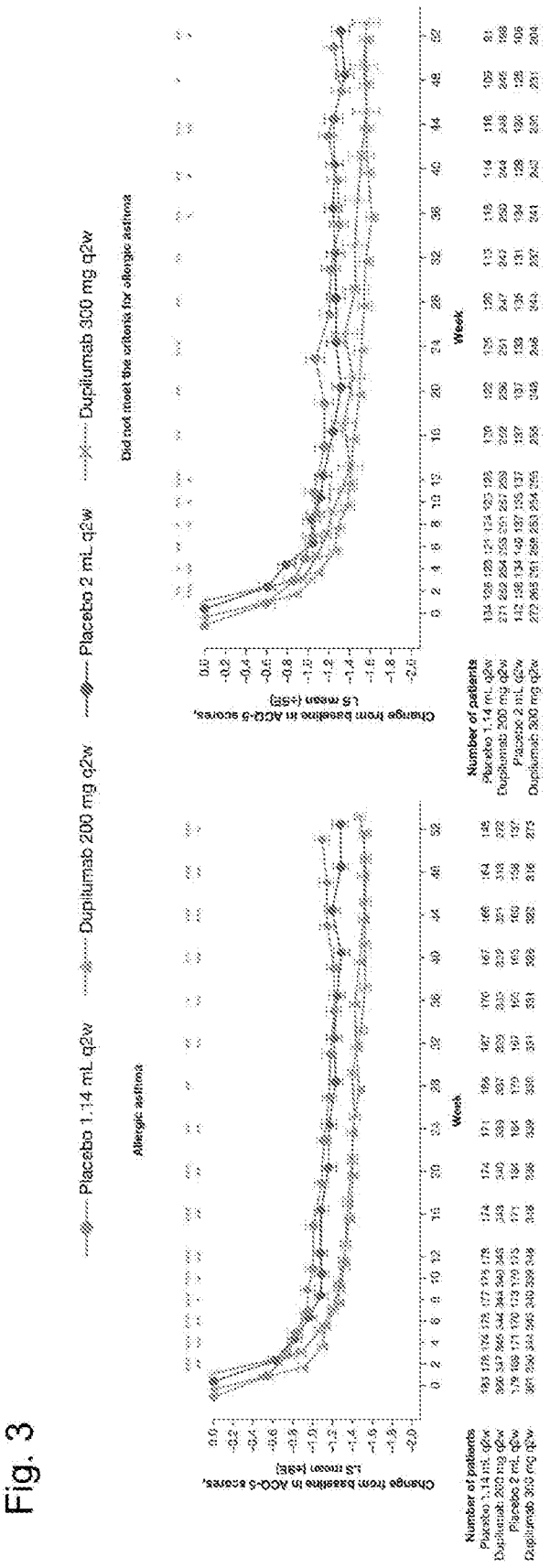

Placebo 1:14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
Allergic asthma
Did not meet the criteria for allergic asthma
Change from baseline in ACQ-5 scores, LS mean (±SE)
Week
Number of patients

Fig. 4A

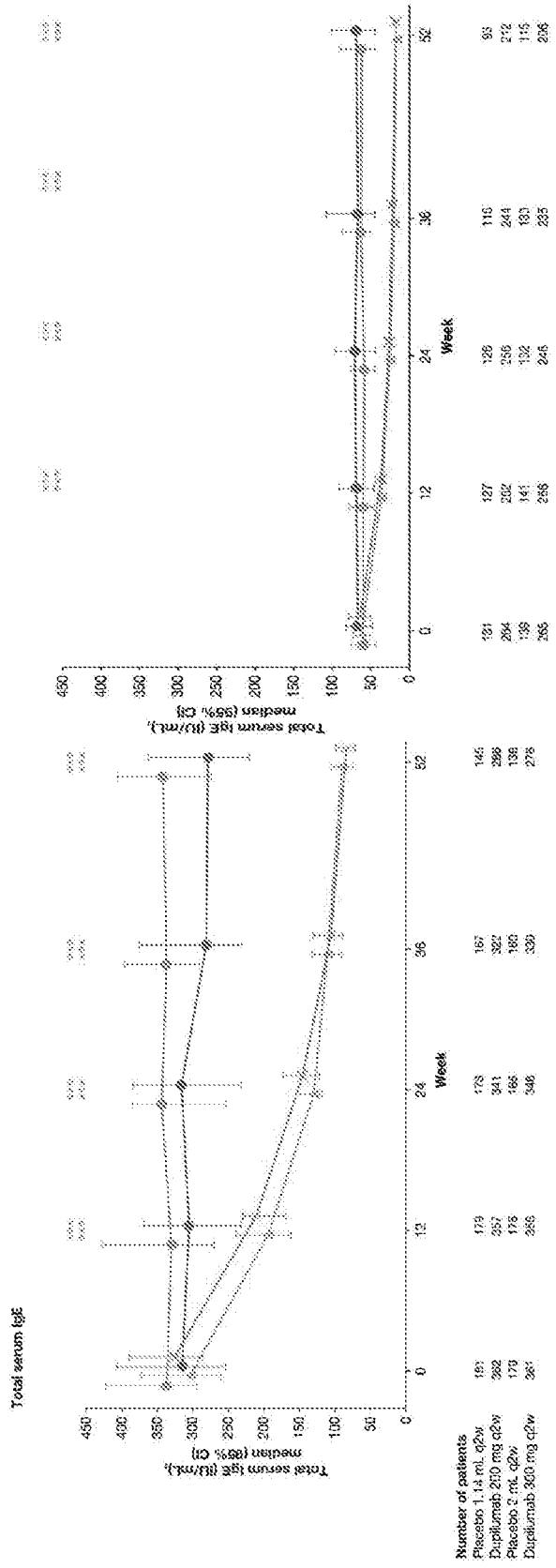

Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
Allergic asthma
Did not meet the criteria for allergic asthma
Total serum IgE
Total serum IgE (IU/mL), median (95% CI)
Week
Number of patients
Placebo 1.14 mL q2w 191 179 173 167 145 191 187 129 116 93
Dupilumab 200 mg q2w 382 357 341 322 289 384 352 256 244 212
Placebo 2 mL q2w 179 176 166 163 138 139 141 132 130 115
Dupilumab 300 mg q2w 381 366 346 339 278 385 366 245 235 206

Fig. 4B

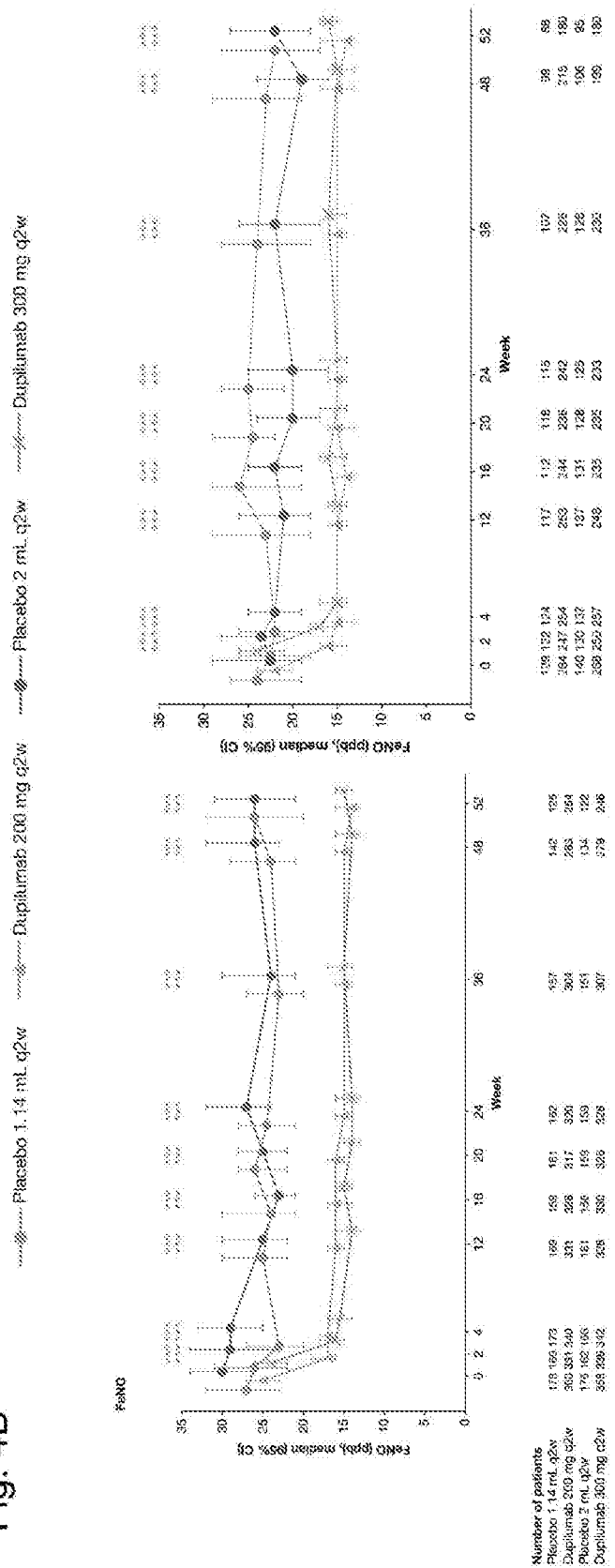

Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
FeNO
FeNO (ppb), median (95% CI)
Week
Number of patients
Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w

Fig. 4C

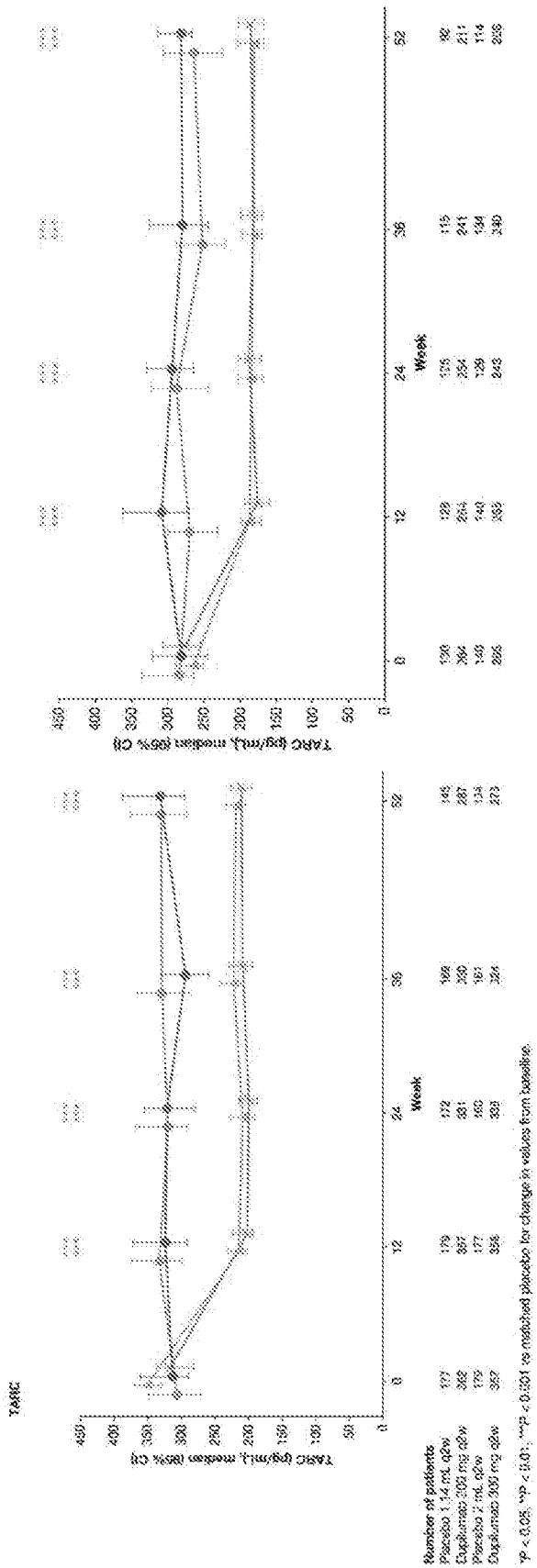

Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
TARC
TARC (pg/mL), median (95% CI)
Week
Number of patients
Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w
*P < 0.05, **P < 0.01, ***P < 0.001 vs matched placebo for change in values from baseline.

Fig. 5A

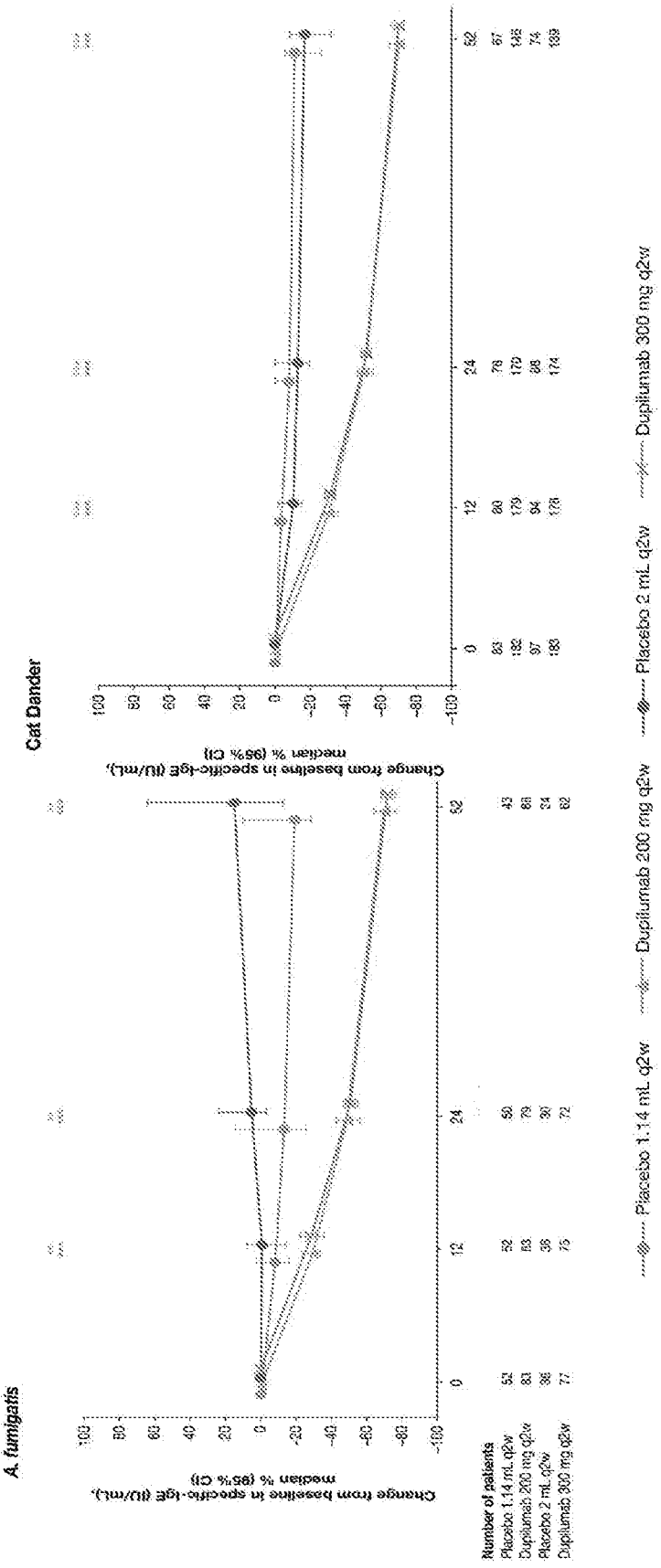

A. fumigatis
Change from baseline in specific-IgE (IU/mL), median % (95% CI)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
12
24
52
Number of patients
Placebo 1.14 mL q2w 51 52 50 43
Dupilumab 200 mg q2w 83 83 79 68
Placebo 2 mL q2w 86 86 80 74
Dupilumab 300 mg q2w 77 75 72 62
Cat Dander
Change from baseline in specific-IgE (IU/mL), median % (95% CI)
0 83 182 97 183
12 80 179 94 178
24 78 179 88 174
52 67 148 74 169
Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w

Fig. 5B

Fig. 5C

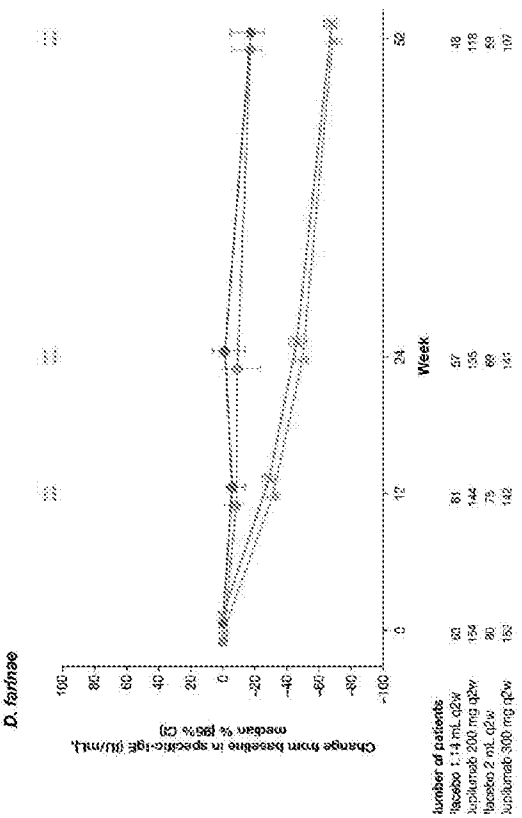

D. farinae
Change from baseline in specific-IgE (kU/mL), median % (95% CI)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
12
24
52
Week
Number of patients:
Placebo 1:14 mL q2w 93 91 87 46
Dupilumab 200 mg q2w 154 144 135 118
Placebo 2 mL q2w 80 75 68 53
Dupilumab 300 mg q2w 163 142 141 107

Fig. 5D

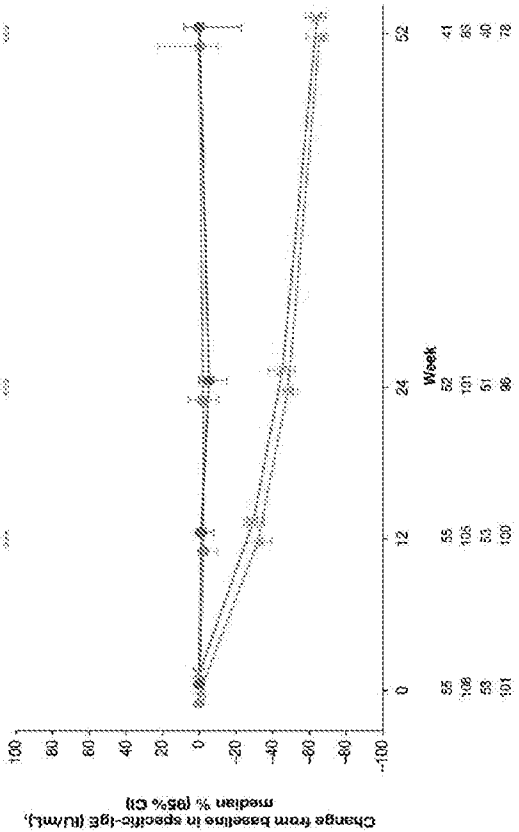

D. pteronyssinus
Change from baseline in specific-IgE (kU/mL), median % (95% CI)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
12
24
52
Week
85 85 55 41
108 105 101 63
53 53 51 40
101 100 96 78
Placebo 1:14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w

Fig. 5E

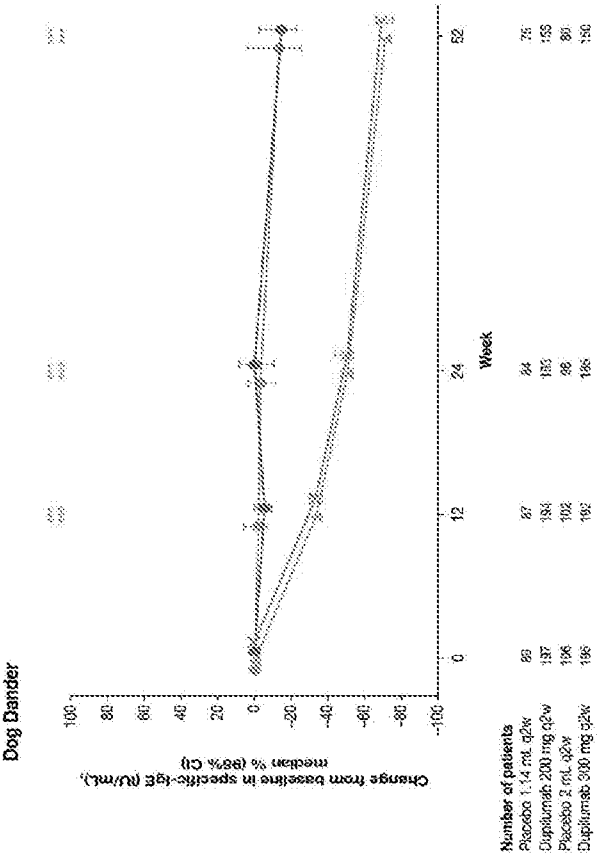
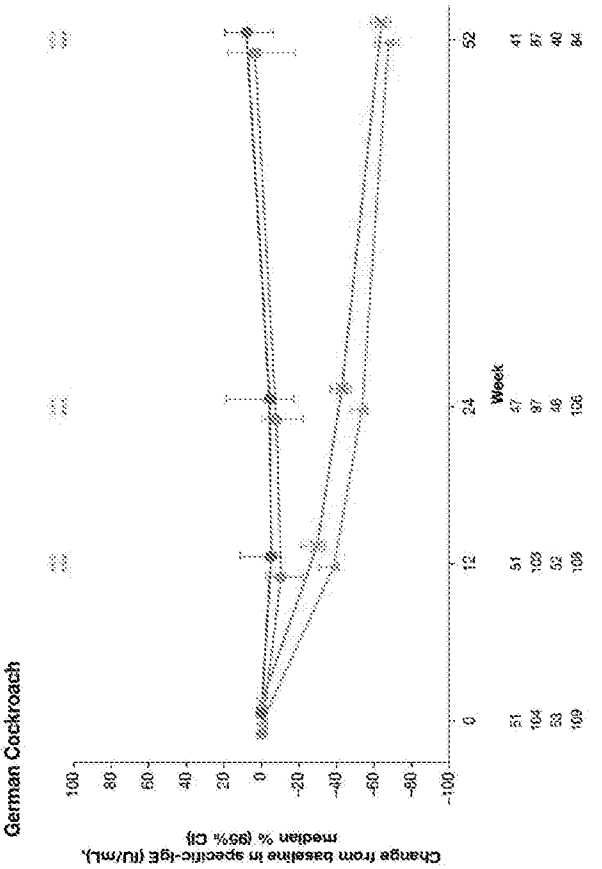


Fig. 5F



Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w

Fig. 5G

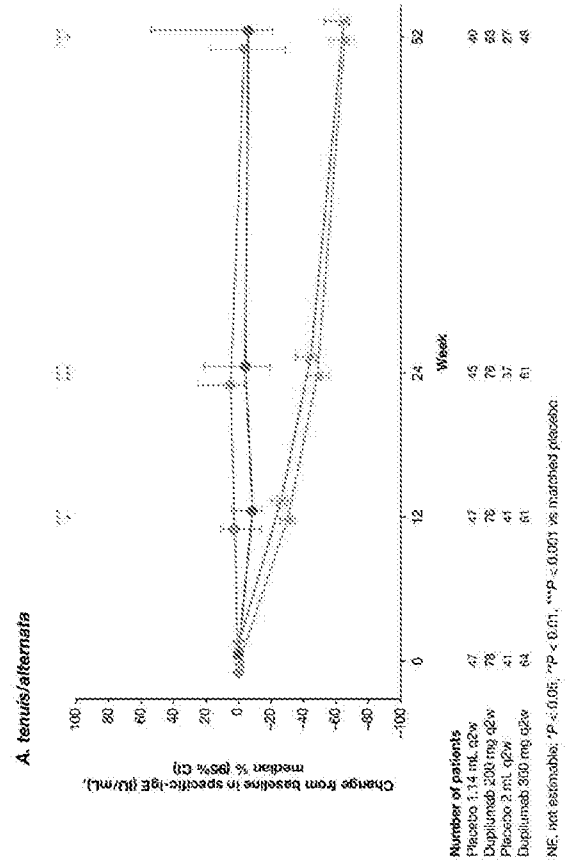

A. tenuis/alternata
Change from baseline in specific-IgE (IU/mL), median % (95% CI)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
12
24
52
Week
Number of patients
Placebo 1.14 mL q2w 47 47 45 40
Dupilumab 200 mg q2w 78 78 78 53
Placebo 2 mL q2w 41 41 37 27
Dupilumab 300 mg q2w 64 61 61 48
NE, not estimable; *P < 0.05; **P < 0.01; ***P < 0.001 vs matched placebo

Fig. 5H

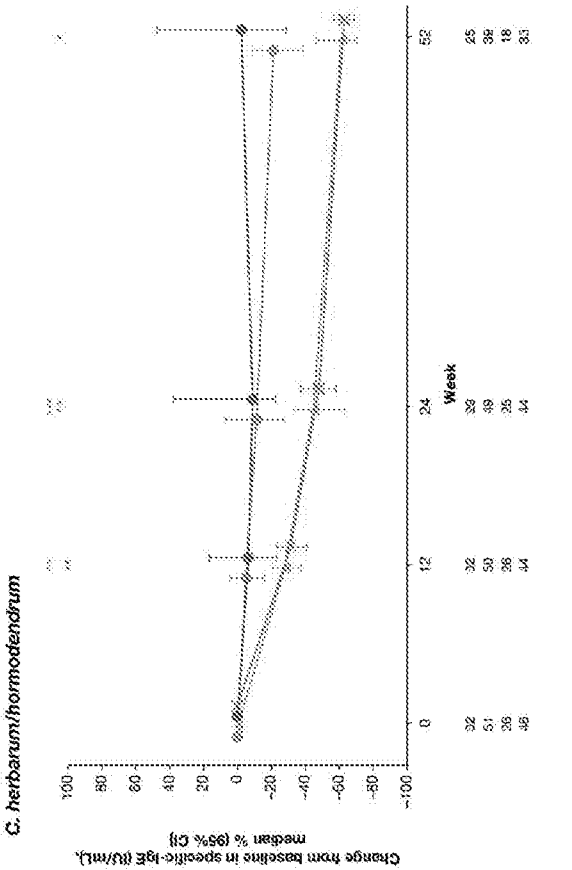

C. herbarum/hormodendrum
Change from baseline in specific-IgE (IU/mL), median % (95% CI)
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
12
24
52
Week
32 32 32 25
51 50 49 38
35 36 35 18
46 44 44 33
Placebo 1.14 mL q2w
Dupilumab 200 mg q2w
Placebo 2 mL q2w
Dupilumab 300 mg q2w

Fig. 6B

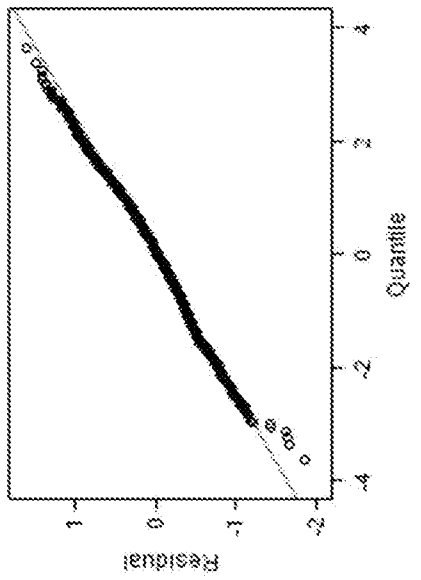
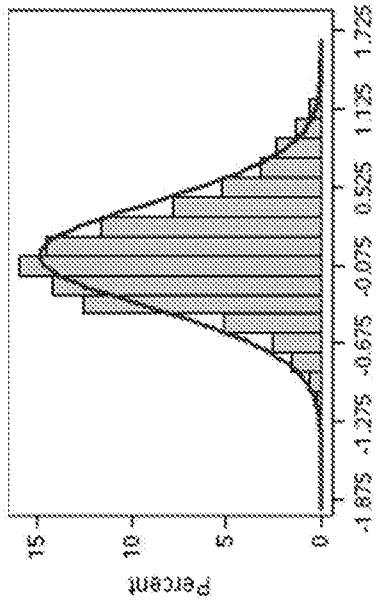

Residual
1
0
-1
-2
-4
-2
0
2
4
Quantile

Fig. 6A


Percent
15
10
5
0
-1.875
-1.275
-0.675
-0.075
0.525
1.125
1.725
Residual

SUBSTITUTE SHEET (RULE 26)

Annualized event rate of severe exacerbation during 52-week treatment period for patients with allergic bronchopulmonary aspergillosis (ABPA) - ITT population

	Combined	
	Placebo (N=12)	**Dupilumab (N=18)**
Patients with ≥1 severe exacerbation events [n(%)]		
Number	12	18
No	4 (33.3%)	15 (83.3%)
Yes	8 (66.7%)	3 (16.7%)
Number of severe exacerbation events		
0	4 (33.3%)	15 (83.3%)
1	3 (25.0%)	2 (11.1%)
2	2 (16.7%)	1 (5.6%)
3	2 (16.7%)	0
≥4	1 (8.3%)	0
Total number of severe exacerbation events	17	4
Total patient-years followed	12.0	17.8
Unadjusted annualized rate of severe exacebation events [a]	1.421	0.225
Estimate [b] (95% CI)	1.419 (0.783, 2.574)	0.225 (0.078, 0.649)
Relative risk [b] vs. matching placebo (95% CI)		0.159 (0.047, 0.534)
P-value [b] vs. matching placebo		0.0043
Risk difference [d] vs. matching placebo (95% CI)		-1.194 (-2.072, -0.317)
Adjusted annualized rate of severe exacerbation events		
Estimate [c] (95% CI)	1.160 (0.507, 2.657)	0.220 (0.075, 0.647)
Relative risk [c] vs. matching placebo		0.189 (0.052, 0.693)
P-value [c] vs. matching placebo		0.0140
Risk difference [d] vs. matching placebo (95% CI)		-0.940 (-1.908, 0.027)

Fig. 7

Pre-bronchodilator FEV1 (L)	Combined	
	Placebo (N=12)	Dupilumab (N=18)
Baseline		
Value		
Number	12	18
Mean (SD)	1.59 (0.49)	2.00 (0.68)
Median	1.51	1.84
Q1:Q3	1.23 : 1.80	1.44 : 2.33
Min:Max	1.0 : 2.5	1.1 : 3.4
Week 24		
Change from baseline		
Number	11	18
Mean (SD)	0.07 (0.30)	0.40 (0.41)
LS Mean (SE) [a]	0.07 (0.10)	0.40 (0.08)
LS Mean Diff vs. matching placebo (95% CI) [a]		0.33 (0.05, 0.60)
P-value vs. matching placebo [a]		0.0202
LS Mean (SE) [b]	0.11 (0.11)	0.37 (0.08)
LS Mean Diff vs. matching placebo (95% CI) [b]		0.26 (-0.04, 0.56)
P-value vs. matching placebo [b]		0.0887
Week 52		
Change from baseline		
Number	11	15
Mean (SD)	0.08 (0.24)	0.51 (0.59)
LS Mean (SE) [a]	0.14 (0.13)	0.55 (0.11)
LS Mean Diff vs. matching placebo (95% CI) [a]		0.41 (0.08, 0.75)
P-value vs. matching placebo [a]		0.0181
LS Mean (SE) [b]	0.18 (0.13)	0.51 (0.10)
LS Mean Diff vs. matching placebo (95% CI) [b]		0.33 (-0.02, 0.68)
P-value vs. matching placebo [b]		0.0654

Fig. 8

Total IgE	Combined	
	Placebo (N=12)	Dupilumab (N=18)
Baseline		
Value		
Number	12	18
Mean (SD)	2128.6 (878.2)	3335.7 (1687.7)
Median	2148.0	3383.0
95% CI of median	1441.0 , 2778.0	1480.0 , 5000.0
Q1:Q3	1445.5 : 2734.0	1480.0 : 5000.0
Min:Max	1014 : 3749	1008 : 5000

Total IgE	Placebo (N=12)	Dupilumab (N=18)
Week 52		
Value		
Number	11	14
Mean (SD)	1719.3 (925.6)	1451.5 (1485.1)
Median	1714.0	691.5
95% CI of median	727.0 , 3048.0	323.0 , 2617.0
Q1:Q3	727.0 : 2402.0	323.0 : 2440.0
Min:Max	630 : 3084	126 : 4524
Change from baseline		
Number	11	14
Mean (SD)	-350.3 (980.1)	-1903.1 (1209.2)
Median	-701.0	-1633.5
95% CI of median	-976.0 , 1274.0	-2560.0 , -868.0
Q1 : Q2	-976.0 : -36.0	-2560.0 : -882.0
Min : Max	-1704 : 1562	-4637 : -476
P-value [a]		0.0047

Fig. 9

Aspergillus fumigatus IgE	Combined	
	Placebo (N=12)	Dupilumab (N=18)
Baseline		
Value		
Number	12	18
Mean (SD)	11.578 (17.026)	7.271 (10.336)
Median	2.955	2.435
95% CI of median	0.520 , 28.800	0.640 , 11.200
Q1:Q3	0.810 : 18.905	0.640 : 11.200
Min:Max	0.43 : 50.40	0.42 : 35.10

Aspergillus fumigatus IgE	Placebo (N=12)	Dupilumab (N=18)
Week 52		
Value		
Number	11	14
Mean (SD)	13.493 (28.292)	1.606 (2.489)
Median	4.610	0.825
95% CI of median	0.630 , 21.500	0.120 , 2.570
Q1:Q3	0.630 : 10.600	0.120 : 1.450
Min:Max	0.15 : 96.70	0.05 : 9.40
Change from baseline		
Number	11	14
Mean (SD)	0.901 (25.371)	-4.337 (6.120)
Median	-0.590	-1.610
95% CI of median	-4.400 , 3.510	-3.390 , -0.360
Q1 : Q3	-4.400 : 1.110	-3.390 : -0.530
Min : Max	-39.80 : 67.90	-19.90 : -0.07
P-value [a]		0.2728

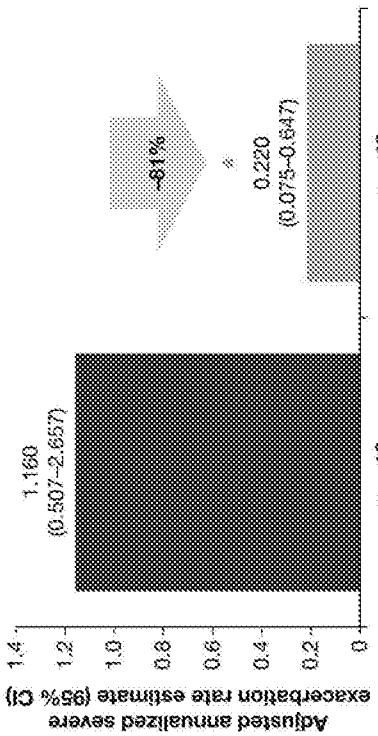
Fig. 10

FeNO	Combined	
	Placebo (N=12)	Dupilumab (N=18)
Baseline		
Value		
Number	12	18
Mean (SD)	39.1 (27.2)	50.3 (30.1)
Median	31.0	49.0
95% CI of median	19.0 , 63.0	24.0 , 68.0
Q1:Q3	19.5 : 53.0	24.0 : 68.0
Min:Max	10 : 104	9 : 129

FeNO	Placebo (N=12)	Dupilumab (N=18)
Week 52		
Value		
Number	8	13
Mean (SD)	27.5 (16.4)	18.8 (8.1)
Median	25.0	18.0
95% CI of median	10.0 , 56.0	12.0 , 26.0
Q1:Q3	15.0 : 38.0	13.0 : 23.0
Min:Max	8 : 56	6 : 33
Change from baseline		
Number	8	14
Mean (SD)	-7.0 (19.6)	-32.5 (31.2)
Median	-3.0	-19.0
95% CI of median	-34.0 , 16.0	-51.0 , -10.0
Q1 : Q3	-23.5 : 8.0	-48.0 : -11.0
Min : Max	-35 : 16	-111 : 4
P-value [a]		0.0485

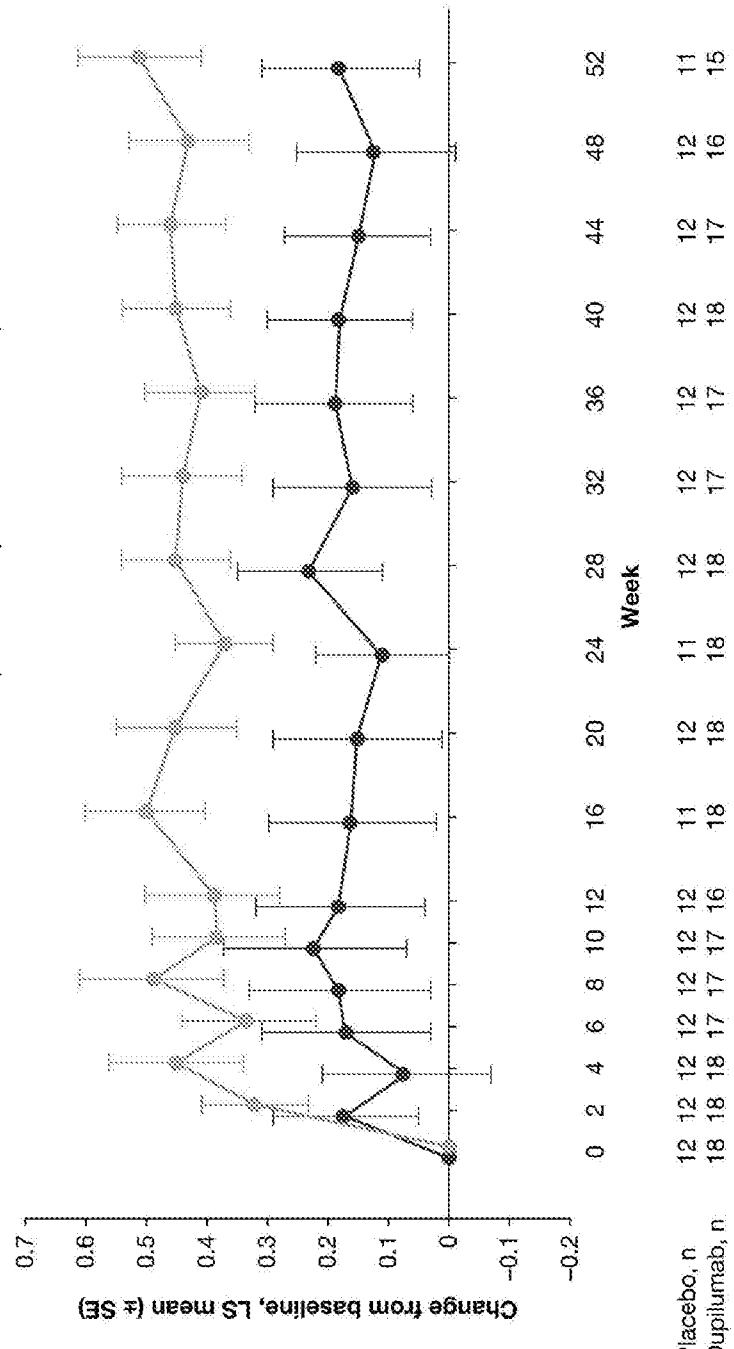
Fig. 11

Fig. 12



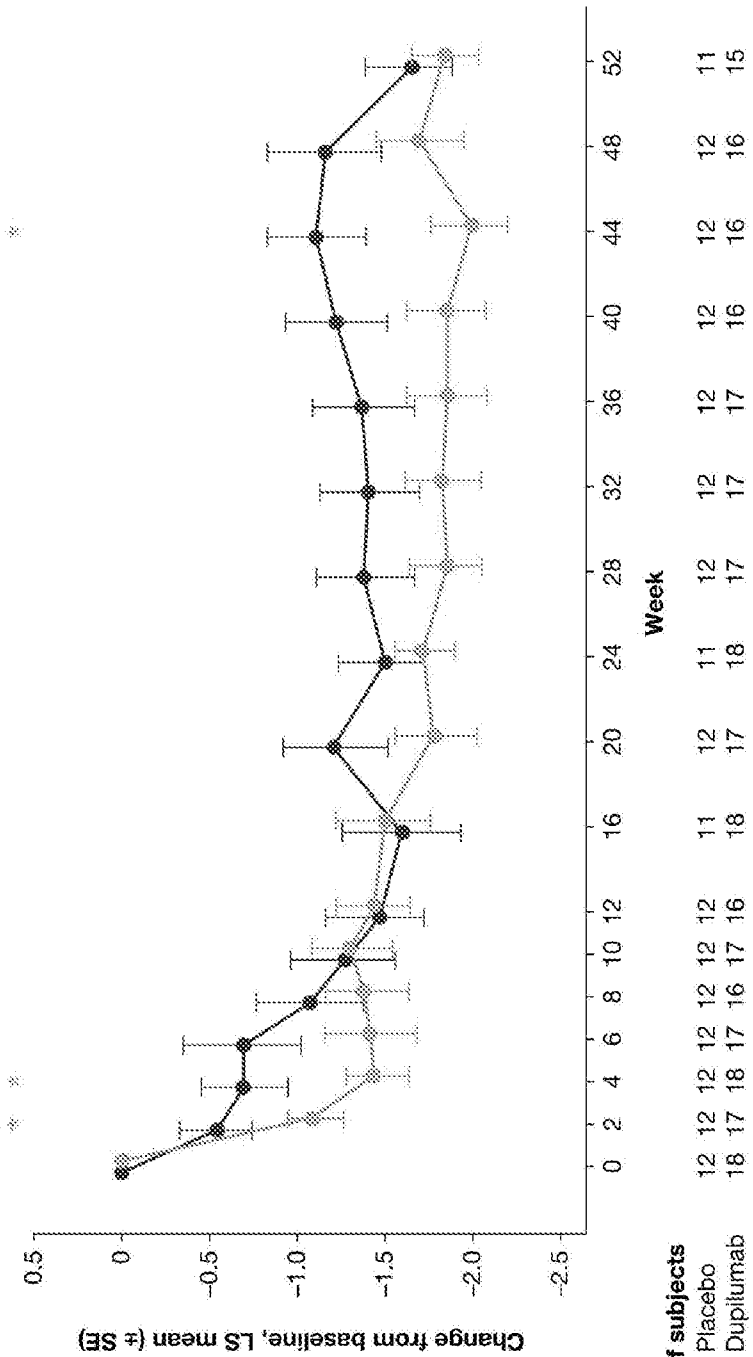
*$P < 0.05$ vs placebo.
ABPA, allergic bronchopulmonary aspergillosis; *CI*, confidence interval; *ITT*, intention-to-treat; *q2w*, every 2 weeks.

Fig. 13



ABPA, allergic bronchopulmonary aspergillosis; FEV_1, forced expiratory volume in 1 second; *ITT*, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

Fig. 14



*$P < 0.05$ vs placebo.
ABPA, allergic bronchopulmonary aspergillosis; *ACQ-5*, 5-item Asthma Control Questionnaire; *ITT*, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

Fig. 15A

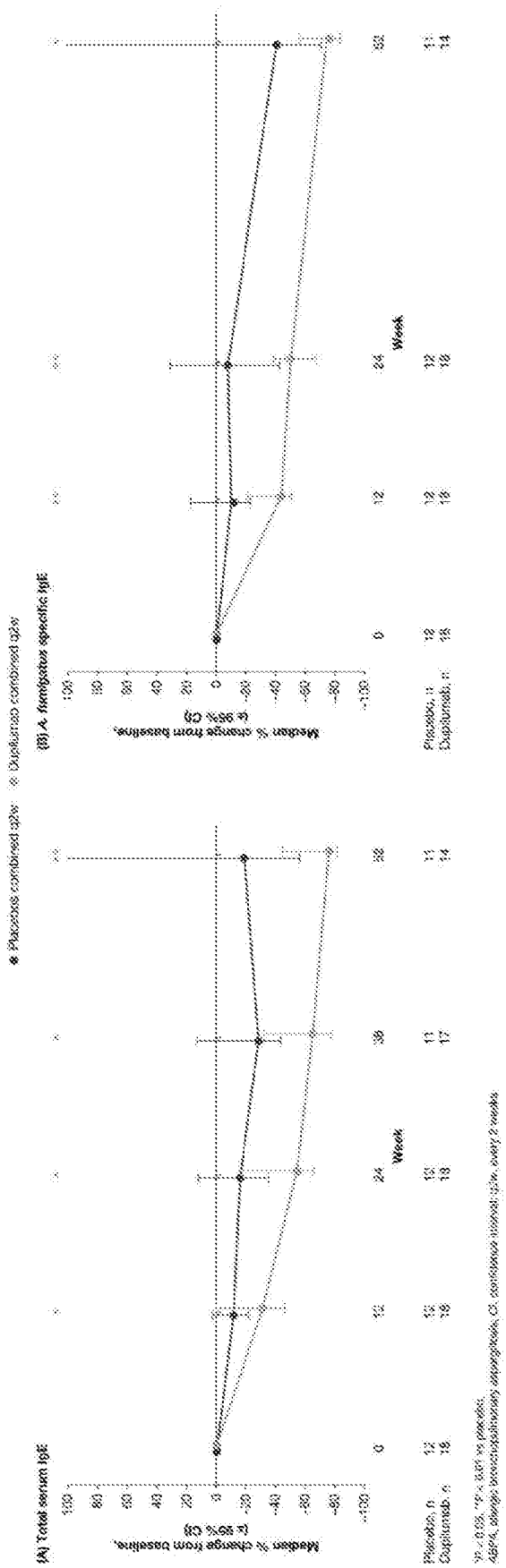


Fig. 15B

Fig. 16A

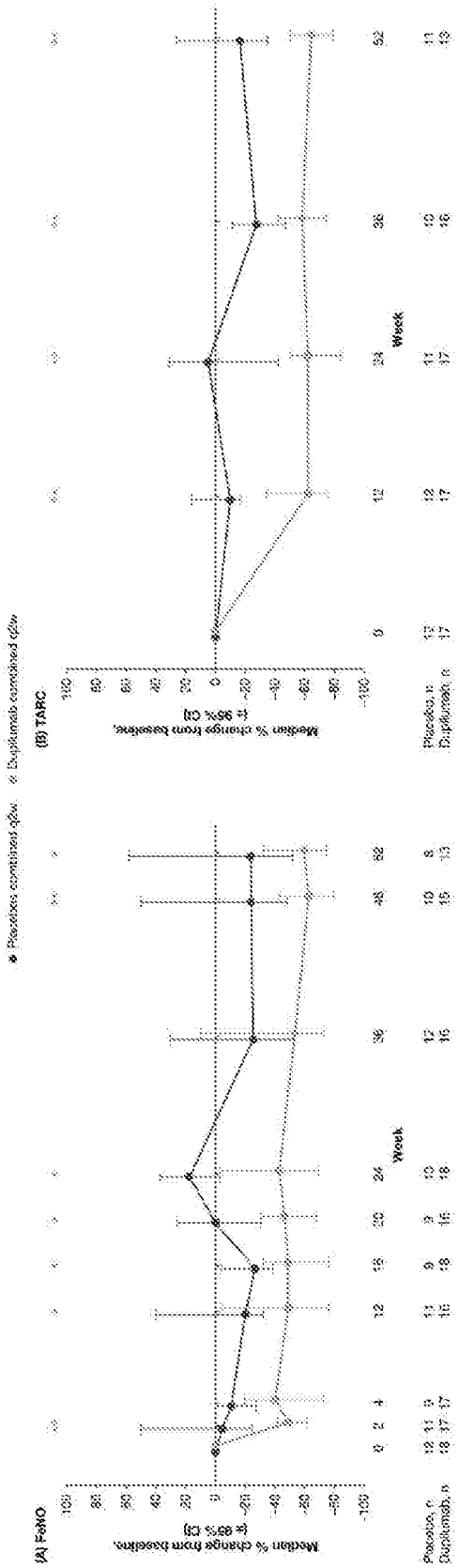


Fig. 16B

Fig. 16C

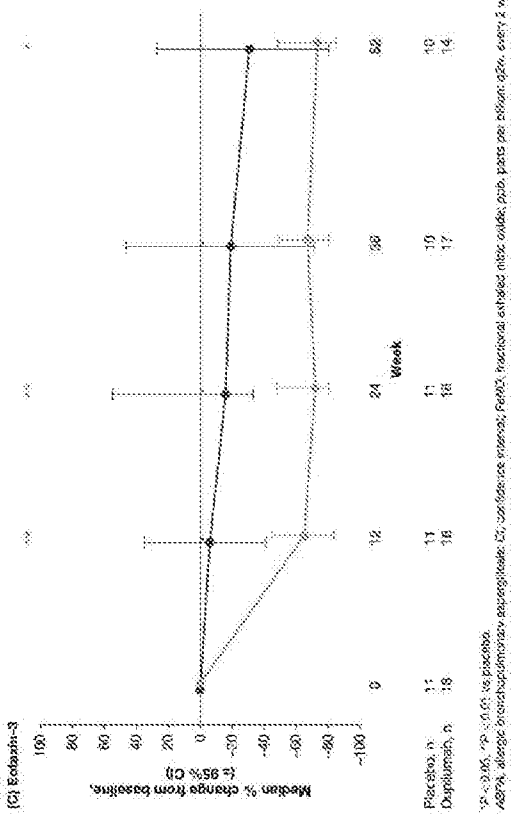
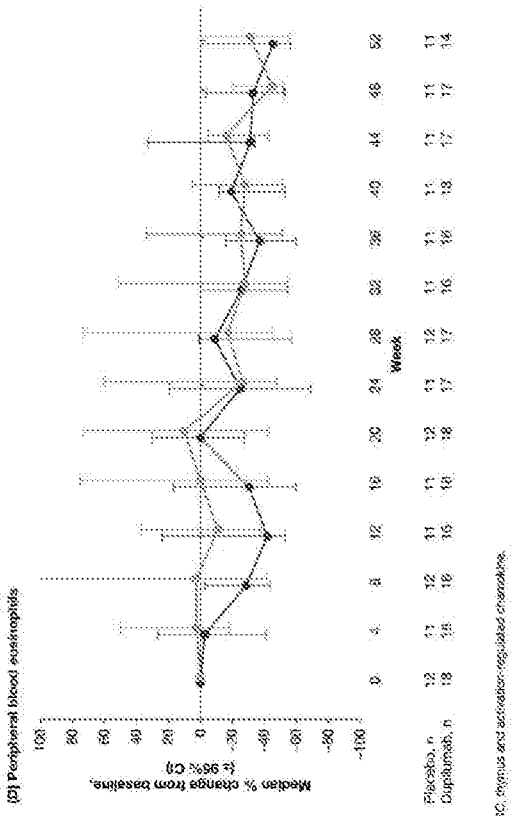


Fig. 16D



*P < 0.05, **P < 0.01 vs placebo.
ABPA, allergic bronchopulmonary aspergillosis; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; q2w, every 2 weeks; TARC, thymus and activation-regulated chemokine.

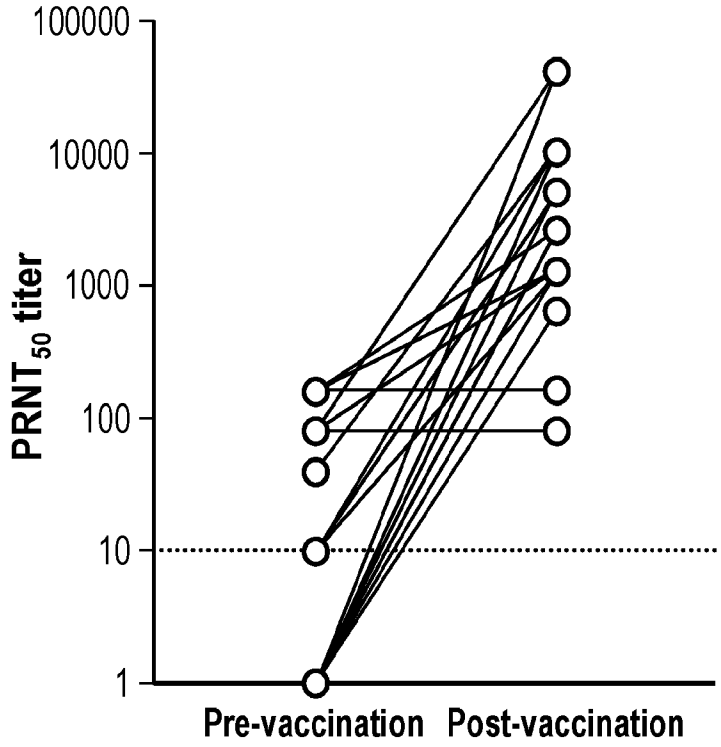


Fig. 17A

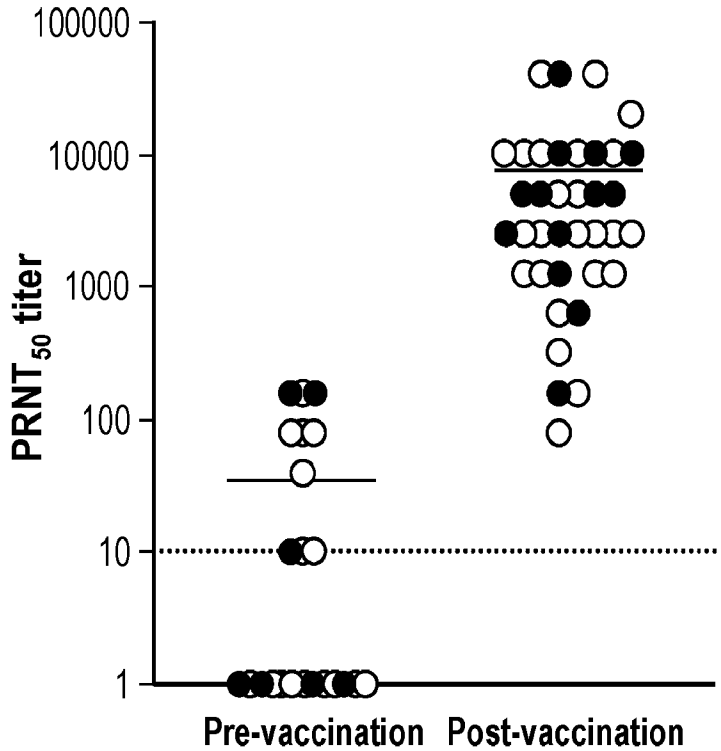


Fig. 17B

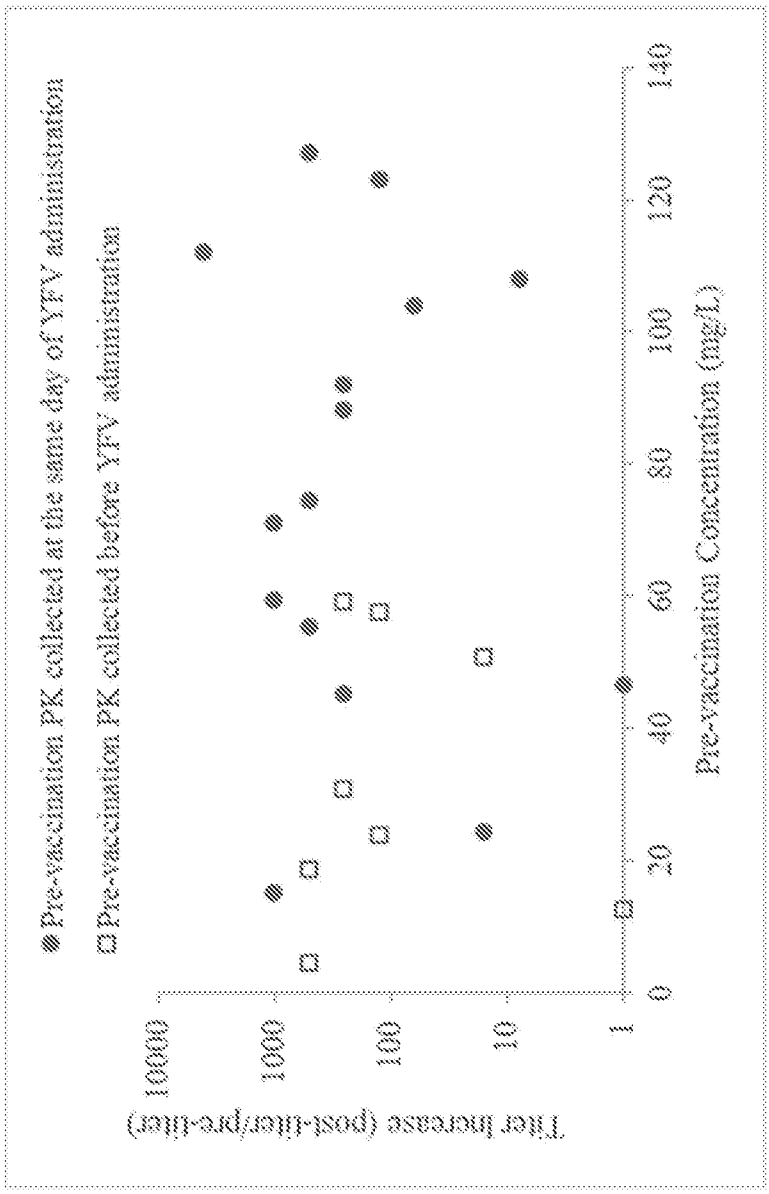
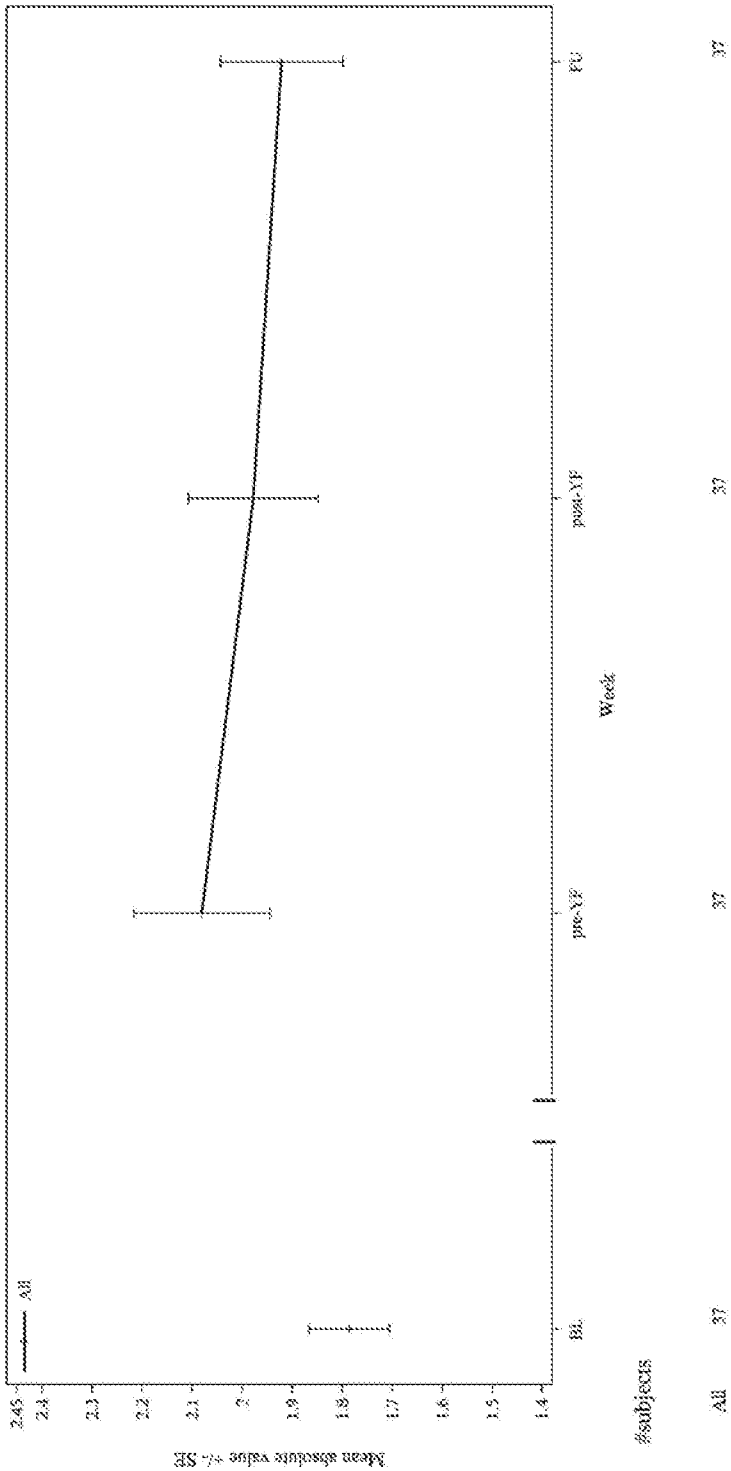

Pre-vaccination PK collected at the same day of YFV administration
Pre-vaccination PK collected before YFV administration
Titer increase (post-titer/pre-titer)
10000
1000
100
10
1
0
20
40
60
80
100
120
140
Pre-vaccination Concentration (mg/L)

Fig. 18

Fig. 19


All
2.45
2.8
2.3
2.2
2.1
2
1.9
1.8
1.7
1.6
1.5
1.4
Mean absolute value +/- SE
BL
pre-YF
post-YF
FU
Week
#subjects
All 37 37 37 37

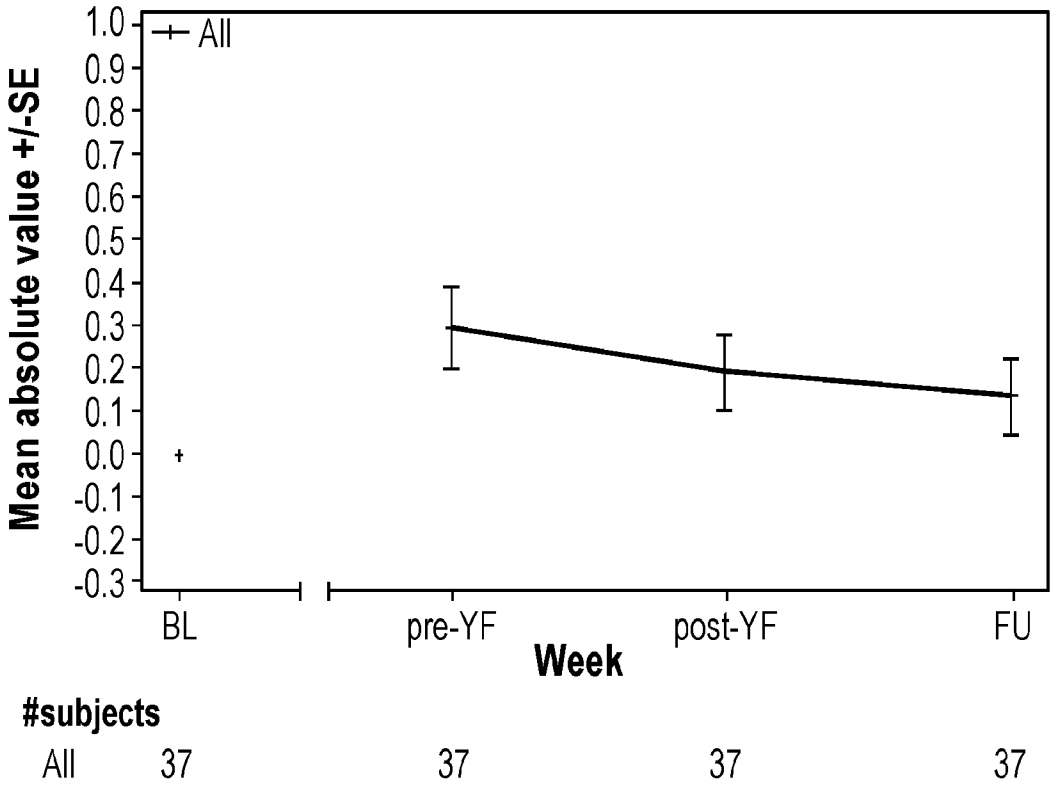

Mean absolute value +/-SE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
All
BL
pre-YF
post-YF
FU
Week
#subjects
All 37 37 37 37

Fig. 20

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/042075

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P11/06 A61P37/08 C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WENZEL SALLY ET AL: "Dupilumab in Persistent Asthma with Elevated Eosinophil Levels", NEW ENGLAND JOURNAL OF MEDICINE, MASSACHUSETTS MEDICAL SOCIETY, US, vol. 368, no. 26, 27 June 2013 (2013-06-27), pages 2455-2466, XP008165248, ISSN: 0028-4793, DOI: 10.1056/NEJMOA1304048 [retrieved on 2013-05-21] abstract; figures 1-3; tables 1-3 page 2455 - page 2466 ----- -/--	214-225, 230-232, 234-236

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2020	16/11/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schulz, Regine

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CASTRO MARIO ET AL: "Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma", NEW ENGLAND JOURNAL OF MEDICINE, MASSACHUSETTS MEDICAL SOCIETY, US , vol. 378, no. 26 28 June 2018 (2018-06-28), pages 2486-2496, XP009510100, ISSN: 0028-4793, DOI: 10.1056/NEJMOA1804092 Retrieved from the Internet: URL:https://ovidsp.ovid.com/ abstract; figures 1, 2; tables 1, 2 page 2487 - page 2494	214-225, 230-232, 234-236
A	Castro, M ET AL: "DUPILUMAB EFFICACY IN UNCONTROLLED, MODERATE-TO-SEVERE ALLERGIC ASTHMA IN THE PHASE 3 LIBERTY ASTHMA QUEST STUDY", Annals of Allergy, Asthma & Immunology, 1 November 2018 (2018-11-01), page S8, XP55738908, Retrieved from the Internet: URL:https://www.sciencedirect.com/science/ article/abs/pii/S1081120618307671?via=ihub [retrieved on 2020-10-12] the whole document	214-225, 230-232, 234-236
X,P	CORREN J ET AL: "D201 DUPILUMAB EFFICACY IN PATIENTS WITH UNCONTROLLED, MODERATE-TO-SEVERE ASTHMA AND SEROLOGIC EVIDENCE OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS", ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 123, no. 5, 1 November 2019 (2019-11-01), XP085896399, ISSN: 1081-1206, DOI: 10.1016/J.ANAI.2019.08.071 [retrieved on 2019-11-08] abstract; table 1	214-225, 230-232, 234-236
A	BLAUVELT ANDREW ET AL: "Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, MOSBY, INC, US, vol. 80, no. 1, 6 August 2018 (2018-08-06) , page 158, XP085556026, ISSN: 0190-9622, DOI: 10.1016/J.JAAD.2018.07.048 abstract; figures 1-3; tables I-III	214-225, 230-232, 234-236

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LOMMATZSCH MAREK ET AL: "Severe asthma: definition, diagnosis and treatment", DEUTSCHES ARZTEBLATT INTERNATIONAL FEB 2013,, vol. 111, no. 50, 12 December 2014 (2014-12-12), pages 847-855, XP002789189, ISSN: 1866-0452 abstract; figure 1; table 4 page 849, left-hand column, paragraph but last -----	214-225, 230-232, 234-236
A	WO 2019/028367 A1 (REGENERON PHARMA [US]; SANOFI BIOTECHNOLOGY [FR]) 7 February 2019 (2019-02-07) abstract; compound dupilumab; sequences SEQ ID NOs: 1, 2 page 41, paragraph [0151]; claims 1-6; example 1; tables 1-6 -----	214-225, 230-232, 234-236
A	SRIAROON PANIDA & BALLOW MARK: "Biological Modulators in Eosinophilic Diseases", CLINICAL REVIEWS IN ALLERGY AND IMMUNOLOGY, HUMANA PRESS, TOTOWA, NJ, US, vol. 50, no. 2, 17 August 2014 (2014-08-17), pages 252-272, XP035951893, ISSN: 1080-0549, DOI: 10.1007/S12016-014-8444-9 [retrieved on 2014-08-17] abstract; figures 1, 2; tables 1, 2 page 254 - page 258 page 259 - page 260 -----	214-225, 230-232, 234-236
A	TSUBOUCHI HIRONOBU ET AL: "Successful treatment with mepolizumab in a case of allergic bronchopulmonary aspergillosis complicated with nontuberculous mycobacterial infection", RESPIRATORY MEDICINE CME, ELSEVIER, AMSTERDAM, NL, vol. 28, 1 January 2019 (2019-01-01), XP085949027, ISSN: 2213-0071, DOI: 10.1016/J.RMCR.2019.100875 [retrieved on 2019-06-05] abstract; figures 1-4 -----	214-225, 230-232, 234-236

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Anonymous: "Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma - Full Text View - ClinicalTrials.gov", , 23 October 2018 (2018-10-23), XP055534115, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT02528214 [retrieved on 2018-12-13] page 2 - page 3 -----	214-225, 230-232, 234-236

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/042075

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-213, 226-229, 233, 237-256
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-213, 226-229, 233, 237-256

For the reasons explained in the request for clarification pursuant to PCT/GL/ISPE 9.34 and 9.35, issued on 21.10.2020, and reiterated in the appended Opinion, the claims so lack clarity, conciseness and unity that it is impossible to carry out a complete search.
The ISA asked the Applicant to indicate ONE independent claim (per category) to be searched, and to provide a list of claims to be deemed dependent on the one independent claim.
In response, the Applicant elected to the SECOND ASPECT, referring to independent claims 76, 97, 118, 139, 143, 147, 151, 172, 193, 214.
The Applicant requested that claims 76 - 236 be search and 'notwithstanding elected claims 76 - 96 for search.
The intentions and requests are unclear.
The ISA interprets this as a request for a search of claims 76 - 236 and, subsidiary, of claims covering at least the subject-matter of claims 76 - 96.
The response is inadequate because it does not provide all of the indications sought, and seems to assume that the Applicants are entitled to a search covering 163 claims of which 10 are independent and in the same category.
This remains in flagrant breach of Rule 6.1(a) and Art. 6 PCT.
The ISA must therefore determines ex officio the appropriate scope of the search.

The request for a search for claims 76 - 236 - that is, 163 claims of which 10 are independent - remains in flagrant breach of Rul e 6.1(a) and Art. 6 PCT, therefore it cannot be granted.
The request for a search for claims 76-96, on the other hand, is acceptable but appears inconsistent with Applicants' arguments. Upon further consideration, the ISA considers:

(i) It is reasonable to claim the medical use of an antibody characterized by the CDRs of dupilumab in treating ABPA-related asthma in patients with high allergy markers, which are defined as abnormally high levels of total serum IgE (>1000 IU/ml) and/or high levels of A. fumigatus-specific IgE (>0.35 kU/L) and/or abnormally high eosinophil counts (>500 cells/ul).

(ii) The independent claim that more closely covers this subject-matter is claim 214 (which encompasses the subject matter of claim 76 but is not so limited).

(iii) The dependent claims 215 - 236 parallel almost verbatim the dependent claims 77 - 96. Therefore here, too, it appears more appropriate, and beneficial

to the Applicant, to focus on these.

(iv) However, of the claims 215 - 236 dependent on claim 214, claims 226 - 229, 233 cannot be searched because they relate purely to desired clinical outcomes. The same would apply to claims 89, 90 - 92, 96.

Accordingly, the search is limited to claims 214 - 225, 230 - 232, 234 - 236 (which cover entirely, but are not limited to, the subject-matter of claims 76 - 96), with the understanding that the treatment is for ABPA-related asthma.

An opinion on patentability is provided only for claims that have been searched, and to the extent they have been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/042075

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019028367 A1	07-02-2019	US 2019040126 A1	07-02-2019
		WO 2019028367 A1	07-02-2019