METHODS FOR REDUCING EXACERBATION RATES OF ASTHMA USING BENRALIZUMAB

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 16, 2014, is named IL5R-603WO1_SL.txt and is 15,960 bytes in size.

BACKGROUND

[0002] More than 300 million people around the world have asthma. Despite the use of long-acting bronchodilators and inhaled corticosteroids, unscheduled visits to doctor offices, visits to emergency departments (ED), and hospitalizations due to asthma exacerbations occur frequently and account for a significant proportion of healthcare costs attributable to asthma. (Masoli M, *et al. Allergy 59*: 469-78(2004)).

[0003] Relapse following acute asthma exacerbation has been reported to range from 41 to 52% at 12 weeks despite the use of systemic steroids upon discharge (Lederle F, *et al. Arch Int Med 147*:2201-03 (1987)). Management of these patients has proved problematic due either to severe refractory disease or inability and/or unwillingness to comply with medical treatment. In one study of patients admitted to the hospital, some with near fatal asthma, 50% were non-compliant with systemic corticosteroids at 7 days following discharge (Krishnan J, *et al. AJRCCM 170*: 1281-85 (2004)). Many factors may contribute to non-compliance including poor access to routine quality healthcare (particularly in the inner city), lack of education or understanding of their disease, unwillingness to accept the chronic nature of their disease, or inability to obtain medications.

[0004] Many lines of evidence implicate eosinophils as one of the main causative cells of asthmatic airway inflammation (James A. *Curr Opin Pulm Med 11*(1):1-6 (2005)). Peripheral blood (PB) eosinophilia is a risk factor for relapse of acute asthma (Janson C and Herala M. *Resp Med 86*(2):101-104 (1992)). In subjects with peripheral blood eosinophilia, the risk of dying from asthma was 7.4 (confidence interval, 2.8-19.7) times greater than in those without eosinophilia (Ulrik C and Fredericksen J. *Chest 108*:10-15

(1995)). Necropsy results have identified 2 distinct pathogenic inflammatory mechanisms of fatal asthma (Restrepo R and Peters J. *Curr Opin Pulm Med 14*: 13-23 (2008)). A neutrophilic infiltrate is more prominent in those dying suddenly (approximately within 2 hours on onset of symptoms), while an eosinophilic infiltrate is more common in those dying from more protracted asthma crises. Sputum and blood eosinophils can also be increased in patients presenting to the ED with rapid onset of asthma symptoms (Bellido-Casado J, *et al. Arch Bronconeumol 46*(11): 587-93 (2010)). Therapies that target eosinophils lead to a reduction in the number and severity of asthma exacerbations as compared to the use of clinical guidelines (Green R, *et al. Lancet 360*:1715-21 (2002); Haldar P, *et al. NEJM 360*:973-84 (2009)).

[0005] Benralizumab (MEDI-563) is a humanized monoclonal antibody (mAb) that binds to the alpha chain of the interleukin-5 receptor alpha (IL-5Rα), which is expressed on eosinophils and basophils. It induces apoptosis of these cells via antibody-dependent cell cytotoxicity. A single intravenous (IV) dose of benralizumab administered to adults with mild asthma provoked prolonged PB eosinopenia likely due to the effects on eosinophil/basophil bone marrow progenitors that express the target (Busse W, *et al. JACI 125*: 1237-1244 e2 (2010)). In addition, a single dose of benralizumab significantly reduced the blood eosinophil count in subjects who presented to the emergency department with a severe asthma exacerbation (WO 2013/066780). Benralizumab does not affect other cell lineages in the bone marrow or periphery. (Kolbeck R, *et al. JACI 125*:1344-53 (2010)).

[0006] Previous studies have demonstrated that an outpatient strategy focused on reducing eosinophils in the sputum reduces the number of subsequent asthma exacerbations (Green R, *et al.* Lancet 360:1715-21 (2002); Haldar P, *et al. NEJM 360*:973-84 (2009)).

[0007] Thus, given the high unmet need of reducing exacerbations of asthma and that some subjects with asthma have an eosinophilic component, the effect of benralizumab on asthma exacerbation rates in adult subjects was examined.

BRIEF SUMMARY

[0008] Methods of reducing the annual exacerbation rate of asthma are provided herein. In certain aspects, a method of reducing the annual exacerbation rate of asthma comprises

administering to an asthma patient an effective amount of benralizumab or an antigen-binding fragment thereof.

[0009] Methods of treating asthma are also provided herein. In certain aspects, a method of treating asthma comprises administering to an asthma patient an effective amount of benralizumab or an antigen-binding fragment thereof, wherein the patient has a blood eosinophil count of at least 300 cells/μl prior to the administration.

[0010] In certain aspects, a method of treating asthma comprises administering to an asthma patient an effective amount of benralizumab or an antigen-binding fragment thereof, wherein the patient has a forced expiratory volume (FEV_1) of at least 75% predicted value prior to the administration.

[0011] In certain aspects, a method of treating asthma comprises administering at least two doses of benralizumab or an antigen-binding fragment thereof to an asthma patient.

[0012] In certain aspects of the methods provided herein, the administration reduces the patient's exacerbation rate. In certain aspects, the administration reduces the patient's annual exacerbation rate. In certain aspects, the annual exacerbations rate following administration of benralizumab or an antigen-binding fragment thereof is reduced by at least 35%. In certain aspects, the annual exacerbation rate following administration of benralizumab or an antigen-binding fragment thereof is reduced by at least 40%. In certain aspects, the annual exacerbation rate following administration of benralizumab or an antigen-binding fragment thereof is reduced by at least 50%. In certain aspects, the annual exacerbations rate following administration of benralizumab or an antigen-binding fragment thereof is reduced by at least 60%.

[0013] In certain aspects of the methods provided herein, the asthma is eosinophilic asthma. In certain aspects, the patient has a blood eosinophil count of at least 300 cells/μl.

[0014] In certain aspects of the methods provided herein, the patient has a forced expiratory volume (FEV_1) of at least 75% predicted value prior to the administration. In certain aspects, the patient has an asthma control questionnaire score of at least 1.5 prior to the administration. In certain aspects, the patient uses high-dose inhaled corticosteroids (ICS). In certain aspects, the patient uses long-acting β2 agonists (LABA). In certain aspects, the patient has a history of exacerbations. In certain aspects, the history of exacerbations comprises at least two exacerbations in the year prior to the

administration of benralizumab or an antigen-binding fragment thereof. In certain aspects, the history of exacerbations comprises no more than six exacerbations in the year prior to the administration of benralizumab or an antigen-binding fragment thereof

[0015] In certain aspects of the methods provided herein, at least two doses of benralizumab or an antigen-binding fragment thereof are administered to the patient.

[0016] In certain aspects of the methods provided herein, benralizumab or an antigen-binding fragment thereof is administered at about 2 mg to about 100 mg per dose. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered at about 20 mg per dose. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered at about 30 mg per dose. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered at about 100 mg per dose.

[0017] In certain aspects of the methods provided herein, benralizumab or an antigen-binding fragment thereof is administered once every four weeks to once every twelve weeks. In certain aspects, the benralizumab or antigen-binding fragment thereof is administered once every four weeks. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered once every eight weeks. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered once every four weeks for twelve weeks and then once every eight weeks.

[0018] In certain aspects of the methods provided herein, benralizumab or an antigen-binding fragment thereof is administered parenterally. In certain aspects, benralizumab or an antigen-binding fragment thereof is administered subcutaneously.

[0019] In certain aspects of the methods provided herein, benralizumab or an antigen-binding fragment thereof is administered in addition to corticosteroid therapy.

[0020] In certain aspects, a method of reducing the annual exacerbation rate of asthma comprises administering to an asthma patient 20-100 mg of benralizumab or an antigen-binding fragment thereof, wherein the patient has an blood eosinophil count of at least 300 cells/μl prior to the administration. In certain aspects, the method comprises administering 20 mg of benralizumab or an antigen-binding fragment thereof. In certain aspects, the 20 mg of benralizumab is administered once every four weeks for twelve weeks and then once every eight weeks. In certain aspects, the method comprises administering 30 mg of benralizumab or an antigen-binding fragment thereof. In certain aspects, the 30 mg of benralizumab is administered once every four weeks for eight

weeks and then once every eight weeks. In certain aspects, the 30 mg of benralizumab is administered once every four weeks. In certain aspects, the method comprises administering 100 mg of benralizumab or an antigen-binding fragment thereof. In certain aspects, the 100 mg of benralizumab is administered once every four weeks for twelve weeks and then once every eight weeks.

[0021] In certain aspects, a method of treating asthma in an asthma patient comprises administering to the patient a dose of at least 2 and less than 100 mg of benralizumab or an antigen-binding fragment thereof. In certain aspects, the method comprises administering 20 mg of benralizumab or an antigen-binding fragment. In certain aspects, the method comprises administering 30 mg of benralizumab or an antigen-binding fragment. In certain aspects, the method comprises administering a dose of at least 20 and less than 100 mg of benralizumab or an antigen-binding fragment. In certain aspects, the method comprises administering a dose of at least 30 and less than 100 mg of benralizumab or an antigen-binding fragment. In certain aspects, the method decreases exacerbation rates of asthma. In certain aspects, the method decreases annual exacerbation rates of asthma. In certain aspects, the administration is subcutaneous.

[0022] In certain aspects of the provided methods, administration of benralizumab or an antigen-binding fragment thereof results in the reduction in exacerbation rates as shown in Figures 2-8.

[0023] In certain aspects of the provided methods, administration of benralizumab or an antigen-binding fragment thereof results in the reduction in exacerbation rates as shown in Examples 1-2.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0024] **Figure 1** shows the study flow diagram.

[0025] **Figure 2** shows the interim (24 weeks) and annual (Stage I; 52 weeks) exacerbation rates after treatment with placebo, 2 mg benralizumab, 20 mg benralizumab, or 100 mg benralizumab in patients with fewer than 300 eosinophils/μl and patients with at least 300 eosinophils/μl.

[0026] **Figure 3** shows the interim (24 weeks) and annual (Stage I; 52 weeks) exacerbation rates after treatment with placebo, 2 mg benralizumab, 20 mg benralizumab,

or 100 mg benralizumab in patients with medium or high use of inhaled corticosteroids (ICS).

[0027] **Figure 4** shows the interim (24 weeks) and annual (Stage I; 52 weeks) exacerbation rates after treatment with placebo, 2 mg benralizumab, 20 mg benralizumab, or 100 mg benralizumab in patients with fewer than 300 eosinophils/μl and (i) medium use of ICS or (ii) high use of ICS.

[0028] **Figure 5** shows the interim (24 weeks) and annual (Stage I; 52 weeks) exacerbation rates after treatment with placebo, 2 mg benralizumab, 20 mg benralizumab, or 100 mg benralizumab in patients with at least 300 eosinophils/μl and (i) medium use of ICS or (ii) high use of ICS.

[0029] **Figure 6** shows the annual exacerbation rates in patients with fewer than 300 eosinophils/μl and patients with at least 300 eosinophils/μl.

[0030] **Figures 7A and 7B** show the number of exacerbations in patients with various eosinophil counts.

[0031] **Figure 8** shows the time course of eosinophil depletion in patients with at least 300 eosinophils/μl.

DETAILED DESCRIPTION

[0032] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "an anti-IL-5α antibody" is understood to represent one or more anti-IL-5α antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0033] Provided herein are methods for reducing exacerbations of asthma. The methods provided include administering an effective amount of benralizumab or an antigen-binding fragment thereof.

[0034] Information regarding benralizumab (or fragments thereof) for use in the methods provided herein can be found in U.S. Patent Application Publication No. US 2010/0291073 A1, the disclosure of which is incorporated herein by reference in its entirety. Benralizumab and antigen-binding fragments thereof for use in the methods provided herein comprise a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. In a further aspect, benralizumab or an antigen-binding fragment thereof for use in the methods provided herein includes any one of the amino

acid sequences of SEQ ID NOs: 1-4. In a specific aspect, benralizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:1 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:3. In a specific aspect, benralizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 2 and heavy chain comprising the amino acid sequence of SEQ ID NO:4. In a specific aspect, benralizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 7-9, and wherein the light chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 10-12. Those of ordinary skill in the art would easily be able to identify Chothia-defined, Abm-defined or other CDRs. In a specific aspect, benralizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises the variable heavy chain and variable light chain CDR sequences of the KM1259 antibody as disclosed in U.S. 6,018,032, which is herein incorporated by reference in its entirety.

[0035] In certain aspects, a patient presenting at a physician's office or ED with asthma is administered benralizumab or an antigen-binding fragment thereof. Given the ability benralizumab to reduce or deplete eosinophil counts for up to 12 weeks or more (*see* US 2010/0291073), benralizumab or an antigen-binding fragment thereof can be administered only once or infrequently while still providing benefit to the patient in reducing exacerbations. In further aspects the patient is administered additional follow-on doses. Follow-on doses can be administered at various time intervals depending on the patient's age, weight, ability to comply with physician instructions, clinical assessment, eosinophil count (blood or sputum eosinophils), Eosinophilic Cationic Protein (ECP) measurement, Eosinophil-derived neurotoxin measurement (EDN), Major Basic Protein (MBP) measurement and other factors, including the judgment of the attending physician. The intervals between doses can be every 4 weeks, every 5 weeks, every 6 weeks, every 8 weeks, every 10 weeks, every 12 weeks, or longer intervals. In certain aspects the intervals between doses can be every 4 weeks, every 8 weeks, or every 12 weeks. In

certain aspects, the single dose or first dose is administered to the asthma patient shortly after the patient presents with an exacerbation, *e.g.*, a mild, moderate or severe exacerbation. For example, benralizumab or an antigen-binding fragment thereof can be administered during a presenting clinic or hospital visit, or in the case of very severe exacerbations, within 1, 2, 3, 4, 5, 6, 7, or more days, *e.g.*, 7 days of the acute exacerbation, allowing the patient's symptoms to stabilize prior to administration of benralizumab.

[0036] In some embodiments, at least two doses of benralizumab or an antigen-binding fragment thereof are administered to the patient. In some embodiments, at least three doses, at least four doses, at least five doses, at least six doses, or at least seven doses are administered to the patient. In some embodiments, benralizumab or an antigen-binding fragment thereof is administered over the course of four weeks, over the course of eight weeks, over the course of twelve weeks, over the course of twenty-four weeks, or over the course of a year.

[0037] The amount of benralizumab or antigen-binding fragment thereof to be administered to the patient will depend on various parameters such as the patient's age, weight, clinical assessment, eosinophil count (blood or sputum eosinophils), Eosinophilic Cationic Protein (ECP) measurement, Eosinophil-derived neurotoxin measurement (EDN), Major Basic Protein (MBP) measurement and other factors, including the judgment of the attending physician. In certain aspects, the dosage or dosage interval is not dependent on the eosinophil level.

[0038] In certain aspects the patient is administered one or more doses of benralizumab or an antigen-binding fragment thereof, wherein the dose is about 2 mg to about 100 mg, for example about 20 mg to about 100 mg, or about 30 mg to about 100 mg. In certain specific aspects, the patient is administered one or more doses of benralizumab or an antigen-binding fragment thereof where the dose is about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg. In some embodiments, the dose is about 20 mg. In some embodiments the dose is about 30 mg. In some embodiments, the dose is about 100 mg.

[0039] In certain aspects, administration of benralizumab or an antigen-binding fragment thereof according to the methods provided herein is through parenteral administration.

For example, benralizumab or an antigen-binding fragment thereof can be administered by intravenous infusion or by subcutaneous injection.

[0040] In certain aspects, benralizumab or an antigen-binding fragment thereof is administered according to the methods provided herein in combination or in conjunction with additional asthma therapies. Such therapies include, without limitation, inhaled corticosteroid therapy, long- or short-term bronchodilator treatment, oxygen supplementation, or other standard therapies as described, *e.g.*, in the National Asthma Education and Prevention Program (NAEPP) Guidelines. In certain aspects, use of the methods provided herein, *i.e.*, administration of benralizumab or an antigen-binding fragment thereof to an asthma patient with a history of exacerbations serves as adjunct therapy in situations of poor compliance with standard forms of asthma management.

[0041] The methods provided herein can significantly reduce exacerbations of asthma. Reduction can be measured based on the expected exacerbations predicted based on a large patient population, or based on the individual patient's history of exacerbations. In certain aspects, the patient population is those patients who had ≥2 exacerbations requiring systemic corticosteroid bursts in the past year. In certain aspects, the patient population is those patients who had ≥2 exacerbations requiring systemic corticosteroid bursts in the past year and ≤6 exacerbations requiring systemic corticosteroid bursts in the past year. In certain aspects, the patient population is patients having an eosinophil count of at least 300 cells/μl.

[0042] In certain aspects, use of the methods provided herein, *i.e.*, administration of benralizumab or an antigen-binding fragment thereof reduces the number of exacerbations experienced by the patient over a 24-week period following administration of benralizumab or an antigen-binding fragment thereof, as compared to the number of exacerbations expected according to the patient's history, as compared to the average number of exacerbations expected in a comparable population of patients, or as compared to a comparable population treated with placebo over the same time period. In certain aspects, the patient can receive follow on doses of benralizumab or an antigen-binding fragment thereof at periodic intervals, *e.g.*, every 4 weeks, every 5 weeks, every 6 weeks, every 8 weeks, every 12 weeks, or as scheduled based on patient's age, weight, ability to comply with physician instructions, clinical assessment, eosinophil count (blood or sputum eosinophils), Eosinophilic Cationic Protein (ECP) measurement, Eosinophil-

derived neurotoxin measurement (EDN), Major Basic Protein (MBP) measurement and other factors, including the judgment of the attending physician. Use of the methods provided herein can reduce the frequency of exacerbations by 10%, 20%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% over the 24-week period.

[0043] In other aspects, use of the methods provided herein, *i.e.*, administration of benralizumab or an antigen-binding fragment thereof to an asthma patient, reduces the number of exacerbations experienced by the patient over a 52-week period (i.e., the annual exacerbation rate) following administration of benralizumab or an antigen-binding fragment thereof, as compared to the number of exacerbations expected according to the patient's history, as compared to the average number of exacerbations expected in a comparable population of patients, or as compared to a comparable population treated with placebo over the same time period. In certain aspects, the patient can receive follow on doses of benralizumab or an antigen-binding fragment thereof at periodic intervals, *e.g.*, every 4 weeks, every 5 weeks, every 6 weeks, every 8 weeks, every 12 weeks, or as scheduled based on patient's age, weight, ability to comply with physician instructions, clinical assessment, eosinophil count (blood or sputum eosinophils), Eosinophilic Cationic Protein (ECP) measurement, Eosinophil-derived neurotoxin measurement (EDN), Major Basic Protein (MBP) measurement and other factors, including the judgment of the attending physician. In certain aspects, the interval is every 4 weeks, every 8 weeks or every 12 weeks. Use of the methods provided herein can reduce the annual exacerbations by 10%, 20%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% , 80%, 85%, 90%, 95% or 100%.

[0044] In certain aspects, use of the methods provided herein, *i.e.*, administration of benralizumab or an antigen-binding fragment thereof to an asthma patient, reduces the annual exacerbation rate, increases forced expiratory volume (FEV_1), and/or improves an asthma questionnaire score (e.g., the asthma control questionnaire (ACQ)).

[0045] In certain aspects, the patient is "eosinophilic positive" meaning the patient is one whose asthma is likely to be eosinophilic.

[0046] In certain aspects, the asthma patient has a particular blood eosinophil count, *e.g.*, prior to the administration of benralizumab or an antigen-binding fragment thereof.

Blood eosinophil counts can be measured, for example, using a complete blood count (CBC) with cell differential.

[0047] In certain aspects, the asthma patient has a blood eosinophil count of at least 300 cells/μl prior to the administration of benralizumab or an antigen-binding fragment thereof. In certain aspects, the asthma patient has a blood eosinophil count of at least 350 cells/μl, at least 400 cells/μl, at least 450 cells/μl, or at least 500 cells/μl prior to the administration of benralizumab or an antigen-binding fragment thereof.

[0048] In certain aspects, the asthma patient has a blood eosinophil count of less than 300 cells/μl prior to the administration of benralizumab or an antigen-binding fragment thereof. In certain aspects, the asthma patient has a blood eosinophil count of at least 100 cells/μl, at least 150 cells/μl, at least 180 cells/μl, at least 200 cells/μl, or at least 250 cells/μl prior to the administration of benralizumab or an antigen-binding fragment thereof.

[0049] In certain aspects, the asthma patient was prescribed or has been using a medium-dose of inhaled corticosteroids (ICS) use prior to the administration of benralizumab or an antigen-binding fragment thereof. A medium-dose of ICS can be a dose of at least 600 μg to 1,200 μg budesonide daily or an equivalent dose of another ICS.

[0050] In certain aspects, the asthma patient was prescribed or had been using a high-dose of ICS use prior to the administration of benralizumab or an antigen-binding fragment thereof. A high-dose of ICS can be a dose of at least 1,200 μg budesonide daily or an equivalent dose of another ICS. A high dose of ICS can also be a dose of greater than 1,200 μg to 2000 μg budesonide daily or an equivalent dose of another ICS.

[0051] In certain aspects, the asthma patient was prescribed or has been using oral corticosteroids prior to the administration of benralizumab or an antigen-binding fragment thereof. In certain aspects, administration of benralizumab or an antigen-binding fragment thereof decreases the use of oral corticosteroids in an asthma patient. In certain aspects, the administration decreases the use of oral corticosteroids in an asthma patient by at least 50%.

[0052] In certain aspects, the asthma patient was prescribed or had been using a long-acting beta agonist (LABA) prior to the administration of benralizumab or an antigen-binding fragment thereof.

[0053] In certain aspects, the asthma patient was prescribed or had been using both ICS and LABA prior to the administration of benralizumab or an antigen-binding fragment thereof.

[0054] In certain aspects, the asthma patient has a blood eosinophil count of at least 300 cells/μl and high ICS use prior to the administration of benralizumab or an antigen-binding fragment thereof.

[0055] In certain aspects, the asthma patient had a forced expiratory volume in 1 second (FEV_1) of at least 40% and less than 90% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was greater than 70% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was greater than 70% and less than 90% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was at least 75% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was at least 75% and less than 90% prior predicted value to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was at least 80% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof. In some embodiments, the FEV_1 was at least 80% and less than 90% predicted value prior to the administration of benralizumab or an antigen-binding fragment thereof.

Examples

EXAMPLE 1: Patients and Methods

SUBJECTS

[0056] Subjects in this study were required to be 18 to 75 years of age with a weight of greater than 45 kg and less than or equal to 150 kg (greater than 100 pounds, but less than or equal to 330 pounds). They also must have had a physician diagnosis of asthma for a minimum of 12 months prior to screening as well as physician prescribed daily use of medium-dose or high-dose inhaled corticosteroids (ICS) plus long-acting beta agonist (LABA) or any combination of sequential dosing of either medium-dose or high-dose

ICS/LABA for at least 12 months prior to screening. Medium and high-doses of ICS as defined in this study are shown in Table 1 below.

Table 1: Estimated Comparative Daily Dosages for Inhaled Corticosteroids

Drug	Medium Daily Dose (Adult)	High Daily Dose (Adult)
Beclamethazone HFA/MDI 40 or 80 µg/puff	> 240-480 µg	> 480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	> 600-1,200 µg	> 1,200 µg
Ciclesonide HFA/MDI 80 or 160 µg/inhalation	> 160-320 µg	> 320-1280 µg
Flunisolide CFC/MDI 250 µg/puff	> 1,000-2,000 µg	> 2,000 µg
Flunisolide HFA/MDI 80 µg/puff	> 320-640 µg	> 640 µg
Fluticasone HFA/MDI: 44, 110, or 220 µg/puff DPI: 50, 100, or 250 µg/puff	> 264-440 µg > 300-500 µg	> 440 µg > 500 µg
Mometasone DPI 200 µg/inhalation	400 µg	> 400 µg
Triamcinolone acetonide CFC/MDI 75 µg/puff	> 750-1,500 µg	> 1,500 µg

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered dose inhaler.

[0057] The dose of other asthma controller medications must have been stable in the subjects for at least 30 days prior to screening. Subjects must also have had at least 2, but no more than 6, documented asthma exacerbations in the 12 months prior to screening that required the use of a systemic corticosteroid burst. Subjects must also have had a morning pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of at least 40% and less than 90% predicted during the screening/run-in period (described below). Subjects must also have fulfilled one of the following criteria:

(a) Proof of post-bronchodilator reversibility of airflow obstruction ≥ 12% and ≥ 200 mL documented within 36 months prior to randomization or proof of a positive response [PC20 ≤ 8 mg/mL] to a methacholine challenge documented within 36 months prior to randomization; OR

(b) A post-bronchodilator increase in FEV_1 ≥ 12% and ≥ 200 mL at Week -3 screening visit; OR

(c) If a) and b) were not met and all other inclusion/exclusion criteria were met, subjects with a FEV_1 of $\geq$ 1.5 L and $\geq$ 60% predicted on the Week -2 screening visit were eligible to undergo a methacholine challenge at the Week-2 screening visit at sites where methacholine testing was available. If the subject achieved a positive response, (PC20 $\leq$ 8 mg/mL), then this inclusion criterion was met.

[0058] Subjects must also have had an Asthma Control Questionnaire (ACQ) score of at least 1.5 at least twice during the screening/run-in period.

[0059] Subjects were not able to participate if they had a cigarette exposure of 10 pack-years or more or had been smoking within 12 months prior to screening or had any condition (e.g., any eosinophilic lower respiratory disease other than asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis) that, in the opinion of the investigator or medical monitor, would interfere with the evaluation. Subjects were also not able to participate if they had received an oral corticosteroid burst or short-acting systemic corticosteroid within 30 days prior to screening or during the screening/run-in period.

DESIGN OF THE STUDY

[0060] The study was a phase 2b randomized, double-blind, placebo-controlled, dose-ranging, multicenter study (ClinicalTrials.gov number: NCT01238861) in which multiple doses of benralizumab were administered subcutaneously to asthma patients. Benralizumab was administered at 2, 20, or 100 mg doses, and patients were followed for 1 year. The study flow diagram is shown in Figure 1.

[0061] A 3-week screening/run-in period preceded administration of benralizumab or placebo. During the 3-week period, subjects continued to use the same medium-dose or high-dose ICS/LABA combination product as prior to the participation in the study (doses of ICS/LABA were required to be stable for 30 days prior to the 3-week screening/run-in period). Subjects remained on the same dose of ICS/LABA throughout the study.

[0062] The administered benralizumab composition contained benralizumab (50 mg/mL), 10 mM histidine, 10 mM histidine HCl monohydrate, 9% (w/v) trehalose dihydrate, and 0.004% (w/v) polysorbate-20, pH 6. The administered placebo composition contained 10 mM histidine, 10 mM histidine hydrochloride monohydrate, 9% (w/v) trehalose dihydrate, and 0.02% (w/v) polysorbate-20, pH 6.

[0063] Subjects received two subcutaneous (SC) injections of 1 ml of benralizumab or placebo every four weeks for the first 3 doses on Weeks 1 (Day 1), 4, and 8 and then every 8 weeks thereafter for the last 4 doses on Weeks 16, 24, 32, and 40. After Week 40, subjects were followed for an additional 12 weeks (through Week 52) for assessment of acute exacerbations. The day of receipt of the first dose of benralizumab or placebo was considered Day 1.

[0064] For the purpose of this study, an asthma exacerbation was defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) that did not resolve after the initiation of rescue medications and remained troublesome for the subject resulting in either 1) use of systemic corticosteroids (tablets, suspension or injection) or increase of a stable systemic maintenance dose for a duration of at least 3 days as prescribed or administered by the investigator or healthcare provider; or 2) subject initiation of systemic corticosteroids for a duration of at least 3 days. An asthma exacerbation event was considered resolved 7 days after the last dose of oral corticosteroid was administered (10 days after administration of an injectable corticosteroid). Courses of corticosteroids initiated after this time period were considered a separate new asthma exacerbation. Asthma exacerbations were classified as "moderate" if worsening symptoms required systemic corticosteroids or "severe" if worsening symptoms required systemic corticosteroids and urgent care evaluation and/or hospital admission.

[0065] Asthma exacerbations were assessed at weeks -3, -2, -1, 1 (on Day 1 and Day 6), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 46, and 52.

[0066] Annual exacerbation rate was defined as the number of exacerbations from Week 1 (Day 1) to Week 52. If a subject discontinued before the Week 52 visit, the annual exacerbation rate for that subject was calculated according to the following formula: observed number of asthma exacerbations/observed Days × 364.

[0067] Weighted mean rate of asthma exacerbations was estimated by pooling all the asthma exacerbations in a treatment group and dividing by the total follow-up time in that treatment group.

SAFETY ASSESSMENTS

[0068] Adverse events were monitored following administration of placebo or benralizumab. Other assessments included physical examination, vital sign monitoring, and laboratory measurements.

EXAMPLE 2: Results

ENROLLMENT AND BASELINE CHARACTERISTICS

[0069] The baseline characteristics of all randomized subjects who received any dose of investigational product are provided in Table 2 below. The mean population ICS dose was 1100 budesonide equivalents overall, 700 budesonide equivalents in the medium dose stratum, and 1600 budesonide equivalents in the high dose stratum.

Table 2: Demographics for Baseline Eosinophils (EOS)

POPULATION	**PLACEBO EOS < 300**	**BENRALIZUMAB EOS < 300**	**PLACEBO EOS >= 300**	**BENRALIZUMAB EOS >= 300**
N	139	151	83	232
Mean Age (yrs)	50.3	51.2	45.2	46.3
Gender Female (%)	71	70	66	68
Race White (%)	76	80	64	65
BMI (mean)	29.6	29.2	28.8	28.5
EOS mean cells/ ul	149	156	542	548-615
Chronic OCS (%)	2.2%	7.9%	4.8%	4.3%
FEV_1 (L) % pred	70.0	54-69	65	64-67
Reversibility (%)	12.5	13-18	15.5	17-19
Historical Exacerbations	2.2	2.3-2.5	2.2	2.3-2.5
ACQ at Baseline	2.5	2.5-2.8	2.6	2.4-2.7

Childhood Asthma YES	32%	33-38%	40%	37-41%
History Nasal Polyps YES	10.8%	11.9%	14.5%	19.3%
FE_{NO} mean ppb	22.1	21-39	34.8	34-42

OCS = oral corticosteroids; FEV_1 = forced expiratory volume in 1 second; ACQ = asthma control questionnaire; and FENO = fraction of exhaled nitric oxide.

[0070] The baseline characteristics of randomized subjects who received any dose of investigational product and had a baseline eosinophil count of at least 300 cells/µl are shown in Table 3 below.

Table 3: Demographics for ICS with Baseline EOS at Least 300 Cells/µl

POPULATION	PLACEBO MED ICS	BENRALIZUMAB MED ICS	PLACEBO HIGH ICS	BENRALIZUMAB HIGH ICS
N	43	121	40	111
Mean Age (yrs)	45	46-47	45	45-47
Gender Female (%)	65	63	68	70-79
Race White (%)	56	66	73	63
BMI (mean)	27.3	27.6-28.3	30.3	27.8-30.0
EOS mean cells / ul	480	462-625	608	605-656
Chronic OCS (%)	0	0	10%	9%
FEV_1 (L) % pred	68.8	64-70	60	63-65
Reversibility (%)	16%	17-23%	15%	14-21%
Historical Exacerbations	2.2	2.1-2.5	2.3	2.4-2.5
ACQ at Baseline	2.6	2.3-2.6	2.7	2.6-2.8
Childhood Asthma YES	42%	36%	38%	27-53%
History Nasal	14%	11%	15%	23-37%

Polyps YES				
FE_{NO} mean ppb	38.3	35-45	31.0	33-39

OCS = oral corticosteroids; FEV_1 = forced expiratory volume in 1 second; ACQ = asthma control questionnaire; and FENO = fraction of exhaled nitric oxide.

EFFICACY

[0071] The effects of administration of benralizumab on exacerbation rates are shown in Figures 2-8. Only about 30% of the subjects had exacerbations. In addition, administration of 20 mg or 100 mg of benralizumab significantly reduced ($p<0.169$) annual exacerbation rates in asthma patients with a blood eosinophil count of at least 300 cells/µl and in asthma patients with both a blood eosinophil count of at least 300 cells/µl and a high baseline ICS status.

[0072] In patients with a blood eosinophil count of at least 300 cells/µl, administration of 20 mg of benralizumab reduced the annual exacerbation rate by 57% ($p = 0.014$), and administration of 100 mg of benralizumab reduced the annual exacerbation rate by 43% ($p = 0.049$) compared to treatment with placebo (Figure 2).

[0073] In patients with a blood eosinophil count of at least 300 cells/µl and a high baseline ICS status, administration of 20 mg of benralizumab reduced the annual exacerbation rate by 52% ($p = 0.118$), and administration of 100 mg of benralizumab reduced the annual exacerbation rate by 46% ($p = 0.102$) compared to treatment with placebo (Figure 5).

[0074] Reductions in exacerbation rates were also observed in patients with a blood eosinophil count of less than 300 cells/µl (Figures 2 and 4) as well as patients with a medium or high baseline ICS (Figure 3).

[0075] A comparison of the reduction in exacerbation rates in patients with less than 300 cells/µl and patients with at least 300 cells/µl prior to treatment is shown in Figure 6, and the number of exacerbations at various eosinophil counts are provided in Figure 7.

[0076] In addition, eosinophils were reduced in patients receiving any dose of benralizumab as compared to patients receiving placebo. Figure 8.

SAFETY

[0077] Treatment emergent adverse events (TEAEs) occurred at an approximate 10 percentage point higher frequency in patients treated with benralizumab compared with

those treated with placebo. Treatment emergent severe adverse events (TE-SAEs) occurred at similar frequencies in patients treated with benralizumab and placebo. TEAEs and TE-SAEs were not dose dependent in patients treated with benralizumab.

ANTI-DRUG ANTIBODIES

[0078] The development of anti-drug antibodies (ADA) to benralizumab was inversely related to dose, with the highest proportion of ADA-positive subjects at the 2 mg dose (see Table 4 below). The incidence of high titer ADA (≥ 400) was 12% and 9% in the 20 and 100 mg dose groups, respectively. High titer ADAs were associated with reduced benralizumab concentration and varying degrees of eosinophil recovery when present. The pharmacokinetic/pharmacodynamic (PK/PD) impact of high titer ADA was reduced at higher drug exposures. No pattern was observed between TEAEs and ADA.

Table 4: Anti-Drug Antibodies at Week 24

Treatment Group	Total Number of Subjects	% Subjects with Positive ADA Titres	% Subjects with ADA Titres ≥ 400
Placebo	222	8.1% (n = 18)	3% (n = 6)
Benralizumab 2 mg	81	34.6% (n = 28)	23% (n = 19)
Benralizumab 20 mg	81	18.5% (n = 15)	12% (n = 10)
Benralizumab 100 mg	222	21.2% (n = 47)	9% (n = 20)

[0079] Based on both PK and immunological considerations, additional patients will receive dosing of 30 mg benralizumab. In some patients, the 30 mg benralizumab dose will be administered every four weeks. In some patients, the 30 mg benralizumab dose will be administered once every four weeks for three doses and then once every eight weeks thereafter.

DISCUSSION

[0080] This study demonstrates that benralizumab reduced exacerbations in eosinophilic asthma patients (i.e., patients with a baseline blood eosinophil count of at least 300 cells/μl) on medium or high-dose ICS/LABA. In particular, benralizumab significantly reduced exacerbation rates in asthma patients with blood eosinophil counts of at least 300 cells/μl as well as patients with both a blood eosinophil counts of at least 300 cells/μl and a high ICS status. In these patients, exacerbation rates were reduced at both interim (24-

week) and annual (52-week) time points and in patients receiving either 20 mg or 100 mg of benralizumab.

EXAMPLE 3: Additional Dose Evaluation

[0081] Dose-efficacy modeling was performed to identify additional doses of benralizumab that reduce annual exacerbation rates and are safe and well tolerated. The modeling indicated that a dose of about 30 mg is the minimum effective dose to produce 90% maximum treatment effect. Therefore patients with uncontrolled asthma receive subcutaneous injections of 30 mg of benralizumab or placebo. The 30 mg doses are administered (i) every four weeks or (ii) every four weeks for eight weeks (3 doses) and then every eight weeks (i.e., every 8 weeks including an additional dose at week 4). The number of exacerbations in patients receiving 30 mg benralizumab is compared to the number of exacerbations in patients receiving placebo in order to demonstrate that 30 mg doses of benralizumab decrease annual exacerbation rates. In addition, the number of exacerbations in patients with baseline blood eosinophil count of at least 300 cells/μl is analyzed in order to demonstrate that 30 mg doses of benralizumab can be effective in decrease annual exacerbation rates in such patients.

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[0082] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific aspects of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

[0083] Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

[0084] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications can be practiced within the scope of the appended claims.

SEQUENCE LISTING

SEQ ID NO:1

>US20100291073_1 Sequence 1 from Patent US 20100291073 Organism: Homo sapiens

DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQQKPGKAPKLLIYHTSRLQSGVPSR

FSGSGSGTDFTLTISSLQP

EDFATYYCQQGYTLPYTFGQGTKVEIK

SEQ ID NO:2

>US20100291073_2 Sequence 2 from Patent US 20100291073 Organism: Homo sapiens

DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQQKPGKAPKLLIYHTSRLQSGVPSR

FSGSGSGTDFTLTISSLQP

EDFATYYCQQGYTLPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY

PREAKVQWKVDNALQSGNSQ

ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:3

>US20100291073_3 Sequence 3 from Patent US 20100291073 Organism: Homo sapiens

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIHWVRQRPGQGLAWMGYINPYNDG

TKYNERFKGKVTITSDRSTSTVY

MELSSLRSEDTAVYLCGREGIRYYGLLGDYWGQGTLVTVSS

SEQ ID NO:4

>US20100291073_4 Sequence 4 from Patent US 20100291073 Organism: Homo sapiens

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TKYNERFKGKVTITSDRSTSTVY

MELSSLRSEDTAVYLCGREGIRYYGLLGDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTS

GGTAALGCLVKDYFPEPVTV

SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE

PKSCDKTHTCPPCPAPELLG

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ

YNSTYRVVSVLTVLHQDWLNG

KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:5
>US20100291073_5 Sequence 5 from Patent US 20100291073 Organism: Homo sapiens
DLLPDEKISLLPPVNFTIKVTGLAQVLLQWKPNPDQEQRNVNLEYQVKINAPKEDDYET
RITESKCVTILHKGFSASVRT
ILQNDHSLLASSWASAELHAPPGSPGTSIVNLTCTTNTTEDNYSRLRSYQVSLHCTWLVG
TDAPEDTQYFLYYRYGSWTE
ECQEYSKDTLGRNIACWFPRTFILSKGRDWLAVLVNGSSKHSAIRPFDQLFALHAIDQINP
PLNVTAEIEGTRLSIQWEK
PVSAFPIHCFDYEVKIHNTRNGYLQIEKLMTNAFISIIDDLSKYDVQVRAAVSSMCREAGL
WSEWSQPIYVGNDEHKPLR
EWFVIVIMATICFILLILSLICKICHLWIKLFPPIPAPKSNIKDLFVTTNYEKAGSSETEIEVIC
YIEKPGVETLEDSVF

SEQ ID NO:6
>US20100291073_6 Sequence 6 from Patent US 20100291073 Organism: Mus musculus
DLLNHKKFLLLPPVNFTIKATGLAQVLLHWDPNPDQEQRHVDLEYHVKINAPQEDEYDT
RKTESKCVTPLHEGFAASVRT
ILKSSHTTLASSWVSAELKAPPGSPGTSVTNLTCTTHTVVSSHTHLRPYQVSLRCTWLVG
KDAPEDTQYFLYYRFGVLTE
KCQEYSRDALNRNTACWFPRTFINSKGFEQLAVHINGSSKRAAIKPFDQLFSPLAIDQVN
PPRNVTVEIESNSLYIQWEK
PLSAFPDHCFNYELKIYNTKNGHIQKEKLIANKFISKIDDVSTYSIQVRAAVSSPCRMPGR
WGEWSQPIYVGKERKSLVE
WHLIVLPTAACFVLLIFSLICRVCHLWTRLFPPVPAPKSNIKDLPVVTEYEKPSNETKIEVV
HCVEEVGFEVMGNSTF

SEQ ID NO:7 - VH CDR1
SYVIH

SEQ ID NO:8 – VH CDR2
YINPYNDGTKYNERFKG

SEQ ID NO:9 – VH CDR3
EGIRYYGLLGDY

SEQ ID NO:10 – VL CDR1
GTSEDIINYLN

SEQ ID NO:11 – VL CDR2
HTSRLQS

SEQ ID NO:12 – VL CDR3
QQGYTLPYT

WHAT IS CLAIMED IS:

1. Use of benralizumab or an antigen-binding fragment thereof in the manufacture of a medicament for reducing the annual exacerbation rate of asthma, wherein a fixed dose of the medicament comprising 30 mg of benralizumab is to be administered to an asthma patient once every four weeks for twelve weeks then once every eight weeks, wherein the administration reduces the patient's exacerbation rate.

2. Use of benralizumab or an antigen-binding fragment thereof in the manufacture of a medicament for the treatment of asthma, wherein a fixed dose of the medicament comprising 30 mg of benralizumab is to be administered to an asthma patient once every four weeks for twelve weeks then once every eight weeks, wherein the patient has a blood eosinophil count of at least 300 cells/µl prior to the administration.

3. Use of benralizumab or an antigen-binding fragment thereof in the manufacture of a medicament for the treatment of asthma, wherein a fixed dose of the medicament comprising 30 mg of benralizumab is to be administered to an asthma patient once every four weeks for twelve weeks then once every eight weeks, wherein the patient has a forced expiratory volume in one second (FEV_1) of at least 40% and less than 90% predicted value prior to the administration.

4. Use of benralizumab or an antigen-binding fragment thereof in the manufacture of a medicament for the treatment of asthma, wherein a fixed dose of the medicament comprising 30 mg of benralizumab is to be administered to an asthma patient once every four weeks for twelve weeks then once every eight weeks, wherein the patient has a forced expiratory volume in one second (FEV_1) of below 75% predicted value prior to the administration.

5. The use of any one of claims 2-4, wherein the administration reduces the patient's exacerbation rate.

6. The use of claim 5, wherein the administration reduces the patient's annual exacerbation rate.

7. The use of any one of claims 1 or 3-6, wherein the asthma is eosinophilic asthma.

8. The use of any one of claims 1 or 3-7, wherein the patient has a blood eosinophil count of at least 300 cells/µl.

9. The use of any one of claims 1-2, wherein, the patient has a forced expiratory volume in one second (FEV_1) of at least 75% predicted value prior to the administration.

10. The use of any one of claims 1-9, wherein at least two doses of the medicament are to be administered to the patient.

11. The use of any one of claims 1 or 6-10, which reduces the annual exacerbations rate following administration of the medicament.

12. The use of any one of claims 1 or 6-11, wherein the annual exacerbation rate is reduced by at least 35%.

13. The use of claim 12, wherein the annual exacerbation rate is reduced by at least 40%.

14. The use of claim 13, wherein the annual exacerbation rate is reduced by at least 50%.

15. The use of claim 14, wherein the annual exacerbation rate is reduced by at least 60%.

16. The use of any one of claims 1-15, wherein the patient uses high-dose inhaled corticosteroids (ICS).

17. The use of any one of claims 1-16, wherein the patient uses long-acting β2 agonists (LABA).

18. The use of any one of claims 1-17, wherein the patient has a history of exacerbations.

19. The use of claim 18, wherein the history of exacerbations comprises at least two exacerbations in the year prior to the administration of the medicament.

20. The use of claim 18 or 19, wherein the history of exacerbations comprises no more than six exacerbations in the year prior to the administration of the medicament.