METHODS FOR TREATING NASAL POLYPOSIS BY ADMINISTERING AN IL-4R ANTAGONIST

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/837,912, filed June 21, 2013 and European Application No. 14305670.3, filed May 7, 2014, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to the field of therapeutic treatments of inflammatory conditions. More specifically, the invention relates to the administration of interleukin-4 receptor (IL-4R) antagonists to treat nasal polyposis.

BACKGROUND

[0003] Nasal polyposis (NP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex. NP is a T helper cell-2 (Th-2) driven inflammatory process affecting the mucosa of the nose and paranasal sinuses. Eosinophils and their products are thought to be a hallmark of nasal polyp-associated inflammation as elevated levels of interleukin-5 (IL-5; promotes eosinophil survival and differentiation), eosinophil cationic protein (ECP), and eotaxin (eosinophil chemoattractant), factors that attract and activate eosinophils, are typically found in nasal polyps. Eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps, and nasal polyps are also associated with elevated levels of IgE. NP is characterized by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. Current treatment options range from local or systemic corticosteroids to functional endoscopic sinus surgery.

BRIEF SUMMARY OF THE INVENTION

[0004] In one aspect, the invention provides a method for treating nasal polyposis, where the method includes administering to a subject in need thereof a pharmaceutical composition containing an interleukin-4 receptor (IL-4R) antagonist, such as an anti-IL-4R antibody or antigen-binding fragment thereof. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or

antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

[0005] A subject suitable for treatment with an IL-4R antagonist may have one or more of sinusitis, rhinitis, asthma, aspirin hypersensitivity, non-steroidal anti-inflammatory drug (NSAID) hypersensitivity, or have previously undergone surgery to treat nasal polyposis. In some embodiments, the subject has chronic sinusitis or chronic rhinosinusitis. For example, the subject may have nasal polyposis with severe symptoms of sinusitis.

[0006] In some embodiments, the IL-4R antagonist is administered at a dose of 0.1 mg to 600 mg (e.g., 100 mg to 400 mg, such as 150 mg, 200 mg, 250 mg, 300 mg or 350 mg). In certain embodiments, the pharmaceutical composition is administered to the subject systemically or locally. For example, the pharmaceutical composition may be administered subcutaneously, intravenously, or intranasally.

[0007] In one embodiment, the pharmaceutical composition is administered to the subject subcutaneously at a dose of 300 mg.

[0008] In certain embodiments, one or more additional therapeutic agents are administered to the subject before, after or concurrent with the pharmaceutical composition comprising the IL-4R antagonist, such as the IL-4R antibody or antigen-binding fragment thereof. For example, in one embodiment, the one or more additional agents, such as a second therapeutic agent can be a TNF inhibitor, an IL-1 inhibitor, an IL-5 inhibitor, an IL-8 inhibitor, an IgE inhibitor, an NSAID (non-steroidal anti-inflammatory drug), an antibiotic, an anti-fungal agent, an intranasal corticosteroid, an inhaled corticosteroid, a systemic corticosteroid, a long-acting $beta_2$ agonist, a decongestant, or any combination thereof. In one embodiment, the second therapeutic agent is an inhaled corticosteroid, such as fluticasone or budesonide, or an intranasal corticosteroid, such as mometasone furoate nasal spray (MFNS). In another embodiment, the second therapeutic agent further includes a long-acting $beta_2$ agonist, such as salmeterol or formoterol.

[0009] In certain embodiments, administration of the IL-4R antagonist is followed by an improvement in one or more symptoms of nasal polyposis. For example, the administration of the antagonist can be followed by an improvement in one or more nasal polyposis-associated parameters, such as an improvement in a 22-item Sinonasal Outcome Test (SNOT-22) score; a nasal symptom score; number of nocturnal awakenings; a Visual Analog Score (VAS), such as for rhinosinusitis symptom severity; a five-item Asthma Control Questionnaire (ACQ5) score; nasal peak inspiratory flow (NPIF); the University of Pennsylvania Smell Identification Test (UPSIT); Lund-McKay Score; and three dimensional volumetric measurement of the maxillary sinus. In certain embodiments, administration of the antibody or antigen binding fragment thereof is followed by one or more of an increase in one or both of NPIF and UPSIT, and a

decrease in one or more of SNOT-22 score, nasal symptom score, VAS, Lund-McKay Score and 3D-Volumetric Score. In some embodiments, administration of the IL-4R antagonist is followed by a decrease in nasal polyp score in the patient.

[0010] In one aspect, the invention provides a method for treating nasal polyposis, by sequentially administering to a subject in need thereof a single initial dose of an interleukin-4 receptor (IL-4R) antagonist, such as an IL-4R antibody or an antigen-binding fragment thereof, followed by one or more secondary doses of the IL-4R antagonist. In some embodiments, each secondary dose is administered 1 to 15 weeks after the immediately preceding dose. In other embodiments, at least three secondary doses of the IL-4R antagonist are administered to the subject, and each secondary dose is administered days or weeks (e.g., 1 week or 2 weeks or more) after the immediately preceding dose. In another embodiment, the initial dose and the one or more secondary doses each include 50 mg to 500 mg of the IL-4R antagonist, e.g., 100 mg to 400 mg of the IL-4R antagonist, e.g., 150 mg, 200 mg, 250 mg, 300 mg, or 350 mg of the IL-4R antagonist. In some embodiments, the initial dose and the one or more secondary doses each contain the same amount of the IL-4R antagonist. In other embodiments, the initial dose comprises a first amount of the IL-4R antagonist, and the one or more secondary doses each comprise a second amount of the IL-4R antagonist. For example, the first amount of the IL-4R antagonist can be 1.5x, 2x, 2.5x, 3x, 3.5x, 4x or 5x or more than the second amount of IL-4R antagonist.

[0011] In one embodiment, the subject (e.g., a patient) has one or more of sinusitis, rhinitis, asthma, aspirin hypersensitivity, non-steroidal anti-inflammatory drug (NSAID) hypersensitivity, or has undergone surgery for nasal polyps. In some embodiments, the subject has chronic sinusitis or chronic rhinosinusitis. For example, the subject may have nasal polyposis with severe symptoms of sinusitis.

[0012] The initial dose and the secondary doses of the IL-4R antagonist can be administered by the same or different routes of administration. For example, the initial dose and the secondary doses can be administered subcutaneously, intravenously, or intranasally.

[0013] In certain embodiments, administration of the initial dose and the one or more secondary doses is followed by an improvement in one or more nasal polyposis associated parameters, such as an improvement in a 22-item Sinonasal Outcome Test (SNOT-22) score; a nasal symptom score; number of nocturnal awakenings; a Visual Analog Score (VAS), such as for rhinosinusitis symptom severity; a five-item Asthma Control Questionnaire (ACQ5) score; nasal peak inspiratory flow (NPIF); the University of Pennsylvania Smell Identification Test (UPSIT); Lund-McKay Score; and three dimensional volumetric measurement of the maxillary sinus. In certain embodiments, administration of the antibody or antigen binding fragment thereof is followed by one or more of an increase in one or both of NPIF and UPSIT, and a decrease in one or more of SNOT-22 score, nasal symptom score, VAS, Lund-McKay Score

and 3D-Volumetric Score. In some embodiments, administration of the IL-4R antagonist is followed by a decrease in nasal polyp score in the patient.

[0014] In certain embodiments, one or more additional therapeutic agents are administered to the subject before, after or concurrent with the pharmaceutical composition comprising the IL-4R antagonist, such as the IL-4R antibody or antigen-binding fragment thereof. For example, in one embodiment, the one or more additional agents, such as a second therapeutic agent can be a TNF inhibitor, an IL-1 inhibitor, an IL-5 inhibitor, an IL-8 inhibitor, an IgE inhibitor, an NSAID, an antibiotic, an anti-fungal agent, an intranasal corticosteroid, an inhaled corticosteroid, a systemic corticosteroid, a long-acting $beta_2$ agonist, a decongestant, or any combination thereof. In one embodiment, the second therapeutic agent is an inhaled corticosteroid, such as fluticasone or budesonide, or an intranasal corticosteroid, such as mometasone furoate nasal spray (MFNS). In another embodiment, the second therapeutic agent further includes a long-acting $beta_2$ agonist, such as salmeterol or formoterol.

[0015] In one aspect, the invention provides a method for treating nasal polyposis, by selecting a patient with a minimum bilateral nasal polyp score of 5, or at least two or more of the chronic symptoms of sinusitis selected from the group consisting of: nasal blockade/obstruction/congestion, anterior or posterior nasal drip, facial pain or pressure, and reduction or loss of smell; and administering to the selected patient a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), such that the patient's nasal polyp score is reduced or the two or more chronic symptoms of sinusitis are improved. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

[0016] In one aspect, the invention provides a method for treating nasal polyposis, by selecting a patient with a minimum bilateral nasal polyp score of 5, or at least two or more of the chronic symptoms of sinusitis selected from the group consisting of: nasal blockade/obstruction/congestion, anterior or posterior nasal drip, facial pain or pressure, and reduction or loss of smell; and sequentially administering to the patient a single initial dose of a

pharmaceutical composition an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), followed by one or more secondary doses of the antibody or antigen binding fragment thereof, such that the patient's nasal polyp score is reduced or the two or more chronic symptoms of sinusitis are improved. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

[0017] In one aspect, the invention provides a method for treating nasal polyposis, by determining in a subject the expression level of one or more genes selected from the group consisting of thymus and activation-regulated chemokine (TARC), eotaxin-3, periostin, carcinoembryonic antigen (CEA), and YKL-40; selecting the subject as a candidate for treatment with an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), if the subject has an elevated expression level of the one or more genes; and administering to the selected subject a pharmaceutical composition comprising an antibody or antigen binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), such that the level of the one or more genes is reduced. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

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[0019] In one aspect, the invention provides a method for treating nasal polyposis, by determining in a subject the level of blood eosinophils or sputum eosinophils; selecting the subject as a candidate for treatment with an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), if the subject has an elevated level of blood eosinophils or sputum eosinophils; and administering to the selected subject a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), such that the level of blood eosinophils or sputum eosinophils is reduced. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or

antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

[0020] In one aspect, the invention provides a method for treating nasal polyposis, by determining in a subject the level of blood eosinophils or sputum eosinophils; selecting the subject as a candidate for treatment with an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), if the subject has an elevated level of blood eosinophils or sputum eosinophils; and sequentially administering to the selected subject a single initial dose of a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist, such as antibody or antigen-binding fragment thereof that specifically binds an interleukin-4 receptor (IL-4R), followed by one or more secondary doses of the antibody or antigen binding fragment thereof, such that the level of blood eosinophils or sputum eosinophils is reduced. In one embodiment, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4Rα, such as an antibody or antigen binding fragment that comprises heavy and light chain CDR sequences from a heavy chain variable region (HCVR) of SEQ ID NO:1, and a light chain variable region (LCVR) of SEQ ID NO:2. For example, in one embodiment, the antibody or antigen binding fragment thereof comprises heavy chain CDR sequences of SEQ ID NOs:3, 4, and 5, and light chain CDR sequences of SEQ ID NOs:6, 7 and 8. For example, in one embodiment, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:2. In one embodiment, the IL-4R antagonist is dupilumab or an antigen-binding fragment thereof. Other exemplary anti-IL-4R antibodies or antigen-binding fragments thereof are described, for example, in US Patent Nos. 7,605,237 and 7,608,693.

[0021] Other embodiments will become apparent from the below figure and the Detailed Description.

BRIEF DESCRIPTION OF THE FIGURES

[0022] **FIG. 1** shows the schematic representation of an example of background therapy withdrawal time period in the treatment of an asthma patient.

DETAILED DESCRIPTION

[0023] Before the present 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.

[0024] 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. 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.).

[0025] All publications mentioned herein are incorporated herein by reference in their entirety.

Methods for Treating Nasal Polyposis

[0026] The present invention provides methods for treating nasal polyposis. As used herein, a "nasal polyp" is an overgrowth of tissue in one or more of the nasal cavities. The condition of nasal polyps is called “nasal polyposis.” About 80% of nasal polyps are highly edematous and filled with eosinophils. Nasal polyps can also present as fibrous, glandular or cystic.

[0027] Nasal polyposis (NP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex. NP is a T helper cell-2 (Th-2) driven inflammatory process affecting the mucosa of the nose and paranasal sinuses. Eosinophils and their products are thought to be a hallmark of nasal polyp-associated inflammation as elevated levels of interleukin-5 (IL-5; promotes eosinophil survival and differentiation), eosinophil cationic protein (ECP), and eotaxin (eosinophil chemoattractant), factors that attract and activate eosinophils, are typically found in nasal polyps. Eosinophils are the predominant inflammatory cell found in the sinuses and nasal polyps, and nasal polyps are also associated with elevated levels of IgE.

[0028] NP is characterized by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, anterior and posterior rhinorrhea, and facial pain. The presence or absence of nasal polyps can be confirmed for example by performing endoscopy, and the presence and extent of sinus and polyp involvement can be confirmed by methods such as coronal computed tomography (CT) scans.

[0029] An IL-4R antagonist can be used to treat nasal polyposis associated with a variety of conditions. For example, nasal polyposis is associated with sinusitis, rhinitis (e.g., allergic and non-allergic rhinitis), asthma (e.g., moderate-to-severe asthma), NSAID sensitivity (e.g., aspirin sensitivity), and infection, such as bacterial and fungal infection. Bacterial infections include, for example, staphylococcus infections. A subject with nasal polyposis can have a chronic infection, such as a chronic bacterial infection, e.g., a chronic staphylococcus aureus infection.

In some embodiments, the subject has recurring nasal polyposis, such as may be associated with recurring sinusitis. In other embodiments, the subject as cystic fibrosis or NARES (Non-Allergic Rhinitis with Eosinophilia Syndrome). In other embodiments, the subject has a relapse of nasal polyposis after receiving surgery to treat the polyps. Risk factors for nasal polyposis include genetic susceptibility, anatomic abnormality, mucociliary impairment, infection, and local immunologic imbalance.

[0030] An IL-4R antagonist can also be used to treat nasal polyposis in patients who have never previously received a treatment or surgery for NP. An IL-4R antagonist can also be used to treat nasal polyposis in patients who have previously undergone surgery, such as a nasal surgery, such as for treatment of nasal polyps. In certain embodiments, an IL-4R antagonist is administered to a subject whose nasal polyposis has relapsed after the subject received prior treatment for the polyps, such as a prior nasal surgery.

[0031] As used herein, the term "sinusitis" refers to any inflammatory condition characterized by inflammation of the paranasal sinuses, including inflammation of the maxillary, frontal, ethmoid and/or sphenoid paranasal sinuses. An IL-4R antagonist is suitable for treatment of nasal polyposis is associated with acute sinusitis, subacute sinusitis, chronic sinusitis and recurrent sinusitis. Acute sinusitis is characterized by a sudden onset of cold-like symptoms such as runny, stuffy nose and facial pain that does not go away after 10 to 14 days. Acute sinusitis typically lasts less than four weeks. Subacute sinusitis lasts four to eight weeks. Chronic sinusitis lasts eight weeks or longer, and recurrent sinusitis is characterized by sinusitis episodes that occur three or more times in one year. More than 80% of patients with chronic sinusitis with nasal polyps have eosinophilic upper airway inflammation.

[0032] Many patients with chronic sinusitis have "chronic hyperplastic eosinophilic sinusitis," which is characterized by marked inflammation of the sinuses, increased eosinophils and mixed mononuclear cells, and a relative paucity of neutrophils. Some of these patients have one or more of associated nasal polyps, asthma, and aspirin or NSAID sensitivity. In certain embodiments, an IL-4R antagonist can be used to treat nasal polyposis in a subject who has chronic hyperplastic eosinophilic sinusitis.

[0033] The term "rhinitis" refers to an allergic response, such as to a common allergen ("allergic rhinitis," e.g., perennial allergic rhinitis) or to an environmental irritant ("non-allergic rhinitis"). Symptoms of allergic rhinitis include sneezing; stuffy or runny nose; sinus pressure, and pain or throbbing in the cheeks or nose; and itching in the nose, throat, eyes and ears.

[0034] Symptoms of non-allergic rhinitis include constriction or inflammation in the nasal passages which leads to many of the same symptoms of allergic rhinitis. Non-allergic rhinitis can be caused, for example, by strong chemical or smoky environments, or by long-term use of certain medications or dependency on nasal sprays.

[0035] As used herein, the term "rhinosinusitis" refers to a condition that has symptoms of both rhinitis and sinusitis. Rhinosinusitis includes acute rhinosinusitis and chronic rhinosinusitis.

Acute rhinosinusitis can be caused by an infection, such as a bacterial, viral or fungal infection, or by a chemical irritation. Cigarette-smoke-induced acute rhinosinusitis and chlorine fume-induced chronic rhinosinusitis are examples of acute rhinosinusitis. NP is most commonly associated with chronic rhinosinusitis (CRS), which is characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 8 weeks. Chronic eosinophilic rhinosinusitis with nasal polyps is a condition that lasts longer than 8 weeks.

[0036] Chronic sinusitis (CS) and chronic rhinosinusitis (CRS) are conditions that last longer than eight weeks. The underlying causes of acute sinusitis and acute rhinosinusitis may lead to chronic sinusitis or chronic rhinosinusitis if the resulting inflammation persists for more than 8 weeks. Chronic rhinosinusitis includes for example, eosinophilic chronic hyperplastic rhinosinusitis.

[0037] Additional subcategories of chronic sinusitis (and chronic rhinosinusitis) include, *e.g.*, superantigen-induced eosinophilic chronic sinusitis (*e.g.*, sinusitis induced by exo- and endo-toxins produced by bacteria such as *Staphylococcus aureus*); allergic fungal sinusitis (*e.g.*, sinusitis induced by fungi such as *Aspergillus* or *Alternaria*); non-allergic fungal eosinophilic chronic sinusitis; and aspirin-exacerbated eosinophilic chronic sinusitis.

[0038] An IL-4R antagonist can be used to treat nasal polyposis in subjects having any of the disorders described above.

Methods for Improving Nasal Polyp-Associated Parameters

[0039] The present invention includes methods for improving one or more nasal polyp-associated parameters in a subject in need thereof, wherein the methods include administering a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist to the subject. For example, an IL-4R receptor antagonist can reduce endoscopic nasal polyp score in a patient. A nasal polyp score of 0 indicates the presence of no polyps. A nasal polyp score of 1 indicates the presence of small polyps in the middle meatus not reaching below the inferior border of the middle turbinate. A nasal polyp score of 3 indicates large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate. A nasal polyp score of 4 indicates large polyps causing complete obstruction of the inferior nasal cavity (see Table 15 below). The maximum score is 8 (4 points per nasal cavity). Treatment with an IL-4R antagonist can decrease nasal polyp score by about 1 to about 8 points. For example, treatment with an IL-4R antagonist can decrease nasal polyp score by about 1 point or more, by about 2 points or more, or by about 3 points or more. In some embodiments, treatment with an IL-4R antagonist can decrease nasal polyp score by about 1 point, or a fraction thereof; by 2 points, or a fraction thereof; by 3 points, or a fraction thereof; by 4 points, or a fraction thereof; by 5 points, or a fraction thereof; by 6 points, or a fraction thereof; by 7 points, or a fraction thereof; or by 8 points or a fraction thereof. A reduction in nasal polyp score may correlate with an improvement

in one or more other nasal polyp-associated parameters. Such a correlation, however, is not necessarily observed in all cases.

[0040] Other examples of "nasal polyp-associated parameters" include: (a) 22-item SinoNasal Outcome Test (SNOT-22) score; (b) subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip) and loss of sense of smell; (c) number of nocturnal awakenings; (d) Visual Analog Score (VAS) to assess patient-rated rhinosinusitis symptom severity; (e) five-item Asthma Control Questionnaire (ACQ5) score, such as in patients with asthma; (f) Nasal Peak Inspiratory Flow (NPIF); (g) smell test (University of Pennsylvania Smell Identification Test (UPSIT)); (h) physiological parameters, such as measured by nasal endoscopy and CT scan; (i) Lund-Mackay Score; and (j) Three Dimensional volumetric measurement of the maxillary sinus.

[0041] 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 questionnaire to assess the impact of chronic rhinosinusitis (CRS) on quality of life. The questionnaire measures items related to sinonasal conditions and surgical treatments. The score ranges from 0 to 110, and higher scores imply greater impact of CRS on Health Related Quality of Life (HRQoL) (Hopkins et al 2009, Clin. Otolaryngol. 34: 447-454).

[0042] The present invention includes therapeutic methods that result in a decrease in SNOT-22 score from baseline of at least 1 point at week 4 to week 16 following administration of the IL-4R antagonist. For example, administration of an IL-4R antagonist will result in a decrease in SNOT-22 score at week 4, week 6, week 8, week 12, or week 16 following initiation of treatment. In some embodiments, administration of an IL-4R antagonist to a subject in need thereof causes 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 4, week 6, week 8 or week 12.

[0043] Individual and Total Nasal Symptom Score. Subject-assessed symptoms are assayed by responding to morning and evening individual rhinosinusitis symptom questions using a 0-3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), and including the symptoms of congestion and/or obstruction, anterior rhinorrhea, posterior rhinorrhea, and loss of sense of smell. A measure of night-time awakenings can also be tracked. For example, a measure of night-time awakenings can be assessed according to the following scores based on subject self-assessment: 0= no symptoms, slept through the night; 1= slept well, but some complaints in the morning; 2= woke up once because of rhinosinusitis symptoms (including early awakening); 3= woke up several times because of symptoms (including early awakening); 4= bad night, awake most of the night because of symptoms. Administration of an IL-4R antagonist can result, for example, in a decrease in average number of nighttime awakenings per night from baseline of at least about 0.10 times per night at week 4 to week 16 following initiation of treatment with a pharmaceutical

composition comprising an anti-IL-4R antagonist. For example, a decrease in frequency of nighttime awakenings per night from baseline of at least about 0.10 times per night can be detected at week 4, week 6, week 8, week 12, or week 16 following initiation of treatment. Administration of an IL-4R antagonist to a subject in need thereof can cause a decrease in average number of nighttime awakenings per night from baseline by 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 time per night, 2.0 times per night, or more at week 4, week 8, week 12, or week 16, for example.

[0044] Visual Analog Score (VAS). The VAS is a measure to assess patient-related rhinosinusitis symptom severity on a scale of 1 to 10. Mild symptoms are indicated by a score of 0 to 3, moderate symptoms are indicated by a VAS score of >3 to 7, and severe symptoms are indicated by a VAS score of >7 to 10. Administration of an IL-4R antagonist to a subject in need thereof causes a decrease in VAS score from baseline of about 0.5 point, 1 point, 1.5 points, 2 points, 2.5 points, 3 points, 3.5 points, 4 points, or more at week 4, week 6 or week 12. The decrease in VAS score can be detected as early as week 4, and as late as week 12 or later following administration of the IL-4R antagonist.

[0045] 5-Item Asthma Control Questionnaire (ACQ) Score. The ACQ5 measures both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment. The five questions on the ACQ5 reflect the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients respond to the symptom questions on a 7-point scale (0=no impairment, totally controlled; 6= maximum impairment, severely uncontrolled).

[0046] The present invention includes therapeutic methods which result in a decrease in ACQ5 score from baseline of at least 0.10 point at week 12 following initiation of treatment with a pharmaceutical composition comprising an anti-IL-4R antagonist. For example, according to the present invention, 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 4, week 6 or week 12. The decrease in ACQ score can be detected as early as week 4, and as late as week 12 or later following administration of the IL-4R antagonist.

[0047] Nasal Peak Inspiratory Flow (NPIF). The Nasal Peak Inspiratory Flow (NPIF) represents a physiologic measure of air flow through both nasal cavities during forced inspiration and/or expiration expressed in liters per minute. Nasal inspiration correlates most with the subjective feeling of obstruction and is used to monitor nasal flow. Administration of an IL-4R

antagonist to a subject in need thereof causes an increase in NPIF from baseline by about 0.10 liters per minute, 0.15 liters per minute, 0.20 liters per minute, 0.25 liters per minute, 0.30 liters per minute, 0.35 liters per minute, 0.40 liters per minute, 0.45 liters per minute, 0.50 liters per minute, 0.55 liters per minute, 0.60 liters per minute, 0.65 liters per minute, 0.70 liters per minute, 0.75 liters per minute, 0.80 liters per minute, 0.85 liters per minute, or more at week 4, week 6 or week 12. The increase in NPIF score can be detected as early as week 4, and as late as week 12 or later following administration of the IL-4R antagonist.

[0048] University of Pennsylvania Smell Identification Test (UPSIT). The UPSIT is a method to quantitatively assess human olfactory function. The test consists of samples of odorants, and the subject has to describe the odor. The score is based on the number of correct answers. This test can distinguish patients with a normal sense of smell ("normosmia") from those with different levels of reduction ("mild, moderate and severe microsmia") or loss ("anosmia"). Administration of an IL-4R antagonist to a subject in need thereof causes an increase in UPSIT score from baseline by about 0.5 points, 1 point, 1.5 points, 2 points, 2.5 points, 3 points, 3.5 points or more at week 4, week 6 or week 12. The increase in UPSIT score can be detected as early as week 4, and as late as week 12 or later following administration of the IL-4R antagonist.

[0049] Physiological parameters. Efficacy of an IL-4R antagonist can be assayed by measuring the effect of physiological parameters, such as within the nasal cavities, such as by nasal endoscopy or computed tomography (CT) scan.

[0050] Lund-Mackay Score. The Lund-Mackay scoring system is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side. For patients in whom the osteomeatal complex (OC) is missing (because of a previous surgery) the location of the former OC is considered and a score is provided, as if the OC was there. Administration of an IL-4R antagonist to a subject in need thereof causes a decrease in Lund-Mackay score from baseline by 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 4, week 6 or week 12. The decrease in Lund-Mackay score can be detected as early as week 4, and as late as week 12 or later following administration of the IL-4R antagonist.

[0051] Three-Dimensional volumetric measurement of maxillary sinus. This value is used to calculate the volume of air (mL); the volume of mucosa (mL); the percent sinus occupied by disease; and the thickness of lateral wall in the maxillary sinus. Administration of an IL-4R antagonist to a subject in need thereof causes an increase in the Three-Dimensional volumetric measurement.

[0052] Quality of Life (QoL) Questionnaires. Various QoL Questionnaires can be used to monitor efficacy of an IL-4R antagonist, including Short-Form-36 (SF-36) Questionnaire, the Euroqol-5D (EQ-5D), nasal polyp related resource use questionnaire, and the patient qualitative self-assessment.

[0053] The SF-36 is a 36 item questionnaire that measures eight multi-item dimensions of health: physical functioning (10 items) social functioning (2 items) role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). For each dimension, item scores are coded, summed, and transformed on a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardized summary scores can also be calculated from the SF-36; the physical component summary (PCS) and the mental health component summary (MCS).

[0054] The EQ-5D is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal and inter-disease comparisons. EQ-5D, designed for self-completion by patients, consists of two parts, the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; and each dimension has 3 levels: no problem, some problems, severe problems. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

[0055] The nasal polyp related resource use questionnaire is a questionnaire of health care resource utilization for nasal polyposis, including specialist visits, emergency care visits, sick leaves, days off etc.

[0056] Improvement of a nasal polyp-associated parameter, such as a nasal polyp-associated parameter described above, can be expressed as a percentage. For example, a score can be improved by 30% or more, by 40% or more, by 50% or more, by 60% or more, by 70% or more, or by 80% or more.

[0057] An "improvement in a nasal polyp-associated parameter" means an increase from baseline of one or more of NPIF, UPSIT, and/or a decrease from baseline of one or more of SNOT-22 score, subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip) and loss of sense of smell; number of nocturnal awakenings; VAS score; Lund-Mackay score; and 3D volumetric scores; and ACQ5 score in patients with asthma. As used herein, the term "baseline," with regard to a nasal polyp-associated parameter, means the numerical value of the nasal polyp-associated parameter for a patient prior to or at the time of administration of a pharmaceutical composition of the present invention.

[0058] To determine whether a nasal polyp-associated parameter has "improved," the parameter is quantified at baseline and at a time point after administration of the pharmaceutical composition of the present invention. For example, a nasal polyp-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 a pharmaceutical composition of the present invention. In some embodiments, the parameter is measured daily (e.g., once or twice per day), weekly, biweekly, or monthly. In other embodiments, the parameter is measured daily and the mean value determined over the course of a month is compared to baseline.

[0059] 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 nasal associated parameter (*e.g.*, an increase or decrease, as the case may be, depending on the specific parameter being measured).

Interleukin-4 Receptor Antagonists

[0060] In one embodiment, a subject in need thereof is administered a therapeutic composition comprising an interleukin-4 receptor (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, peptide-based IL-4R antagonists (*e.g.*, "peptibody" molecules), and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R.

[0061] The term "human IL-4R" (hIL-4R), as used herein, is intended to refer to the IL-4Rα subunit, which is a component of the IL-4 receptors Type I and Type II, as well as the IL-13 receptor system. An IL-4R antagonist, such as an anti-IL-4Rα antibody or antigen-binding fragment thereof, blocks the function of both IL-4 and IL-13 signal transduction.

[0062] The term "antibody", as used herein, is intended to refer 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 some embodiments, the FRs of the anti-Ang-2 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.

[0063] The term "antibody," as used herein, 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 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.

[0064] 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," as used herein.

[0065] 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 which 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.

[0066] 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 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 which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody 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)).

[0067] 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, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an anti-IL-4R antibody using routine techniques available in the art.

[0068] 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.

[0069] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies featured in the invention 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", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0070] The term "recombinant human antibody", as used herein, is intended to include 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*.

[0071] 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.

[0072] 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. The instant invention encompasses 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.

[0073] An "isolated antibody," as used herein, 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.

[0074] 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, as used herein, 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.

[0075] The anti-IL-4R antibodies useful for the methods featured herein may include one or more amino acid substitutions, insertions and/or 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. The present invention includes methods involving the use of antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or 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"). 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 which 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 present invention.

[0076] The present invention also includes 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 present invention includes 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.

[0077] The term "surface plasmon resonance", as used herein, 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).

[0078] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0079] 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.

[0080] According to certain exemplary embodiments of the present invention, the IL-4R antagonist is an anti-IL-4Rα antibody, or antigen-binding fragment thereof comprising a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the anti-IL-4R antibodies as set forth in US Patent Nos. 7,608,693 and 7,605,237. In certain exemplary embodiments, the anti-IL-4Rα antibody or antigen-binding fragment thereof that can be used in the context of the methods of the present invention comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:2. According to certain embodiments, the anti-IL-4Rα antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3; the HCDR2 comprises the amino acid sequence of SEQ ID NO:4; the HCDR3 comprises the amino acid sequence of SEQ ID NO:5; the LCDR1 comprises the amino acid sequence of SEQ

ID NO:6; the LCDR2 comprises the amino acid sequence of SEQ ID NO:7; and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8. In yet other embodiments, the anti-IL-4R antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO:1 and an LCVR comprising SEQ ID NO:2. According to certain exemplary embodiments, the methods of the present invention comprise the use of the anti-IL-4Rα antibody referred to and known in the art as dupilumab, or a bioequivalent thereof.

[0081] The term “bioequivalent” as used herein, refers to a molecule having similar bioavailability (rate and extent of availability) after administration at the same molar dose and under similar conditions (e.g., same route of administration), such that the effect, with respect to both efficacy and safety, can be expected to be essentially same as the comparator molecule. Two pharmaceutical compositions comprising an IL-4R antagonist are bioequivalent if they are pharmaceutically equivalent, meaning they contain the same amount of active ingredient (e.g., IL-4R antagonist), in the same dosage form, for the same route of administration and meeting the same or comparable standards. Bioequivalence can be determined, for example, by an *in vivo* study comparing a pharmacokinetic parameter for the two compositions. Parameters commonly used in bioequivalence studies include peak plasma concentration (C_{max}) and area under the plasma drug concentration time curve (AUC).

[0082] Other anti-IL-4Rα antibodies that can be used in the context of the methods of the present invention include, *e.g.*, the antibody referred to and known in the art as AMG317 (Corren *et al*., 2010, *Am J Respir Crit Care Med., 181*(8):788-796), or any of the anti-IL-4Rα antibodies as set forth in US Patent No. 7,186,809, or US Patent No. 8,092,804.

[0083] The anti-IL-4Rα antibodies used in the context of the methods of the present invention may have pH-dependent binding characteristics. For example, an anti-IL-4Rα antibody for use in the methods of the present invention may exhibit reduced binding to IL-4Rα at acidic pH as compared to neutral pH. Alternatively, an anti-IL-4Rα antibody of the invention may exhibit enhanced binding to its antigen at acidic pH as compared to neutral pH. The expression "acidic pH" includes pH values less than about 6.2, *e.g.*, about 6.0, 5.95, 5,9, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

[0084] In certain instances, "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" is expressed in terms of a ratio of the K_D value of the antibody binding to IL-4Rα at acidic pH to the K_D value of the antibody binding to IL-4Rα at neutral pH (or vice versa). For example, an antibody or antigen-binding fragment thereof may be regarded as exhibiting "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" for purposes of the present invention if the antibody or antigen-binding fragment thereof exhibits an acidic/neutral K_D ratio of about 3.0 or greater. In certain exemplary embodiments, the acidic/neutral K_D ratio for an antibody or antigen-binding fragment of the present invention can be about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0,

6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 20.0. 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 100.0 or greater.

[0085] Antibodies with pH-dependent binding characteristics may be obtained, *e.g.*, by screening a population of antibodies for reduced (or enhanced) binding to a particular antigen at acidic pH as compared to neutral pH. Additionally, modifications of the antigen-binding domain at the amino acid level may yield antibodies with pH-dependent characteristics. For example, by substituting one or more amino acids of an antigen-binding domain (*e.g.*, within a CDR) with a histidine residue, an antibody with reduced antigen-binding at acidic pH relative to neutral pH may be obtained. As used herein, the expression "acidic pH" means a pH of 6.0 or less.

Pharmaceutical Compositions

[0086] The present invention includes methods which include administering an IL-4R antagonist to a patient, where the IL-4R antagonist is contained within a pharmaceutical composition. The pharmaceutical compositions featured in the invention 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.

[0087] 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 preferred 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).

[0088] Various delivery systems are known and can be used to administer a pharmaceutical composition containing an IL-4R antagonist, including 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, 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.

[0089] A pharmaceutical composition can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition. Such a pen delivery device, including an autoinjection 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.

[0090] 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 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.

[0091] For direct administration to the sinuses, the pharmaceutical compositions containing IL-4R antagonists may be administered using, *e.g.*, a microcatheter (*e.g.*, an endoscope and microcatheter), an aerosolizer, a powder dispenser, a nebulizer or an inhaler.

[0092] 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.

[0093] 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 preferably filled in an appropriate ampoule.

[0094] 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.

Dosage

[0095] The amount of IL-4R antagonist (*e.g.*, anti-IL-4R antibody, or antigen binding fragment thereof) administered to a subject according to the methods featured herein is generally a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of IL-4R antagonist that results in a detectable improvement in one or more symptoms associated with nasal polyps, or a dose of IL-4R antagonist that inhibits, prevents, lessens, or delays the progression of nasal polyps or a condition associated with nasal polyps. In the case of an anti-IL-4R antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 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, or about 600 mg, of the anti-IL-4R antibody or antigen binding fragment.

[0096] 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.

Combination Therapies

[0097] The methods, according to certain embodiments, include 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. 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.

[0098] 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), an IL-13 antagonist, 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, an antibiotic (e.g., doxycycline), an anti-fungal agent, a leukotriene, an antihistamine, an α-adrenergic decongestant, a mucolytic, an NSAID, a long-acting $beta_2$ agonist (*e.g.*, salmeterol or formoterol), a short-acting $beta_2$ agonist, a steroid (e.g., an oral steroid), a corticosteroid, such

as an intranasal corticosteroid (*e.g.*, mometasone furoate (MFNS; e.g., Nasonex®)), or an inhaled corticosteroid (e.g., fluticasone or budesonide), an allergen immunotherapy, 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)]).

[0099] In some embodiments, the IL-4R antagonist is administered after a subject receives surgery to treat nasal polyposis.

Administration Regimens

[00100] According to certain embodiments, multiple doses of an IL-4R antagonist may be administered to a subject over a defined time course. The methods include, for example, 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). The present invention includes methods which 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.

[00101] 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 which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of IL-4R antagonist, but will generally 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 will vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment.

[00102] 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," as used herein, means, in a sequence of multiple administrations, the dose of IL-4R antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[00103] These 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.

[00104] 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.

[00105] In certain embodiments, the initial dose (e.g., a “loading dose”) is higher than either or both of the secondary and tertiary doses. For example, the initial dose can be a loading dose, which is 1.5x, 2x, 2.5x, 3x or more greater than the secondary dose.

Treatment Populations

[00106] The methods featured in the present invention including administering to a subject in need thereof a therapeutic composition comprising an IL-4R antagonist. As used herein, the expression "a subject in need thereof" means a human or non-human animal that exhibits one or more symptoms or indication of nasal polyposis, or who has been diagnosed with nasal polyposis, or chronic symptoms of sinusitis. For example, a subject in need thereof has bilateral nasal polyps, and a nasal polyp score of at least 5 out of a maximum of 8 for both nostrils, with at least a score of 2 for each nostril. In certain embodiments, the polyps are in the middle meatus. In certain embodiments, the presence of nasal polyps is confirmed by endoscopy. In some embodiments, the subject also has bilateral mucosal disease, which is confirmed by a method such as CT scan. As used herein “bilateral mucosal disease” is an infection of the mucous lining of the sinus cavities, e.g., the maxillary sinus cavities. In some embodiments, nasal polyposis (e.g., a nasal polyp score of at least 5 out of a maximum of 8 for both nostrils, with at least a score of 2 for each nostril) persists even after a treatment regimen of inhaled corticosteroids (INCS), such as where the INCS was administered for at least 6 weeks, at least 7 weeks, at least 8 weeks, or longer.

[00107] In certain embodiments, a subject in need thereof has anterior and/or posterior mucopurulent drainage, nasal obstruction, and a decreased sense of smell. In certain embodiments, a subject in need thereof has had symptoms of nasal polyposis for 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks or more. In yet other embodiments, the subject has received a previous treatment, such as with an intranasal corticosteroid (e.g.,

MFNS), for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks or longer, prior to receiving treatment with an IL-4R antagonist. In some embodiments the subject will continue to receive the INCS while receiving treatment with the IL-4R antagonist. In other embodiments, the subject stops receiving the INCS before receiving treatment with the IL-4R antagonist, or the subject stops receiving treatment with the INCS if administration with the IL-4R antagonist is effective to treat the nasal polyposis. In some embodiments, the subject tapers the dose of the INCS before stopping treatment completely.

[00108] A subject in need thereof may further have been diagnosed with nasal polyposis on the basis of one or more of the following: (a) 22-item SinoNasal Outcome Test (SNOT-22) score; (b) subject-assessed nasal congestion/obstruction, anterior rhinorrhea, posterior rhinorrhea and loss of sense of smell; (c) number of nocturnal awakenings; (d) Visual Analog Score (VAS) to assess patient-rated rhinosinusitis symptom severity; (e) five-item Asthma Control Questionnaire (ACQ5) score in patients with asthma; (f) Nasal Peak Inspiratory Flow (NPIF); (g) smell test (University of Pennsylvania Smell Identification Test (UPSIT); (h) physiological parameters, such as measured by nasal endoscopy and CT scan; (i) Lund-Mackay Score; and (k) Three Dimensional volumetric measurement of the maxillary sinus.

[00109] For example, in certain embodiments, a “subject in need thereof” is a human patient with chronic symptoms of sinusitis, which are the presence of at least two of the following symptoms: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; and reduction or loss of smell.

[00110] In certain embodiments, a "subject in need thereof" is a human patient with a SNOT-22 score of greater than about 7, greater than about 10, greater than about 15, greater than about 20, greater than about 25, greater than about 30, greater than about 35, greater than about 40, greater than about 45, or greater than about 50. A "subject in need thereof" may also be a human patient who exhibits a Lund-Mackay score of greater than about 4, greater than about 5, greater than about 6, greater than about 7, greater than about 8, greater than about 9, greater than about 10, greater than about 11, greater than about 12, or greater than about 13.

[00111] 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 another medication, “a background therapy.” The background therapy can be, for example, an intranasal corticosteroid (INCS, or ICS), such as Mometasone furoate nasal spray (MFNS; Nasonex®). In some embodiments, a “subject in need thereof” is an asthma patient who prior to receiving an IL-4R antagonist, has been prescribed or is currently taking an INCS in combination with a long-acting beta$_2$-adronergic antagonist (LABA). Examples of INCS/LABA therapies include fluticasone/salmeterol combination therapy and budesonide/formoterol combination therapy. In some embodiments, the background therapy is a nasal saline, a topical decongestant, a topical anesthetic, a leukotriene antagonist or a systemic antihistamine. In some embodiments, the

"subject in need thereof" continues the background therapy after the subject receives the IL-4R antagonist, and in other embodiments, the subject in need thereof stops receiving the background therapy (e.g., at once or gradually) before receiving the IL-4R antagonist.

EXAMPLES

[00112] 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.

Example 1: Clinical Trial of Subcutaneously Administered Anti-IL-4R Antibody (mAb1) In Patients with Persistent Moderate-to-Severe Eosinophilic Asthma, Including Asthma Patients with Chronic Hyperplastic Eosinophilic Sinusitis

A. Study Objectives and Overview

[00113] A randomized, placebo-controlled, double-blind, parallel group study was conducted with once-a-week subcutaneous administration of either 300 mg dupilumab ("mAb1") or placebo for 12 weeks to patients with persistent moderate-to-severe eosinophilic asthma who were partially controlled/uncontrolled by inhaled corticosteroid (ICS) and long-acting beta2 agonist (LABA) therapy. Dupilumab is an anti-IL-4R antibody having a heavy chain variable region of SEQ ID NO:1, and a light chain variable region of SEQ ID NO:2. Dupilumab is described in US 7,608,693.

[00114] The primary objective of the study was to investigate the effects of mAb1 administered subcutaneously once weekly for 12 weeks as compared to placebo on reducing the incidence of asthma exacerbations in patients with persistent moderate-to-severe eosinophilic asthma. The secondary objectives of the study were to assess the safety and tolerability of mAb1 administered subcutaneously once weekly for 12 weeks in patients with persistent moderate to severe eosinophilic asthma, and to assess mAb1 serum concentrations following once weekly subcutaneous dosing for 12 weeks in patients with persistent moderate to severe eosinophilic asthma.

[00115] Prior to screening, patients were required to be on a stable dose of any of the following doses and formulations of ICS/LABA combination therapy (also called "background therapy") for at least 1 month:

Fluticasone/salmeterol combination therapy

- Advair® Diskus – dry powder inhaler (DPI): 250/50 ug BID or 500/50 ug BID; or

- Advair® HFA – metered dose inhaler (MDI): 230/42 ug BID or 460/42 ug BID; or Budesonide/formoterol combination therapy (Symbicort® 160/9 ug BID or 320/9 ug BID); or Mometasone/formoterol combination therapy (Dulera® 200/10 ug BID or 400/10 ug BID)

[00116] Patients who were on budesonide/formoterol or mometasone/formoterol were switched to an equivalent dose of fluticasone/salmeterol at randomization (Day 1) and patients who had been on fluticasone/salmeterol remained on the same as background therapy.

[00117] Patients who satisfied the inclusion and exclusion criteria (see below) were randomized to one of the following treatments: 300 mg of mAb1 administered subcutaneously once weekly for 12 weeks; or placebo administered subcutaneously once weekly for 12 weeks.

[00118] The study comprised a 2-week screening period, a 12-week treatment period comprising a 4-week background therapy stable phase and an 8-week background therapy withdrawal phase post-randomization, followed by an 8-week post-treatment follow-up period.

Algorithm for background therapy (ICS/LABA) withdrawal:

[00119] Patients remained on BID fluticasone/salmeterol background therapy for 4 weeks after starting add-on therapy or treatment of 300 mg mAb1 (or placebo). At 4 weeks post-randomization, patients were switched from the BID fluticasone/salmeterol combination therapy to an equivalent ICS dose of fluticasone monotherapy (comprising either Flovent® Diskus – DPI formulation of 250ug or 500 ug BID; or Flovent® HFA – MDI formulation of 220 ug or 440 ug BID). The LABA component (i.e., salmeterol) was discontinued. At subsequent visits, beginning with week 6, the fluticasone dose was reduced by approximately 50%, provided the patient did not meet any of the criteria for an asthma exacerbation (as defined below). If no asthma exacerbations occurred, the ICS withdrawal proceeded according to the following dosing schedule:

Background therapy stable phase		Background therapy withdrawal phase				
		Week 4	Week 6	Week 7	Week 8	Week 9
Fluticasone/salmeterol (DPI): 250/50 μg BID		Fluticasone (DPI): 250 μg BID	100 μg BID	50 μg BID	0 μg BID	0 μg BID
Fluticasone/salmeterol (DPI): 500/50 μg BID		Fluticasone (DPI): 500 μg BID	250 μg BID	100 μg BID	50 μg BID	0 μg BID
Fluticasone/salmeterol (MDI): 230/42 μg BID		Fluticasone (MDI): 220 μg BID	110 μg BID	44 μg BID	0 μg BID	0 μg BID
Fluticasone/salmeterol (MDI): 460/42 μg BID		Fluticasone (MDI): 440 μg BID	220 μg BID	110 μg BID	44 μg BID	0 μg BID

[00120] Upon completing 12 weeks of treatment with investigational product (or after early discontinuation), patients were placed on their original dose of fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol (dose at study entry) and albuterol or levalbuterol as-needed to control their symptoms for an additional 8 weeks off study medication before a final safety evaluation.

[00121] A schematic of the study protocol is provided in **Figure 1**.

[00122] Adult patients were included in the study based on the following criteria: (1) physician's diagnosis of persistent asthma for at least ≥ 12 months based on the Global Initiative for Asthma (GINA) 2009 Guidelines, whose airway inflammation is likely to be eosinophilic; and (2) whose asthma is partially controlled or uncontrolled in inhaled corticosteroids/long acting beta-agonists combination therapy according to the following criteria: (i) stable dose of either fluticasone/salmeterol combination therapy (DPI formulation: 250/50 µg BID or 500/50 µg BID or MDI formulation: 230/42 µg BID or 460/42 µg BID), or budesonide/formoterol combination therapy (160/9 µg BID or 320/9 µg BID), or mometasone/formoterol combination therapy (200/10 µg BID or 400/10 µg BID) for at least 1 month prior to screening; (ii) blood eosinophils ≥ 300 cells/µl or sputum eosinophils ≥ 3% during the screening phase; (iii) Juniper asthma control questionnaire (5-question version, ACQ) score of ≥ 1.5 and ≤ 3.0 at screening; (iv) FEV1 ≥ 50% predicted normal during the screening phase (3 attempts maximum) and on the randomization day prior to the first dose (3 attempts maximum); (v) has had within the 2 years prior to screening either treatment with one or more systemic (oral and/or parenteral) steroid bursts for worsening asthma or in-patient hospitalization or an emergency care visit for worsening asthma; and (vi) documented history of reversibility within 12 months of screening that meets the criterion – at least 12% and 200 mL in FEV1 after 200 µg to 400 µg (2 to 4 inhalations) of albuterol during the screening phase (3 attempts maximum), or documented history of a positive methacholine challenge (PD20 methacholine ≤ 8 mg) within 12 months prior to screening. Patients with moderate-to-severe asthma that is partially controlled or uncontrolled with moderate to high doses of combination therapy with inhaled corticosteroids and long-acting beta agonists (ADVAIR®, SYMBICORT® or DULERA®) and with blood eosinophils greater than or equal to 300 cells per microliter, or sputum eosinophils greater than or equal to 3% during the screening phase, were included in the study.

[00123] Patients who met all the inclusion criteria were screened for the following exclusion criteria: (1) patients less than 18 years of age or greater than 65 years of age; (2) clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further evaluation; (3) chronic obstructive pulmonary disease (COPD) and/or other lung diseases impairing pulmonary function tests; (4) patients requiring beta-adrenergic receptor blockers for any reason; (5) current smoker or cessation of smoking within the 6 months prior to screening; (6) previous smoking with a smoking history > 10 cigarette pack-years; (7) in-patient hospitalization or emergency care visit due to asthma exacerbation in the 2 months prior to

screening; (8) plans to begin allergen immunotherapy within the study period; (9) exposure to another investigative antibody within a time period prior to screening that is less than 5 half-lives of the antibody but not less than 30 days, or if the half life of the antibody is not known, then a time period prior to screening that is at least 6 months; (10) previous enrollment into the current study; (11) patient was the investigator, his/her family member or an employee at the investigational site; (12) known or suspected non-compliance, alcohol or drug abuse; (13) inability to follow the procedures of the study (e.g., due to language problems or psychological disorders); (14) reversal of sleep pattern (e.g., night shift worker); (15) treatment with drugs known to prolong QTc interval; (16) concomitant severe disease(s) for which the use of ICS (e.g., active or inactive pulmonary tuberculosis) or LABA (e.g., diabetes, cardiovascular diseases, hypertension, hyperthyroidism, thyrotoxicosis, etc) are contra-indicated; (17) use of injectable glucocorticosteroids or oral systemic glucocorticosteroids within 2 months prior to screening or more than 3 courses within the 6 months prior to screening; (18) pre-treatment with variable doses of ICS, either alone or in combination with a non-steroidal controller (other than fluticasone/salmeterol combination therapy, budesonide/formoterol combination therapy, or mometasone/formoterol combination therapy); (19) patients receiving prohibited concomitant medications (listed below); (20) known allergy to doxycycline or related compounds; (21) pregnancy or intention to become pregnant during the course of the study, breast feeding or unwillingness to use an effective method of contraception; and (22) recent history of a parasitic infection or travel to a parasitic endemic area within 6 months prior to screening.

[00124] Patients remained on a constant dose of the background asthma therapy for the first four weeks of the study after which the dose of background therapy was reduced gradually. First, the long-acting beta agonist component of the background therapy was withdrawn at week 4, and then the inhaled corticosteroid dose was reduced by half every 2 weeks until week 12. Patients continued on study treatment until the end of the study or until they were withdrawn due to an asthma exacerbation or for any other reason.

B. Study Treatments

[00125] Investigational Product: Sterile mAb1 150 mg/mL solution for SC injection was provided in a 5 mL glass vial. Each vial contained a withdrawable volume of 2 mL. A 300 mg dose was administered subcutaneously at the study site once weekly in the morning for 12 weeks. Placebo: Sterile placebo for SC injection was provided in an identically matched 5 mL glass vial. Each vial contained a withdrawable volume of 2 mL. Placebo was administered subcutaneously at the study site once weekly in the morning for 12 weeks.

[00126] The following concomitant medications were not allowed during the duration of the study: any other inhaled steroid other than fluticasone/salmeterol combination therapy or fluticasone administered per the protocol (or budesonide/formoterol or mometasone/formoterol during the screening period); systemic or ocular steroids; LABAs other than the salmeterol

component of the fluticasone/salmeterol combination therapy administered per the protocol; any other ICS/LABA combination products other than those given above; any inhaled anti-cholinergic agents (e.g., Ipratropium bromide or tiotropium); methylxanthines (theophylline, aminophyllines); cromones; anti-IgE therapy; lipoxygenase inhibitors; and leukotriene receptor antagonists or leukotriene synthesis inhibitors.

C. Efficacy of treatment

[00127] The primary endpoint of this study was the occurrence of an exacerbation of asthma as defined by any of the following: (1) a 30% or greater reduction from baseline in morning peak expiratory flow (PEF) on two consecutive days; or (2) six or more additional reliever puffs of albuterol or levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days; or (3) deterioration of asthma, as determined by the Investigator, requiring: (a) systemic (oral and/or parenteral) steroid treatment, or (b) an increase in ICS ≥4 times the last dose received prior to discontinuation from the study, or (c) hospitalization.

[00128] Secondary endpoints of the study included mean changes from baseline of the following parameters: (1) Forced expiratory volume in 1 second (FEV1) in liters measured at every visit; (2) Morning and evening peak expiratory flow rate (AM PEF and PM PEF) in liters/minute measured daily; (3) Daily Albuterol/Levalbuterol use in inhalations/day; (4) Five-item Asthma Control Questionnaire (ACQ5) score at every visit; and (5) Nighttime awakenings (no. of times per night) measured daily and (6) a 22-item Sino-Nasal Outcome Test (SNOT-22), evaluated at baseline and end of treatment (at Week 12), to assess upper airway symptoms. Secondary endpoints also included proportion of patients with a composite asthma event defined by a 30% or greater reduction from baseline in morning PEF on two consecutive days together with ≥ 6 additional reliever puffs of albuterol or levalbuterol in a 24-hour period 9compared to baseline) on 2 consecutive days. PEF, ACQ5, asthma symptoms scores, nocturnal awakenings, and reliever medication use were captured in an electronic daily diary. Mean daily nocturnal awakenings, ranging from 0-10, were averaged from the previous 7 days. Morning and evening asthma symptom scores consisted of a non-validated patient-reported outcome assessed on a 5-point Likert-type scale, with higher scores indicating worse outcomes (Table 2). Patients recorded overall symptom scores twice a day prior to measuring PEF. Data were described as the average for the 7 days prior to the specified time point.

Table 2: Asthma Symptom Score Assessment

A) Morning symptom score: 0 = No asthma symptoms, slept through the night 1 = Slept well, but some complaints in the morning. No nighttime awakenings 2 = Woke up once because of asthma (including early awakening) 3 = Woke up several times because of asthma (including early awakening) 4 = Bad night, awake most of the night because of asthma

B) Evening symptom score:
0 = Very well, no asthma symptoms
1 = One episode of wheezing, cough, or breathlessness
2 = More than one episode of wheezing, cough, or breathlessness without interference of normal activities
3 = Wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities
4 = Asthma very bad. Unable to carry out daily activities as usual

D. Adverse Events Monitoring

[00129] Safety was assessed throughout the study by monitoring Adverse Events and Serious Adverse Events.

[00130] An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the Investigator to be clinically significant; and any untoward medical occurrence.

[00131] A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

E. Statistical methods

[00132] For the primary analysis of proportion of patients experiencing an asthma exacerbation, a logistic regression model was used to compare SAR group with placebo. The model included terms for treatment and stratification factor (prior ICS/LABA combination therapy dose). The primary analysis was performed based on modified intent-to-treat (mITT) population which included all randomized patients who received at least one dose of mAb1. A stratified chi-square test was also used to corroborate the primary analysis.

[00133] For secondary efficacy endpoints except SNOT-22, the change from baseline was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included change from baseline values up to week 12 as response variables, and factors (fixed effects) for treatment, stratification factor, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. Statistical inferences on treatment comparisons for the change from baseline at week 12 were derived from the mixed-effect model. Change from baseline in SNOT-22 was analyzed using an analysis of covariance (ANCOVA), with end of treatment measurements used to impute missing data. Pharmacodynamic effects were evaluated using

MMRM models in a *post hoc* fashion. No adjustments were made for multiplicity, since there was only one primary endpoint and analysis. Safety variables including AEs, laboratory parameter, vital signs, ECG, clinical laboratory observations and physical examinations were summarized using descriptive statistics.

[00134] Demographic and clinical characteristics were summarized using descriptive characteristics. Plots of secondary and pharmacodynamic variables are presented as mean change from baseline over time with standard error. Comparison of treatment effects from the MMRM analyses are based on least square mean change (95% confidence intervals [CI]) from baseline at Week 12.

F. Results

[00135] The results observed with all 104 randomized patients (from 491 screened) who either completed or discontinued the treatment phase of the study are summarized below. All randomized patients were exposed to study treatment and included in the mITT population. Baseline characteristics were similar between groups. The demographic and clinical characteristics were also similar between the two groups (Table 3). As noted above, patients were treated either with 300 mg subcutaneous mAb1 once a week, or with placebo. The study treatment period was completed by 86.5% and 67.3% of the mAb1 and placebo patients, respectively. The most common cause of discontinuation was lack of efficacy, which was more frequent with placebo (21.2%) than mAb1 (1.9%).

Table 3. Baseline Demographic and Clinical Characteristics of Treatment Groups.*

Variable	**Placebo (N = 52)**	**mAb1 300 mg (N = 52)**
Age (yr)	41.6 ± 13.1	37.8 ± 13.2
Male sex, no. (%)	26 (50.0)	26 (50.0)
Race or ethnic group, no. (%)		
White	38 (73.1)	45 (86.5)
Black or African American	9 (17.3)	5 (9.6)
Asian	3 (5.8)	1 (1.9)
Other	2 (3.8)	1 (1.9)
Body mass index		
Mean (kg/m^2)	31.6 ± 7.0	31.3 ± 8.0
≥ 30, no. (%)	25 (48.1)	24 (46.2)
Duration of asthma (yr)	26.9 ± 14.8	24.2 ± 12.6
Number of asthma exacerbations in prior 2 years	1.4 ± 1.3	1.4 ± 1.0
Prior ICS/LABA combination therapy dose, no. (%)		
High Dose	41 (78.8)	42 (80.8)
Low Dose	11 (21.2)	10 (19.2)
Blood eosinophils ($x10^{-9}/l$)	0.47 ± 0.21	0.55 ± 0.19
FEV_1 (l)	2.54 ± 0.66	2.47 ± 0.65
FEV_1 (% of predicted value)	72.0 ± 12.7	72.0 ± 12.6
PEF (l/min)		
Morning	406.9 ± 110.7	393.0 ± 101.1

Variable	Placebo (N = 52)	mAb1 300 mg (N = 52)
Evening	416.6 ± 116.8	414.6 ± 102.3
ACQ5 score	2.1 ± 0.5	2.1 ± 0.5
Asthma symptom score		
Morning	0.73 ± 0.63	0.75 ± 0.81
Evening	1.12 ± 0.73	0.92 ± 0.71
Nocturnal awakenings per day	0.21 ± 0.50	0.44 ± 0.80
SNOT-22	26.2 ± 15.6	30.9 ± 14.8
Inhalations of albuterol or levalbuterol/24-hour period	2.0 ± 1.8	2.2 ± 2.4
FeNO (ppb)	35.0 ± 27.1	37.6 ± 28.1
TARC (pg/ml)	470.5 ± 204.7	496.1 ± 342.4
Eotaxin-3 (pg/ml)	117.3 ± 349.2	75.4 ± 44.0
IgE (IU/ml)	694.7 ± 1837.8	657.7 ± 1482.3

*Plus–minus values are means ± SD, except as otherwise noted. ACQ5 denotes the Asthma Control Questionnaire (5 question version), FeNO fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, IgE immunoglobulin E, PEF peak expiratory volume, SNOT-22 the 22-item Sinonasal Outcome Test,
and TARC thymus and activation regulated chemokine.

(i) Primary Efficacy Endpoint

[00136] The incidence of asthma exacerbations in the placebo and mAb1 treatment groups is presented in Table 4.

Table 4. Incidence of Asthma Exacerbations in mITT population

	Placebo (N=52)	mAb1 (N=52)
Patients With No Asthma Exacerbations	29 (55.8%)	49 (94.2%)
Patients With Asthma Exacerbations	23 (44.2%)	3 (5.8%)
Odds Ratio vs Placebo (95% CI)	--	0.077 (0.021, 0.279)

[00137] There were a total of 26 asthma exacerbations during the treatment period, and no patients were hospitalized for asthma exacerbations. There were 23 patients (44.2%) who experienced an asthma exacerbation in the placebo group, whereas only 3 patients (5.8%) experienced an asthma exacerbation in the mAb1 treatment group. The odds ratio is 0.077 ($p < 0.0001$) and the relative risk reduction is approximately 87%.

[00138] Out of the 26 asthma exacerbations experienced during this study, 9 were considered severe as demonstrated by a need for immediate intervention in the form of treatment with either systemic corticosteroids or with inhaled corticosteroids at 4 or more times the dose taken prior to the event. A summary of the incidence of severe asthma exacerbations is presented in Table 5.

Table 5. Incidence of Severe Asthma Exacerbations in mITT population

	Placebo (N=52)	mAb1 (N=52)
Patients With No Asthma Exacerbations	29 (55.8%)	49 (94.2%)
Patients With Severe Asthma Exacerbations	8 (15.4%)	1 (1.9%)
Patients With Non-Severe Asthma Exacerbations	15 (28.8%)	2 (3.8%)

[00139] As shown in Table 5, eight severe asthma exacerbations were observed in the placebo group, and only 1 severe asthma exacerbation was observed in the mAb1 treatment group. The remaining 15 asthma exacerbations in the placebo group and 2 in the mAb1 group met the protocol definition of exacerbation based on decreased morning PEF and/or increased albuterol/levalbuterol use. Within the active treatment group, a sustained improvement versus baseline was observed during the course of the study for all parameters, despite steroid withdrawal.

Table 6. Exacerbation Events

Outcome	Placebo (N = 52)	mAb1 (N = 52)
≥ 30% reduction from baseline in morning PEF in a 24-hr period on 2 consecutive days	10* (19.2)	1 (1.9)
≥ 6 additional inhalations of albuterol/levalbuterol in a 24-hr period on 2 consecutive days	10 (19.2)	1 (1.9)
Systemic steroid treatment	5 (9.6)	1 (1.9)
≥ 4-fold increase in ICS from the previous dose	3 (5.8)	0
Hospitalization	0	0

*4 Placebo patients met both PEF and systemic steroid treatment criteria, and 1 placebo patient met both PEF and additional albuterol/levalbuterol use.

[00140] With mAb1, the time to exacerbation was longer, and the risk of exacerbation was reduced relative to placebo (hazard ration 0,10; 95% CI 0.03, 0.34; P< 0.001). An analysis of the time to asthma exacerbation by Kaplan-Meier Plot revealed that the effect of treatment with mAb1 is sustained over time, including after 8 weeks when patients are at higher risk of developing exacerbations due to steroid withdrawal.

[00141] Only 1 patient from the placebo group had a composite asthma event. A composite asthma event is defined as a 30% or greater reduction from baseline in morning PEF on 2

consecutive days together with ≥6 additional reliever puffs of albuterol or levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days.

(ii) Other Efficacy Endpoints

[00142] Lung function parameters (FEV1, AM PEF and PM PEF), asthma symptom-based endpoints (ACQ score, nighttime awakenings) and albuterol use were assessed for each patient at each visit. In addition, the SNOT-22 score was assessed at baseline and at the end of treatment. For all parameters, the baseline and Week 12 (LOCF) mean values along with the mean difference between treatment groups (ANOVA model for SNOT-22) are summarized in Table 7. In Table 7, the column labeled "Difference vs. Placebo" reflects the placebo-corrected value from baseline which takes into account changes that are observed in the value of the parameter as compared to the changes that were observed for that parameter in the placebo-treated group.

Table 7. Secondary Parameters of Lung Function and Symptom Scores

	N	Baseline Mean (SD)	Least-Squared Mean Change (SD)	Difference vs. Placebo	p value
FEV1 (L)					
Placebo	52	2.54 (0.66)	-0.22 (0.06)	--	
mAb1	52	2.47 (0.65)	0.05 (0.06)	0.27 (0.11, 0.42)	0.0009
AM PEF (L/min)					
Placebo	52	406.9 (110.7)	-20.7 (9.1)	--	
mAb1	51	393.0 (101.1)	13.9 (8.8)†	34.6 (10.6, 58.5)	0.0051
PM PEF (L/min)					
Placebo	51	416.6 (116.8)	-18.4 (8.9)†	--	
mAb1	52	414.6 (102.3)	4.3 (8.5)	22.7 (-0.7, 46.0)	0.0567
Albuterol Use (Puffs/Day)					
Placebo	52	2.0 (1.8)	0.7 (0.3)	--	
mAb1	50	2.2 (2.4)	-1.3 (0.3)‡	-2.0 (-2.9, -1.2)	<0.0001
ACQ Score					
Placebo	52	2.08 (0.52)	-0.27 (0.16)	--	
mAb1	52	2.09 (0.46)	-1.00 (0.16)	-0.73 (-1.15, -0.30)	0.0011
Night-time Awakenings (No. of times/night)					
Placebo	52	0.2 (0.5)	0.1 (0.1)	--	
mAb1	52	0.4 (0.8)	-0.2 (0.1)	-0.2 (-0.5, -0.0)	0.0518
SNOT22 Average Score					

Placebo	51	26.24 (15.62)	0.23 (2.15)†	--	
mAb1	50	30.92 (14.77)	-8.26 (2.20)‡	-8.49 (-13.96, -3.03)	0.0027

† 51 patients with at least 1 post-baseline assessment.
‡ 50 patients with at least 1 post-baseline assessment.

[00143] Treatment with mAb1 resulted in a significant change from baseline in FEV1 at Week 1, which was maintained through Week 12 despite LABA and ICS withdrawal, with a small decrease in FEV1 at Week 5 coinciding with LABA withdrawal. Similar improvements were observed in morning PEF, but less so in evening PEF. The least-squared (LS) mean change from baseline to week 12 in FEV1 was -0.22 L for placebo and 0.05 L for the mAb1 group. (p=0.0009).

[00144] ACQ5 score improved in both treatment groups at Week 1. However, while ACQ5 improved further with mAb1 between Weeks 1 and 4, the placebo effect stabilized, maintaining the difference through Week 12.

[00145] Morning symptom scores increased from baseline to Week 12 with placebo. With mAb1, there was an initial decrease which remained below baseline through Week 12. A similar pattern (with greater variability) was observed for evening asthma symptom scores.

[00146] Nocturnal awakenings were stable from the placebo group through Week 6, then increased from Weeks 6 to 12. In contrast, nocturnal awakenings decreased in the mAb1 group by Week 1 and remained improved versus baseline through Week 12.

[00147] Changes in albuterol/levalbuterol use were similar to other secondary endpoints: an initial decrease followed by a return towards baseline with placebo. With mAb1, the initial decrease was maintained over time.

[00148] There was a non-significant difference at baseline between the SNOT-22 values with the mean placebo score at 26.24 and the mean mAb1 score at 39.02. At week 12, the LS mean change was a slight increase of 0.23 points for the placebo group and a mean decrease (improvement) of 8.26 points for the mAb1 group. This represented a magnitude of improvement of 8.49 points for the mAb1 group (p=0.0027).

Table 8. Secondary Endpoints

Outcome	**Placebo (N = 52)**	**mAb1 (N = 52)**	**Difference vs Placebo (95% CI)****	**P Value**
Kaplan-Meier estimate at 12 weeks	46.0 (31.8, 60.2)	5.8 (0.0, 2.1)	0.10 (0.03 to 0.34)	<0.001
Change in morning asthma symptom scores, baseline to week 12	0.3 ± 0.1	-0.4 ± 0.1	-0.7 (-0.9 to -0.4)	<0.001

Change in evening asthma symptom scores, baseline to week 12	0.1 ± 0.1	-0.6 ± 0.1	-0.7 (-0.9 to -0.4)	<0.001

Table 9. Change From Baseline at Week 12 in SNOT-22 Items Relevant to Upper Airway Disease.

SNOT-22 Subscale	Least-Squares Mean Change ± Standard Error		Difference vs Placebo (95% CI)	P Value
	Placebo (N = 52)	mAb1 (N = 52)		
Need to blow nose	-0.25 ± 0.17*	0.95 ± 0.17†	-0.70 (-1.13, -0.26)	0.002
Nasal blockage	-0.20 ± 0.19*	-0.94 ± 0.19†	0.75 (-1.22, -0.28)	0.002
Decreased sense of smell/taste	0.04 ± 0.18*	-1.13 ± 0.18†	-1.16 (-1.62, -0.71)	< 0.001

*51and †50 patients with at least 1 post-baseline assessment respectively

[00149] For all secondary endpoints, Week 12 measurements favored mAb1 treatment and were significant except for evening PEF and nocturnal awakenings (Table 7 and 8). Significant improvements with mAb1 were also observed for the three SNOT-22 items relevant to upper airway disease (Table 9)

(iii) Safety

[00150] mAb1 was generally safe and well tolerated. Treatment-emergent adverse events (TEAEs) were reported similarly by 40 (76.9%) of placebo-treated patients and by 42 (80.8%) of mAb1-treated patients (Table 10). TEAEs were non-specific, generally mild to moderate in intensity and the majority recovered by the end of the study. An increased reporting of the following TEAEs was observed for mAb1 in comparison with placebo: injection site reactions were reported by 15 (28.8%) mAb1 patients and by 5 (9.6%) placebo patients; nasopharyngitis was reported by 7 (13.5%) mAb1 patients and 2 (3.8%) placebo patients; headache was reported by 6 (11.5%) mAb1 patients and 3 (5.85) placebo patients and nausea was reported by 4 (7.7%) mAb1 patients and 1 (1.9%) placebo patients.

Table 10. Adverse Events.

Adverse event	Placebo (N = 52)	mAb1 300 mg (N = 52)
	no. of patients (%)	
Any adverse event	40 (76.9)	42 (80.8)
Any serious adverse event	3 (5.8)	1 (1.9)
Study discontinuation owing to adverse event	3 (5.8)	3 (5.8)
Death	0	0
Most common AEs*		
Injection site reactions†	5 (9.6)	15 (28.8)
Nasopharyngitis	2 (3.8)	7 (13.5)

Adverse event	Placebo (N = 52)	mAb1 300 mg (N = 52)
	no. of patients (%)	
Upper respiratory tract infection	9 (17.3)	7 (13.5)
Headache	3 (5.8)	6 (11.5)
Nausea	1 (1.9)	4 (7.7)
Arthropod bite	0	3 (5.8)
Muscle spasms	0	3 (5.8)
Nasal congestion	1 (1.9)	3 (5.8)
Rash	1 (1.9)	3 (5.8)
Urticaria	0	3 (5.8)
Viral upper respiratory tract infection	0	3 (5.8)

*≥ 3 patients in any treatment group by Preferred Term
†Injection site reaction includes events reported as: injection site pain, injection site reaction, injection site erythema, injection site rash, injection site haematoma, injection site urticaria, injection site dermatitis, injection sites inflammation, injection site nodule, injection site pruritus and injection site swelling.

[00151] There were no deaths reported during the study period. Of the 4 treatment emergent serious adverse events (SAEs) reported: 1 mAb1 patient experienced bipolar disorder and 3 placebo patients experienced SAEs of asthma with pneumonia, gunshot wound with left pneumothorax, and right ankle fracture. None of these SAEs were considered as related to the mAb1 and all but the recent ankle fracture were recovered by the end of the study. There were no deaths.

[00152] A total of 6 patients discontinued the study due to a TEAE: 3 patients in the mAb1 group (bipolar disorder, asthma with wheezing, and angioedema) and 3 patients in the placebo group (upper respiratory tract infection, psoriasis and asthma). The TEAE of angioedema occurred in a 42-year old African-American female after the ninth study treatment dose as a pruritic, popular rash observed at, and distant to, the injection site. It persisted for one week, resolved after study treatment discontinuation, and prednisome and diphenhydramine treatment. It was deemed treatment-related. This AE was subsequent to milder rashes at the injection site after the first and sixth study treatment doses.

[00153] Among the most common AEs occurring in ≥3 patients in any treatment group (Table 10), injection site reactions, nasopharyngitis, nausea, and headache occurred more frequently with mAb1 than placebo. No clinically significant changes in vital signs, physical examination, clinical laboratory or ECG findings were reported in either group.

G. Conclusion

[00154] Significant improvements were observed for lung function and other asthma control parameters. Efficacy was observed early and sustained despite background therapy

withdrawal. A relative reduction of approximately 87% (p <0.0001) in the primary endpoint of the incidence of asthma exacerbations in persistent, moderate-to-severe asthma patients with eosinophilia was observed after 12-week treatment with 300mg of mAb1 once weekly (5.8%) compared with placebo (44.2%). As shown in Table 7, clinically meaningful and statistically significant (without multiplicity adjustment) improvements with treatment compared with placebo were observed in lung function parameters (FEV1, PEF AM), asthma symptom scores (ACQ) and albuterol use. Positive trends were observed for PEF PM (p=0.0567) and nocturnal awakenings (p=0.0518). A statistically significant (without multiplicity adjustment) improvement was also observed for the SNOT-22 score. Within the active treatment group, a sustained improvement versus baseline was observed during the course of study for all parameters, despite LABA and ICS withdrawal. mAb1 was generally safe and well tolerated.

Example 2: Biomarker studies

[00155] Biomarker analysis was conducted on samples taken from subjects who participated in clinical trials of mAb1 (see Example 1 above). In particular, serum/plasma biomarkers associated with TH2 inflammation such as thymus and activation chemokine (TARC; CCL17), Immunoglobulin E (IgE), eotaxin-3, periostin, carcinoembryonic antigen (CEA), YKL-40 and blood eosinophils were measured in samples from patients at baseline and at different time points following initiation of study treatment(s). Baseline levels of these biomarkers were assessed for potential predictive value for treatment response. In addition, the fraction of exhaled NO (FeNO) and induced sputum eosinophils and neutrophils were measured as biomarkers of bronchial inflammation. Exhaled nitric oxide assessment was conducted prior to spirometry and following a fast of at least 1 hour using a NIOX instrument (Aerocrine AB, Solna, Sweden). Biomarkers were analyzed using a mixed model and the least square mean derived from the model are reported below.

[00156] Asthma subjects (N=104) were administered either mAb1 (300 mg) or placebo subcutaneously, on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of the study (*i.e.*, 12 weekly doses) (*see* Example 1, above). Samples for biomarker analysis were collected from the antibody- and placebo-treated subjects at week 0, 1, 4, 8 and 12. Antigen-specific IgE was detected using the Phadiatop® test.

[00157] TARC, eotaxin-3 and IgE remained unchanged in response to placebo. In contrast, a rapid reduction in TARC (mean % change -22.7% vs +0.3%; p= 0.0003) and eotaxin-3 (mean % change -39.62% vs 12.69%; p<0.0001) was observed within one week in patients treated with mAb1 and persisted until week 12: TARC: -26.0% vs +7.6% placebo (p=0.0005); Eotaxin-3: -45.67% vs +5.13% placebo (p<0.0001).

[00158] TARC levels responded within a week following exposure to mAb1 at 300 mg administered subcutaneously. TARC levels plateau at approximately 50% of the baseline level in mAb1-treated subjects, regardless of ICS withdrawal. The data suggest that TARC

expression is more directly linked to IL-4R signaling, than FEV1 changes (which drop in parallel to ICS withdrawal [after Week 4]) and that IL-4R blockage induces a shift towards a TH1 signature, as observed with, for example, IFNgamma administration. It might be possible to titrate the mAb1 dose using TARC (and for example CXCL10) in particular in patients requiring long term treatment and at risk for TH1 type immune diseases.

[00159] Total serum IgE also decreased following mAb1 treatment. Total serum IgE response was more heterogeneous and delayed compared to TARC response. Mean (SD) baseline IgE levels were 694.68 IU/L (1837.82) for the placebo group (n=52) and 657.66 (1482.25) for the mAb1 group (n=52), whereas median was 169.95 for the placebo group and 206.15 for the mAb1 group. Despite this heterogeneity, a trend towards IgE decrease in mAb1-exposed patients compared with placebo was observed – however, starting at week 4 only. Serum IgE was significantly reduced in the mAb1 group compared with placebo (mean % change, -10.1% vs +13.5%; p=0.0325) starting from week 4 and continued to decrease until week 12 (mean % change, -36.8% for mAb1 vs -5.5% for placebo; p<0.0001).

[00160] Changes from baseline and placebo at Week 12 for FeNO, TARC, eotaxin-3, and IgE all favored mAb1 (all P< 0.001) (Table 11). No differences from baseline or between treatments were observed in YKL-40 or CEA.

Table 11. Percent Change From Baseline at Week 12 in Pharmacodynamic Endpoints.

Outcome	Least-Squares Mean Percent Change ± Standard Error		P Value
	Placebo (N = 52)	mAb1 (N = 52)	
FeNO	35.0 ± 10.8	28.7 ± 11.2	< 0.001
TARC	7.6 ± 6.9	-26.0 ± 6.9	< 0.001
Eotaxin-3	5.1 ± 4.7	-45.7 ± 4.7	< 0.001
IgE	5.5 ± 3.6	-36.8 ± 3.6	< 0.001
Blood eosinophils	2.7 ± 15.8	41.6 ± 15.7	0.078

[00161] There was a transient decrease in periostin levels, followed by an increase with LABA/ICS withdrawal. Administration of mAb1 delayed the increase, but did not prevent the increase above baseline. No consistent treatment effect was observed with CEA and YKL-40. The number of blood eosinophils remained unchanged through Week 6, but then increased at Weeks 8 and 12. Peripheral blood eosinophil numbers were unchanged on placebo throughout treatment. The difference between the treatments was not significant, with the borderline increase driven by larger blood eosinophil elevations in only a few patients treated with mAb1. Little or no increases were observed in the majority of patients.

Table 12. Proportions of Patients Achieving Thresholds of Change in Blood Eosinophil Levels.

Change in eosinophils	Number (%) of patients	
	Placebo (n = 52)	mAb1 (n = 52)
> 15% Decrease	13 (30.2)	21 (47.7)
15% Decrease – 0% change	7 (16.3)	6 (13.6)
0%-15% Increase	8 (18.6)	4 (9.1)
15% - 100% Increase	13 (30.2)	6 (13.6)
100% - 200% increase	2 (4.7)	3 (6.8)
> 200% increase	0	4 (9.1)

[00162] Since only 3 mAb1 patients experienced asthma exacerbation during the study, no conclusion could be drawn regarding the association between baseline biomarker levels and asthma exacerbations.

[00163] mAb1 treatment was also associated with a significant decrease from baseline in FeNO at Week 4, and FeNo remained below baseline through Week 12, regardless of ICS withdrawal (mean % change at week 12: -28.7 for mAb1 vs 35.0 for placebo; $p<0.0001$). In contrast, placebo FeNo values remained stable through Week 8, followed by an increase at Week 12 coincident with ICS withdrawal.

[00164] Forced expiratory volume in 1 second (FEV_1) improvement significantly correlated with FeNO reduction ($r=-0.408$, $p=0.009$) at week 12. Similarly, improvements in AM-PEF and PM-PEF correlated with FeNO reduction. Other correlations with FeNO were not significant. See Table 13.

Table 13. Correlation between FEV_1 and PD Endpoints.

Outcome	**Correlation**	**P Value**
FeNO	-0.408	<0.009
TARC	-0.248	0.10
Eotaxin-3	-0.146	0.34
IgE	-0.279	0.06
Blood eosinophils	0.165	0.28

[00165] Scatter plot analysis of baseline eosinophils versus change from baseline in FEV1 at week 12 did not seem to suggest association of baseline eosinophils and treatment effect, as measured by change from baseline in FEV1 at week 12 in the study population (baseline eosinophils ≥ 0.3 Giga/L). Baseline eosinophils correlated with decreased ACQ and decreased albuterol/levalbuterol use. Periostin and YKL-40 at baseline correlated with decreased ACQ.

[00166] The FEV1 change from baseline at week 12 was compounded by the withdrawal of ICS (starting at week 4). Similar analyses did not suggest association between baseline TARC or

IgE and change from baseline in FEV1 at week 12 in the study population (baseline eosinophils ≥ 0.3 Giga/L).

H. Summary

[00167] These results show that mAb1 significantly reduced serum biomarkers associated with Th2 inflammation (TARC, eotaxin-3 and IgE) and bronchial inflammation (FeNO) in adult asthma patients. The correlation between FeNO reduction and FEV_1 improvement suggests a relationship between IL-4/IL-13 mediated anti-inflammatory activity and improvement in pulmonary function in moderate-to-severe, uncontrolled asthma.

Example 3. Clinical Trial of Subcutaneously Administered Anti-IL-4R Antibody (mAb1) In Patients with Bilateral Nasal Polyposis and Chronic Symptoms of Sinusitis

A. Study Objectives and Overview

[00168] The positive effect of mAb1 on the SNOT-22 test described in Example 1 suggested that the anti-IL-4R antibody might also be effective for treating nasal polyposis. Further, nasal polyps are most commonly eosinophilic/TH2 driven, and mAb1 significantly reduced biomarkers associated with Th2 inflammation (see Example 2). A clinical trial was therefore designed to test the therapeutic effect of mAb1 on nasal polyposis.

[00169] A randomized, double-blind, phase 2, placebo controlled, 2 arm study will be performed to evaluate mAb1 administered once a week (QW) subcutaneously (SC) for 16 weeks in patients with bilateral nasal polyposis and chronic symptoms of sinusitis. The primary objective of the study will be to evaluate the efficacy of mAb1 in the treatment of bilateral nasal polyposis (NP) by assessment of the endoscopic nasal polyp score in comparison to placebo. Secondary objectives of the study include evaluation of mAb1 in patients with bilateral nasal polyps with regards to symptoms of sinusitis, Computed Tomography (CT) scan changes, Nasal polyp score in the sub-group of patients with co-morbid asthma, safety and tolerability, pharmacodynamic responses based on suppression of TH2 biomarkers, concentrations of mAb1 in serum, immune response to mAb1 (Anti-drug antibodies (ADA)), and effect of mAb1 in patient reported outcomes and Quality of Life (QoL) scales.

[00170] mAb1 will be administered concomitantly with Mometasone furoate nasal spray (MFNS). Also, there is high co-morbidity of NP with asthma, aspirin/ nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity and previous surgeries, and therefore patients will be allowed to enter the study unless they present any of the exclusion criteria described below. Approximately 56 patients will be randomized into 2 treatment groups of 28 patients per group. To ensure at least 28 patients with co-morbid asthma are included in the study, recruitment of NP patients without co-morbid asthma will stop when approximately 28 patients without asthma

are randomized. Both the patient and the investigator will be blinded to the assigned treatment group.

[00171] The study will consist of three periods: 1) a four week screening run in period on MFNS (Visit 1); (2) a 16 week randomized mAb1 or placebo treatment period (Visits 2-18); and (3) a 16 week post-treatment period to assay pharmacokinetics, immunogenicity, safety and efficacy (Visits 19-22). The total duration of the study is up to 36 weeks.

[00172] The primary endpoint will be the change from baseline at Week 16 in bilateral nasal polyp score (NPS).

[00173] Numerous secondary efficacy endpoints will be measured to more comprehensively evaluate the efficacy of mAb1. The study will explore improvement of nasal polyposis and associated sinus inflammation in CT scan, improvement in condition specific and general medical questionnaires in order to obtain a better understanding of the impact of severe nasal polyposis on the subject's quality of life (QOL).

[00174] These endpoints, together with exploratory sub-group analysis and biomarkers will provide the information on the therapeutic value of mAb1 to reduce nasal polyp score and to improve symptoms in NP and its subsets. The sustainability of the effect will be also explored through the 4-month post-treatment evaluation period.

[00175] The 300 mg QW dose regimen is anticipated to saturate apparent target mediated clearance level (10-15 mg/L). This regimen has been tested and provided statistically significant and clinically relevant response in two previous proof of concept studies performed with mAb1 in asthma and atopic dermatitis (see, e.g., Example 1 above, USSN 61/805797 and USSN 61/816191). The first dose will employ a loading dose of 600 mg in order to achieve faster steady-state concentration. This loading dose range is supported by the acceptable safety profile of the highest loading dose (600 mg) demonstrated in a prior study conducted in Japanese healthy subjects.

[00176] In addition, given that the Cmax after 600 mg loading dose is around 70 mg/L and that the steady state Ctrough of 300 mg QW is around 150 mg/L, the Cmax after the proposed dosing regimen (ie, 600 mg loading dose followed by 300 mg QW) will be below the mean Cmax of 12 mg/kg IV dose (421 mg/L), the highest single dose tested in healthy subjects that was well tolerated, providing additional confidence that this dose regimen should have an acceptable safety profile.

[00177] Patient inclusion criteria include (i) a physician endoscopic diagnosis of bilateral nasal polyposis (i.e., a minimum bilateral nasal polyp score of 5 out of a maximum score of 8 for both nostrils, with at least a score of 2 for each nostril, despite completion of a prior INCS (intranasal corticosteroid) treatment) for at least 8 weeks before screening, and (ii) chronic symptoms of sinusitis, which are the presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); facial pain/pressure; and reduction or loss of smell.

[00178] Patients who have met these criteria will be screened for the following exclusion criteria: age <18 or >65 years; any technical/administrative reason that makes it impossible to randomize the patient in the study; previous participation in any clinical trial of mAb1; a SNOT22 score <7; receipt of any other investigational drug or prohibited therapy for this study within 2 months before screening or 5 half-lives, whichever is longer; receipt of oral corticosteroids (OCS) or intranasal corticosteroid drops within 2 months or 1 month before screening or scheduled to receive OCS during the study period for another condition; treatment with mAB or immunosuppressive therapy; treatment with an anti-immunoglobulin E (IgE) therapy (e.g., omalizumab) within 130 days of Visit 1; treatment with a leukotriene antagonist / modifier for patients who were not on a continuous treatment for ≥30 days prior to Visit 1; initiation of allergen immunotherapy within 3 months prior to Visit 1 or a plan to begin therapy during the Screening Period or the Randomized Treatment Period; any nasal surgery within six months before screening or have had more than five sinonasal surgeries in the past of which maximal two were surgeries changing the lateral wall structure of the nose; or a condition/concomitant disease that makes a patient non-evaluable for the primary efficacy endpoint (e.g., antrochoanal polyps; nasal septal deviation that would occlude at least one nostril; acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening; ongoing rhinitis medicamentosa; Churg-Strauss syndrome, Young's syndrome, Kartagener's syndrome or dyskinetic ciliary syndromes, Cystic fibrosis; signs or a CT scan suggestive of Allergic fungal rhinosinusitis). Patients with co-morbid asthma are excluded if: the patient has a forced expiratory volume (FEV1) of 60% or less; an exacerbation requiring systemic (oral and/or parenteral) steroid treatment or Hospitalization (>24h) for treatment of asthma, has occurred within 3 months prior screening; or the patient is receiving a dose higher than 1000 µg fluticasone or the equivalent of inhaled corticosteroids. Other exclusion criteria include patients with short life expectancy (less than 6 months); patients receiving concomitant treatment prohibited in the study; women who are pregnant or intend to become pregnant during the study, or breast-feeding women. Other exclusion criteria include concomitant severe diseases (e.g., active and inactive pulmonary tuberculosis, Diabetes mellitus etc.); diagnosed active parasitic infection; suspected or high risk of parasitic infection; history of human immunodeficiency virus (HIV) infection or positive HIV screen at Visit 1; evidence of acute or chronic infection; known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; live vaccinations within 12 weeks prior to Visit 1 or planned vaccinations during the study; patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, Hashimoto's thyroiditis, Graves' disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematous, multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis); patients with positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody

at Visit 1; patients with liver injury related criteria (e.g., underlying hepatobiliary disease, or ALT>3 ULN).

B. Study Treatments

[00179] Investigational Product: Sterile mAb1 of various concentrations will be provided in 5 mL glass vials. Each vial will contain a withdrawable volume of 2 mL: 150 mg/mL solution (300 mg dose/ 2 mL). Sterile placebo will be provided in identically matched glass 5 mL vials, where each vial contains a deliverable volume of 2 mL.

[00180] mAb1 will be administered every 7 ± 2 days (QW). The doses of mAb1 will be separated by ≥5 days to avoid an overdose. At Visit 2 (V2), 2 injections will be performed. After V2 one injection of mAb1 will be performed weekly at the investigational site throughout the randomized treatment period. The mAb1 will be administered following clinic procedures and blood collection. Patients will be monitored for at least 1 hour after each administration for any signs or symptoms of a local site injection or hypersensitivity reaction. Subcutaneous injection sites will be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) or upper thighs so that the same site is not injected for two consecutive times/weeks.

[00181] On a daily basis throughout the study, the subject will use an electronic diary to record daily use of MFNS. Mometasone furoate (NASONEX ®) 50 micrograms/actuation Nasal Spray, is contained in a bottle, that contains 18 g (140 actuations) of product formulation.

[00182] **Screening Period**: Prior to screening, subjects must be on a stable dose of intranasal corticosteroids (INCS) for ≥2 month prior to Visit 1. If the patient is using an alternative INCS product other than MFNS prior to the screening visit, at V1, the patient will be switched to MFNS. After V1 all patients will enter a run-in period of 4 weeks where they will receive MFNS: 2 actuations (50 µg/actuation) in each nostril twice daily (BID) (total daily dose of 400 µg), unless they are intolerant to BID INCS in which case, they can stay on the lower dose (QD) regimen. To be accepted for the study, patients must also have presence of at least two of the following symptoms prior to screening: Nasal blockade/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); +/- facial pain/pressure or +/- reduction or loss of smell

[00183] **Treatment Period**: The treatment period will proceed as indicated in the Study Flow-chart at Table 14.

Table 14.

	Screening period	Randomized treatment period	Post-treatment period

		RDN																EOT[a]				EOS
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week (DAY)	W-4(D-28)	W0 (D1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	20	24	28	32
Inclusion Criteria including Informed Consent (s)	X	X																				
Exclusion Criteria	X	X																				
Patient Demography	X																					
Medical/Surgical History	X																					
Prior Medication History[b]	X																					
Physical Examination	X																	X				X
Spirometry[c]		X				X				X				X				X				
Randomization		X																				
Treatment:																						
mAb1 weekly SC administration[d]		X (loading)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Dispense or download electronic diary/NPIF[e]	X	X				X				X				X				X	X	X	X	X
NIMP (MFNS)	I----------																					
Record concomitant medication	----------																					
Efficacy																						
Nasal endoscopy[f]	X	X				X				X				X				X				X
CT scan[g]		X																X				
Smell test (UPSIT)		X								X								X				
SNOT- 22	X	X				X				X				X				X				X
Visual analogue scale (VAS)		X				X				X				X				X				X
QoL (SF-36, EQ-5D)		X				X				X				X				X				X
Nasal polyp related resource use questionnaire		X				X				X				X				X				X
ACQ-5[h]		X				X				X				X				X				X
Safety																						
AE /SAE recording (if any)	I----------																					
Vital Signs	X	X				X				X				X				X	X	X	X	X
ECG	X									X				X				X				X

	Screening period	Randomized treatment period																	Post-treatment period			
		RDN																EOT[a]				EOS
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week (DAY)	W-4(D-28)	W0 (D1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	20	24	28	32
Laboratory Testing																						
Clinical laboratory testing[i]	X	X				X				X				X				X		X		X
Urinalysis (dipstick)	X									X								X				X
Pregnancy test (for WOCBP)[j]	X	X				X				X				X				X				X
PK/Anti-drug antibody sampling PK[k]		X		X		X				X				X				X	X	X	X	X
Serum Biomarker sampling		X		X		X				X				X				X	X			X
Archival nasal secretion sampling[m]		X				X				X				X				X	X			
Polyp biopsy[n]		X																X				
Stored DNA sampling		X																				
Stored whole blood RNA sampling[o]		X		X														X				X

The Screening Period is 28 days in duration to run in any patient on MFNS, and to collect baseline data. V2 will take place 28days+/-2 day window after V1

a No mAb1 administration during this visit. Patients who discontinue treatment early will be assessed as soon as possible using the procedures normally planned for the End-of-treatment Visit and the 4 Post-treatment Period Visits.

b Prior to screening, patients must be on a stable dose of INCS for more than 8 weeks

c Spirometry: all patients should have FEV1 anytime during Screening Period (before V2) and at the other scheduled visits during the Randomized treatment period

d Weekly mAb1 administrations starting from V2 at the site investigational site must be separated by at least 5 days.

e Electronic diary/NPIF meter is used for daily recording of MFNS use, nocturnal awakenings, morning and evening NPIF and rhinosinusitis symptom scores 1) nasal congestion/obstruction 2) anterior rhinorrhea (runny nose), 3) posterior rhinorrhea (post nasal drip), and 4) loss of sense of smell, scored using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms); This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days. The average of the last 7 days before V2 is needed to determine the baseline value

f Nasal endoscopy: endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit; Standard video sequences will be downloaded by the investigator to the central reader's secured Internet site. For eligibility central reading of V1 will be used. At V2 investigator review V1 results from central reader to confirm entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria and the V2 endoscopy local reading

g CT scan should be performed anytime during Screening Period before a first administration of mAb1 and at EOT. Central reading will be used for comparison baseline (BL) to EOT

h Only for patients with co-morbid asthma, ACQ-5 is completed in the patient's electronic diary during clinic visits.

i Hematology: hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, differential count, and total red blood cell count. Serum chemistry (Obtain fasting at planned visits but V2): creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 includes hepatitis screen (hepatitis B surface antigen (HBsAg), Hepatitis B IgM core antibody (HBcAb-IgM), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies), anti-nuclear antibody (ANA). Clinical laboratory testing at Visit 2 is limited to hematology and a separate hematology sample obtained for local analysis. Note: Anti-ds DNA antibody will be tested if ANA is positive ($\geq$1:160 titer). Clinical lab testing at Visit 2 consists of hematology only

j Serum pregnancy test at Visit 1 and urine pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization visits

k Serum pharmacokinetic samples, immune response assessment (ADA) samples and optional whole blood RNA samples will be collected prior to administration of investigational product during the Randomized Treatment Period. During the post-treatment period PK samples will be collected at all visits and ADA samples only at EOS visit. Patients with titers >1000 of the ADA at last visit may be followed after the study. Blood samples for PK and ADA assessment will be collected at any time iIn case an SAE occurs.

m Nasal secretion samples will be collected and stored for potential future discovery efforts to identify predictors of treatment response

n Optional polyp biopsies will be collected in selected clinical centers

o Samples will be collected prior to administration of investigational product during the Randomized Treatment Period

[00184] During the Treatment Period, patients will continue the stable dose of mometasone furoate: two actuations of MFNS in each nostril BID or QD (in case patient cannot tolerate the high dose). At Visit 2, patients will be administered the SNOT-22 test, VAS and QoL questionnaires (SF-36, EQ-5D, Nasal polyp related resource use questionnaire), the smell test, and the ACQ-5 in patients with asthma.

[00185] Clinical laboratory testing at Visit 2 is limited to hematology, pharmacokinetics, anti-drug antibodies, biomarkers in serum and plasma, allergen-specific IgE panel sampling. Blood samples are taken prior to administration of mAb1. Nasal secretion sampling for biomarkers. For those patients who have signed a specific informed consent form, collect blood sample for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period).

[00186] Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with mAb1 will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of mAb1 in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met.

[00187] An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

[00188] A serious adverse event (SAE) is any untoward medical occurrence that at any dose: results in death, or is life-threatening, (the term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect; is a medically important event Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above (he following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive: intensive treatment in an

[00189] emergency room or at home for: Allergic bronchospasm, anaphylaxis, blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc), convulsions (seizures, epilepsy, epileptic fit, absence, etc), development of drug dependency or drug abuse); ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN; Suicide attempt or any event suggestive of suicidality; syncope, loss of consciousness (except if documented as a consequence of blood sampling); bullous cutaneous eruptions; Cancers diagnosed during the study or aggravated during the study; chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

[00190] **Post-treatment Period**: Upon completing the Randomized Treatment Period (or following early discontinuation of mAb1), patients will continue treatment with the stable dose of MFNS maintained over the randomized treatment period, or modify treatment based on medical judgment.

[00191] The following concomitant treatments are not permitted during the Screening Period and the Randomized treatment period: use of intranasal medication that would interfere with the symptoms of diseases (antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn), except nasal saline; INCS drops; systemic corticosteroid; decongestion (topical or systemic), except before endoscopy; long term use of systemic antibiotics (for 2 weeks or more); lipoxygenase inhibitors; any immunosupressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrilomus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide; anti-immunoglobulin E (IgE) therapy (omalizumab); and aspirin or NSAID in patients with hypersensitivity to aspirin.

[00192] The following concomitant treatments are allowed: MFNS during the screening and throughout the whole study; Nasal normal saline; Topical decongestants (e.g., Oxymetazoline hydrochloride to reduce the swelling and widen the path for the endoscope), as well as a topical anesthetic e.g. Lidocaine are allowed before endoscopy; short term use of Antibiotics (<2weeks); and for patients with asthma, SABA, LABA, and Methylxanthines (e.g., theophylline, aminophyllines). The following inhaled corticosteroids are allowed for patients on a stable dose ≤1000 µg Fluticasone (or the equivalent dose of another inhaled CS; see Table 16) and only for patients that were on a stable dose ≥30 days prior to Visit 1: Leukotriene antagonists / modifiers are permitted during the study, only for patients that were on a continuous treatment for ≥30 days prior to Visit 1; Systemic antihistamines; and Initiation of allergen immunotherapy (allergen immunotherapy in place for ≥3 months prior to Visit 1 is permitted).

C. Efficacy of treatment

[00193] The primary endpoint of this study is the change from baseline at week 16 in bilateral endoscopic Nasal Polyp Score.

Table 15.

Polyp score		**Polyp size**
0		**No polyps**
1		**Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate**
2		**Polyps reaching below the lower border of the middle turbinate**
3		**Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate**
4		**Large polyps causing complete obstruction of the inferior nasal cavity**

[00215] Nasal endoscopy will be performed at the end of the scheduled visits and preceded by local administration of anaesthetic drugs in combination with a decongestant. Standard video sequences will be downloaded or sent to a centralized reader. Centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at V2, only the V1 central reading will be made available to the site. The final results of central reading will be made available after the study.

[00216] For the analysis of the primary endpoint, central reading of V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader.

[00217] Secondary endpoints of the study will include change from baseline at Week 16 in: patient reported symptoms (including 22-item Sinonasal Outcome Test (SNOT-22)); subject-assessed nasal congestion/obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post nasal drip), and loss of sense of smell, (daily AM and PM e-diary) month average; number of nocturnal awakenings; patient-rated rhinosinusitis symptoms severity using a visual analog scale (VAS); 5-item Asthma control questionnaire (ACQ-5) in asthma sub-group); nasal peak inspiratory flow (NPIF); smell test (UPSIT); NPS in patients with co-morbid asthma; CT scan assessments; Spirometry (overall and in sub-group with asthma); time to first response (≥1 point improvement) in NPS; time to study treatment discontinuation; and incidence of treatment discontinuation due to need for OCS or nasal surgery.

[00218] Quality of life (QoL) end points will include change from baseline at Week 16 in: 36-item short form health survey (SF36); European quality of life scale (EQ-5D); and Nasal polyp related resource use questionnaire.

[00219] Disease-specific efficacy measures include: Computed tomography (CT). CT of the sinuses should be performed before V2 and at EOT. For both Lund-Mackay scores and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data. Central reading of V2 will be used for comparison with EOT. The final results of central reading will be made available after the study.

[00220] For Three-Dimensional volumetric measurement of the maxillary sinus, central reading before V2 will be used for comparison with EOT reading. The sites will remove subject-identifying information from the imaging data header prior to sending the imaging data to the central reader. The % change in opacification from BL to EOT will be calculated.

[00221] At screening (Visit 1), patients will be issued an NPIF meter for recording morning (AM) and evening (PM) NPIF. The patients will be instructed to record the following variables in the e-diary on a daily basis: AM NPIF performed within 15 minutes after arising (between 6 am and 10 am) prior to taking MFNS; and PM NPIF performed in the evening (between 6 pm and 10 pm) prior to taking MFNS.

[00222] Three NPIF efforts will be performed by the patient; all 3 values will be recorded by the patient in the e-diary, and the highest value will be used for evaluation. The baseline AM NPIF will be the mean AM measurement recorded for the 28 days prior to the first dose of investigational product, and baseline PM NPIF will be the mean PM measurement recorded for the 28 days prior to the first dose of investigational product.

[00223] To assess disease-specific, daily symptoms, the patient will use an electronic diary to: respond to the morning and evening individual rhinosinusitis symptom questions using a 0-3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), and including the symptoms of congestion and/or obstruction, anterior rhinorrhea (runny nose), posterior rhinorrhea (post-nasal drip), and loss of sense of smell. The number of nocturnal awakenings will also be recorded.

[00224] The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit.

[00225] Predose blood samples will be collected for determination of serum functional mAb1 and anti-mAb1 antibodies as designated in Table 14.

[00226] Optional sampling for exploratory analysis of DNA and RNA, requiring separate pharmacogenetics informed consent.

[00227] Pharmacokinetics. Functional mAb1 and anti-mAb1 antibodies in serum will be assayed by ELISA. Predose functional mAb1 concentrations in serum at Visit 2 (Day 1), mAb1 trough concentrations at Week 2, Week 4, Week 8, Week 12, Week 16, and follow-up serum mAb1 at Week 20, Week 24, Week 28 and Week 32 will be provided. Anti-mAb1 antibody status (negative or titer value) at Visit 2 (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, and Week 32 will also be provided. Patients with ADA titers ≥1000 at the end of study visit will be scheduled to return approximately 6 months later for an additional assessment of ADA titer. Further follow-up will be considered based on the overall assessment of antibody titers and clinical presentation.

[00228] Pharmacodynamics. Since the secretion of certain proteins is dependent, at least in part, on Th2 cytokines and is associated with chronic inflammation of the airway mucosa, including sinus tissue, expression of certain biomarkers will be assayed to monitor a therapeutic effect of mAb1. These biomarkers also will be assessed for their value in predicting toxicity and/or in documenting the time course of drug response. The values to be used as baselines will be those collected on Day 1 (predose assessments).

[00232] Nasal secretions will be obtained by inserting nasal swabs bilaterally into the nasal cavity for five minutes. The nasal secretions will be preserved for possible analysis of additional biomarkers related to nasal polyposis and responses to mAb1 treatment.

[00233] At selected clinical site (s) and with specific informed consent, nasal polyp tissue will be optionally obtained by biopsy. A baseline biopsy will be obtained at V2 of the study. After

randomization, another biopsy of nasal polyp tissue will be obtained at the end of treatment visit (Week 16).

[00234] The biopsied nasal polyp tissue will be assessed for various biomarkers of inflammation and disease process or response. For example, RNA will be extracted and used for expression profiling (e.g., microarray, transcriptome sequencing or quantitative RT-PCR).

[00235] DNA and RNA samples may be used to determine a possible relationship between genes and response to treatment with mAb1 and possible side effects to mAb1.

[00236] Analysis of proportion of patients with binary events. Proportion of patients with binary events will be assessed for : ≥1 point improvement (reduction) in NPS at week 16 (as read centrally); 10% or more improvement in CT opacification from baseline at week 16; drop-out due to oral CS or surgery; or INCS increase after 8 weeks will be analyzed using a logistic model with the above responses, respectively, as the response variable, and treatment group, pooled countries /regions and the stratification factor(s) prior to the study as covariates.

[00237] Analysis of time to event variables. Time to event (e.g., the first response with ≥1 point improvement (reduction) in NPS, study treatment discontinuation, etc) will be analyzed suing a Cox regression model with time to event as the dependent variable, and treatment, pooled countries/regions, asthma comorbidity prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an event at Week 4, 8, 12 and 16 specific to each treatment group. For analysis during the treatment period, if a patient has no event before treatment discontinuation/completion, then the patient will be considered as free of event till the end of treatment period (last dose date + 7 days).

[00238] Analysis of change from baseline for continuous variables. The change from baseline at week 16 in: NPS for patients with co-morbid asthma; Lund Mackay score; 22-item Sinonasal Outcome Test (SNOT-22); Subject-assessed congestion and/or obstruction score; nasal peak inspiratory flow (NPIF); ACQ-5 in patients with co-morbid asthma; QoL measures (SF36, EQ-5D), and VAS will be analyzed using MMRM same as the primary endpoints. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dose against placebo.

[00239] Analysis of efficacy in baseline biomarker of characteristics defined subsets. To examine baseline biomarkers for their potential value to predict treatment response, analyses of change in NPS will also be performed for the following subsets and the entire ITT population by each dose group and selected pooled dose group.

[00240] Subgroup analysis. To assess the consistency treatment effects across the subgroup levels and to examine baseline biomarkers for their potential value to predict treatment response, exploratory subgroup analyses will be conducted for the change from baseline in NPS with respect to age group, gender, region, race, INCS dose level, baseline NPS, baseline CT scan score, asthma comorbidity, and selected biomarkers prior to the study.

[00241] Listings of anti-mAb1 antibody results (Negative or titer value) will be presented by patient, time point and treatment groups. ADA titer levels will be classified into categories: Low, moderate and high. Low levels of ADA titers are defined as titers below 1000; moderate levels of ADA titers are defined as titers between 1000 and 10,000; high levels of ADA titers are defined as titers >10,000.

[00242] Anti-mAb1 antibody assay results will be described categorically. The following summary will be provided for: Patients with any positive ADA assay response during the TEAE period; Patients with treatment induced positive ADA assay response during the TEAE period; Patients with treatment induced positive ADA assay response during the TEAE period will be further described as patients with transient positive response and patients with persistent positive response. Patients with any positive ADA assay response during the TEAE period is defined as those having at least one sample positive in the ADA assay.

[00243] The treatment induced positive ADA assay response is defined as: Patients with no positive assay response at baseline but with a positive assay response during the TEAE period or patients with a positive ADA assay response at baseline and also have at least a 4-fold increase in titer during the TEAE period.

[00244] A persistent positive response is a treatment induced positive ADA assay response in which at least 2 consecutive post-baseline samples from a patient are positive in the ADA assay or the last post-baseline sample collected is positive in the ADA assay. A transient positive response is defined as any treatment induced positive ADA assay response that is not considered persistent.

Table 16. Allowable Inhaled Glucocorticosteroid / Long-Acting Beta2 Agonist Combination Products and Acceptable Dosage Form, Strength and Dosage Schedule

Generic Name	Brand Name	Acceptable Product	Acceptable Dosage Form, Strength and Dosage Schedule
Fluticasone propionate and salmeterol	Advair® / Seretide®	DPI (250/50 or 500/50) MDI (115/21 or 230/21)	DPI: 1 puff twice daily (500/50) DPI: 1 puffs twice daily (250/50) MDI: 2 puffs twice daily (115/21) MDI: 2 puffs twice daily (230/21)
Budesonide and formoterol	Symbicort®	DPI (200/6 or 400/12 MDI (160/4.5)	DPI: 1 puff twice daily (400/12) DPI: 2 puffs twice daily (200/6) MDI: 2 puffs twice daily (160/4.5)
Mometasone furoate and formoterol	Dulera®	MDI (100/5 or 200/5)	MDI: 2 puffs twice daily (200/5) MDI: 2 puffs twice daily (100/5)

[00245] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the

accompanying figure. Such modifications are intended to fall within the scope of the appended claims.

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CLAIMS

What is claimed is:

1. Use of an antibody, or antigen binding fragment thereof, that specifically binds an interleukin-4 receptor (IL-4R) for the preparation of a pharmaceutical composition for treating chronic rhinosinusitis with nasal polyposis (CRSwNP) in a subject, and wherein the antibody, or antigen-binding fragment thereof, comprises:

   three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence of SEQ ID NO:7, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8.

2. The use of claim 1, wherein the subject has chronic rhinosinusitis with bilateral nasal polyposis.

3. The use of claims 1 or 2, wherein the antibody or antigen-binding fragment thereof comprises: a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 1; and a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 2.

4. The use of any one of claims 1-3, wherein the subject has one or more of asthma, aspirin hypersensitivity, or hypersensitivity to a non-steroidal anti-inflammatory drug (NSAID).

5. The use of any one of claims 1-4, wherein the subject has severe nasal polyposis.

6. The use of any one of claims 1-5, wherein the composition is formulated for administration as a single initial dose and one or more secondary doses.

7. The use of claim 6, wherein the initial dose and one or more secondary doses are each about 300 mg.

8. The use of claim 6 or 7, wherein the pharmaceutical composition is formulated for administration every two weeks.

9. The use of any one of claims 1-8, wherein the pharmaceutical composition is formulated for subcutaneous, intravenous or intranasal administration to the subject.

10. The use of any one of claims 1-9, wherein the subject has nasal polyposis which persists after a treatment regimen with inhaled corticosteroids (INCS) or after the subject stops receiving INCS.

11. The use of any one of claims 1-10, wherein the subject is selected based on one or more of the following criteria:

    i) a minimum bilateral nasal polyp score of 5;

    ii) an elevated level of one or more genes selected from the group consisting of thymus and activation-regulated chemokine (TARC), eotaxin-3, periostin, carcinoembryonic antigen (CEA), and YKL-40; and

    iii) an elevated level of blood eosinophils or sputum eosinophils.

12. The use of any one of claims 1-11, for improving one or more of:

    a) 22-item sinonasal outcome test (SNOT-22) score;

    b) nasal symptom score;

    c) number of nocturnal awakenings;

    d) visual analog score (VAS);

    e) five-item asthma control questionnaire (ACQ5) score;

    f) nasal peak inspiratory flow (NPIF);

    g) University of Pennsylvania Smell fication test (UPSIT);

    h) Lund-McKay Score; and

    i) three-dimensional volumetric measurement of the maxillary sinus,

    in particular an increase in one or both of NPIF and UPSIT and/or a decrease in one or more of SNOT-22 score, nasal symptom score, VAS, Lund-McKay Score and 3D-Volumetric Score.

13. The use of any one of claims 1-12, for decreasing a nasal polyp score.

14. The use of any one of claims 1-13, for increasing one or both of NPIF and UPSIT.

15. The use of any one of claims 9-14, wherein the pharmaceutical composition is formulated for subcutaneous administration to the subject with a pen delivery device or an autoinjector, or formulated for subcutaneous or intravenous administration with a standard syringe and needle.

16. The use of any one of claims 1-15, wherein the antibody is dupilumab.

17. The use of any one of claims 1-16, wherein the pharmaceutical composition is formulated for administration with a second therapeutic agent before, after or concurrently with the second therapeutic agent.

18. The use of claim 17, wherein the second therapeutic agent is selected from the group consisting of an IgE inhibitor, an antibiotic agent, and an anti-fungal agent.

19. The use of claim 17, wherein the second therapeutic agent comprises an intranasal corticosteroid, optionally wherein the intranasal corticosteroid is mometasone furoate nasal spray (MFNS).

20. The use of claim 19, wherein the second therapeutic agent comprises an inhaled corticosteroid, optionally wherein the inhaled corticosteroid is fluticasone or budesonide.

21. The use of claim 17, wherein the second therapeutic agent comprises a long-acting $beta_2$ agonist, optionally wherein the long-acting $beta_2$ agonist is salmeterol or formoterol.

22. The use of any one of claims 1-16, wherein the subject has been prescribed or is currently taking a background therapy for nasal polyposis.

23. The use of claim 22, wherein the background therapy is an intranasal corticosteroid.

24. The use of claim 23, wherein the intranasal corticosteroid is mometasone furoate nasal spray (MFNS).

25. The use of claim 22, wherein the background therapy is an intranasal corticosteroid and a long-acting beta$_2$ agonist.

26. The use of claim 25, wherein the background therapy is fluticasone/salmeterol combination therapy.

27. The use of claim 25, wherein the background therapy is budesonide/formoterol combination therapy.

28. The use of claim 22, wherein the background therapy is selected from the group consisting of a nasal saline, a topical decongestant, a topical anesthetic, a leukotriene antagonist, and a systemic antihistamine.

29. The use of any one of claims 6-28, wherein the initial dose is about 400 mg and the one or more secondary doses are each about 200 mg.

30. The use of any one of claims 6-28, wherein the initial dose is about 600 mg and the one or more secondary doses are each about 300 mg.