(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 August 2015 (27.08.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/126750 A1

(51) International Patent Classification:
*G01N 33/497* (2006.01) *G01N 33/88* (2006.01)
*G01N 33/50* (2006.01)

(21) International Application Number:
PCT/US2015/015806

(22) International Filing Date:
13 February 2015 (13.02.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/941,910 19 February 2014 (19.02.2014) US

(71) Applicant: **ARRAY BIOPHARMA INC.** [US/US]; 3200 Walnut Street, Boulder, Colorado 80301 (US).

(72) Inventors: **BURGESS, Laurence E.**; c/o Array BioPharma Inc., 3200 Walnut Street, Boulder, Colorado 80301 (US). **CHANTRY, David Harry**; c/o Array BioPharma Inc., 3200 Walnut Street, Boulder, Colorado 80301 (US). **EBERHARDT, Christine D.**; c/o Array BioPharma Inc., 3200 Walnut Street, Boulder, Colorado 80301 (US).

(74) Agents: **MALEN, Peter L.** et al.; Viksnins Harris & Padys PLLP, 7900 International Drive, Suite 670, Bloomington, Minnesota 55425 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *of inventorship (Rule 4.17(iv))*

**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: BIOMARKERS PREDICTIVE OF RESPONSIVENESS TO TREATMENT WITH A CRTh2 INHIBITOR

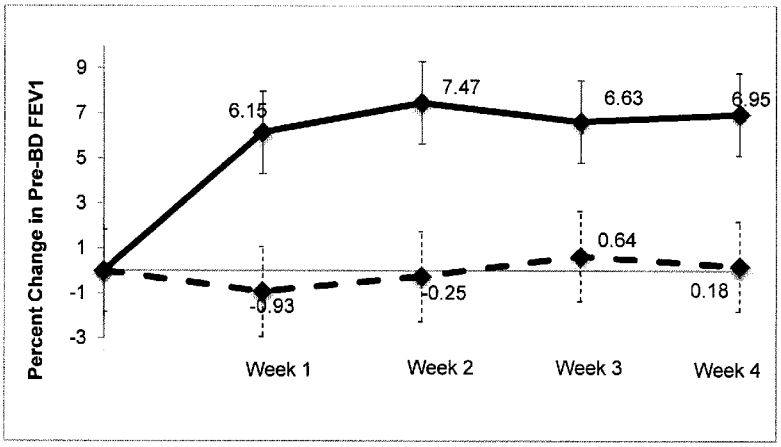



FIG. 1

(57) Abstract: Provided herein is the identification of biomarkers that are predictive of a patient's responsiveness to a therapy comprising treatment with a CRTh2 antagonist, such as ARRY-502. Biomarkers identified include baseline levels of the fraction exhaled nitric oxide and the percentage of eosinophil of the total lymphocyte population in peripheral blood.

WO 2015/126750 A1

# BIOMARKERS PREDICTIVE OF RESPONSIVENESS TO TREATMENT WITH A CRTh2 INHIBITOR

## BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

**[0001]** Provided herein is the identification of biomarkers that are predictive of a patient's responsiveness to a therapy comprising treatment with a CRTh2 antagonist.

DESCRIPTION OF THE STATE OF THE ART

**[0002]** Inappropriate inflammatory responses to environmental allergens underlie allergic reactions such as allergic asthma, allergic rhinitis, atopic dermatitis and food allergies, which collectively affect up to 20% of the United States' population (Bloom B., Cohen R. A., Freeman G., Vital Health Stat. 2009; 10:1-80; Pleis J. R. and Lucas J. W., Vital Health Stat. 2009; 10:1-159). Allergic reactions may be acute or chronic, depending on the allergen or the exposure level, and range in intensity from mild to severe and life threatening (e.g., status asthmaticus). Current treatments vary depending on the specific therapeutic indication and severity, and include both over-the-counter and prescription medications. Specifically, treatments for allergic asthma include inhaled and systemic corticosteroids, long-acting bronchodilators, leukotriene inhibitors, mast cell stabilizers and an antibody against immunoglobulin E (IgE) (Wechsler M. E., Mayo Clin. Proc. 2009; 84:707-17). Despite the range of treatments used to treat allergic asthma, there remains a significant need for patients with severe asthma as well as for more convenient and safer therapies for those with mild to moderate asthma.

**[0003]** Conditions such as allergic asthma are generally characterized as T helper cell 2 (Th2)-polarized immune responses and involve the production of antigen-specific IgE. Localized activation of mast cells in response to encounters with antigen leads to the recruitment of inflammatory cells including Th2 cells, eosinophils and basophils. Activation of mast cells by IgE/antigen complexes leads to the production of multiple inflammatory mediators including histamine, proteases, leukotrienes and prostaglandins. Prostaglandin D2 (PGD2) is one of the major prostaglandins produced by activated mast cells. PGD2, generated from arachidonic acid by the action of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), acts through two G-protein coupled receptors (GPCRs), the D prostanoid receptor 1 (DP1) and the chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTh2, also known as D prostanoid receptor 2 [DP2]) (Pettipher, R., Br. J. Pharmacol. 2008; 153 (Suppl. 1):S191-9). Activation of CRTh2 mediates a number of proinflammatory effects of PGD2, including chemotaxis of

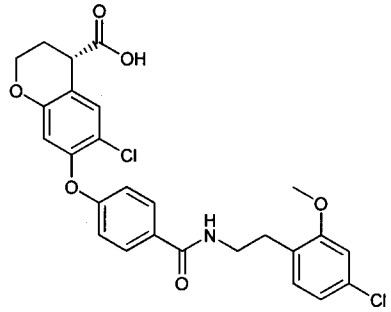
eosinophils, basophils and Th2 lymphocytes (Hirai, H., et al., J. Exp. Med. 2001; 193:255-61). In addition, PGD2, acting via CRTh2, leads to eosinophil degranulation and enhanced release of histamine by basophils (Gervais, F.G., et al., J. Allergy Clin. Immunol. 2001; 108:982-8; Yoshimura-Uchiyama, C., et al., Clin. Exp. Allergy 2004; 34:1283-90).

**[0004]** Based on the role of CRTh2 in mediating the actions of PGD2, selective antagonism of CRTh2 presents an attractive therapeutic approach to the treatment of allergic conditions. Experiments utilizing mice deficient in CRTh2 have demonstrated a critical role in allergic inflammatory responses (Chevalier E., et al., J. Immunol. 2005; 175:2056-60; Satoh T., et al., J. Immunol. 2006; 177:2621-9). Several selective antagonists of CRTh2 are in various stages of clinical development with compounds currently being evaluated in Phase 2 studies in allergic rhinitis, asthma and eosinophilic esophagitis. In allergic asthma, especially that of worsening severity, there is emerging evidence suggesting that increased PGD2 and upregulation of CRTh2 may contribute to the persistence and presence of signs and symptoms such as coughing, difficulty breathing and lower lung function (Huang, J. L., et al., Hum. Mol. Genet. 2004; 13:2691-7; Fajt ML, Balzar S, Trudeau J et al., "CRTH2 receptor and its ligand, PGD2, are increased in severe asthma". Poster presented at: American Thoracic Society Annual Meeting; May 2011; Denver, CO). Activation of CRTh2 has been shown to result in chemotaxis and activation of inflammatory cells and stimulate the production of cytokines that are thought to drive asthma pathophysiology.

**[0005]** Several small molecule antagonists of CRTh2 are currently in clinical development for the treatment of asthma but to date have shown only modest clinical activity. This is most likely due in part to the heterogeneous nature of asthma which represents a significant challenge in the development of therapeutics for asthma. It is now recognized that the traditional view of "allergic inflammation" represents only a subset of the asthma population, specifically those characterized by the local expression of a "Th2 signature" in their bronchial epithelium. It is therefore unlikely that targeting the CRTh2 pathway would provide robust clinical benefit in an unselected patient population. A number of approaches have been used to identify systemic biomarkers of this signature to enrich for patients who are responsive to Th2-targeted therapies such as antibodies to Interleukin (IL)-5 and IL-13. These markers include fraction exhaled nitric oxide ($FE_{NO}$) and serum concentrations of the protein periostin. However, these studies have focused on severe, steroid-resistant asthmatics and potential markers of Th2 signature have not been studied in the mild to moderate asthma population.

**[0006]** Barnes et al. (Clinical & Exp. Allergy, 2011, 1-11) evaluated a CRTh2 antagonist in patients with moderate persistent asthma in which eosinophilic airway inflammation was assessed by induced sputum differential eosinophil count. Periostin levels, in particular levels greater than 25 ng/mL, have been shown to be predictive of a Th2 signature in severe, steroid-refractory asthma, and stratification of patients based on these levels was predictive of response to anti-IL-13 in severe, steroid-refractory asthma (Jia, G. et al., J. Allergy Clin. Immunol., 2012: 130:647-54).

**[0007]** 6-Chloro-7-(4-(4-chloro-2-methoxyphenethylcarbamoyl)phenoxy)chroman-4-carboxylic acid, also known as "ARRY-502" has the structure:



**[0008]** ARRY-502 is exemplified in International Publication No. WO 2009/158426, which is incorporated herein by reference in its entirety. ARRY-502 is a potent and selective small-molecule antagonist of the CRTh2 receptor with demonstrated potent inhibition of CRTh2 activation. ARRY-502 has been shown to be potent and highly efficacious in multiple ex vivo and in vivo nonclinical studies assessing allergic inflammation. In initial Phase 1 clinical studies in healthy subjects, ARRY-502 was well tolerated, showed excellent exposure and demonstrated good activity in pharmacodynamic (PD) assessments (receptor internalization [RI], eosinophil shape change [ESC]) at the doses evaluated.

**[0009]** ARRY-502 has also been tested in a Phase 2 Proof of Concept human clinical trial in mild-to-moderate asthma patients. Initial findings of this study, which determined baseline levels of 8 biomarkers for the enrolled patients, have been published (see "Th2 Signature Selection Strategies for CRTh2 Antagonists: Baseline Characteristics of a Mild to Moderate Persistent Asthma Population", which can also be found at: http://www.arraybiopharma.com/documents/Publication). The results of this study showed that (i) serum markers of allergic inflammation can be readily detected in subjects with mild to moderate persistent asthma; (ii) CRTh2-positive eosinophil levels were elevated in asthma subjects when compared to controls; (iii) urinary tPDGM, a metabolite of $PDG_2$ and a marker of CRTh2-dependent signaling, was elevated in subjects when compared to controls; and (iv)

serum IgE and $FE_{NO}$ (fraction of exhaled nitric oxide) were elevated when compared to controls. The initial results of this study, however, did not evaluate or determine whether any of the studied biomarkers could be useful in predicting the likelihood a patient having Th2-driven allergic asthma would respond to a CRTh2 antagonist such as ARRY-502.

**[00010]** There remains a need for a method of predicting the responsiveness of a patient to a CRTh2 antagonist.

## SUMMARY OF THE INVENTION

**[00011]** The present application is based, at least in part, on the identification of biomarkers that are predictive of a subject's responsiveness to a method of treating mild to moderate Th2-driven allergic asthma comprising administering a CRTh2 inhibitor to a patient in need thereof. Thus, certain biomarkers described herein are useful, for example, in identifying and/or selecting a patient or a subset of patients having mild to moderate Th2-driven allergic asthma that are more likely to benefit from treatment with a CRTh2 inhibitor. In addition, the methods described herein are useful, for example, in selecting appropriate treatment modalities (e.g., therapy comprising a CRTh2 inhibitor) for a patient having mild to moderate Th2-driven allergic asthma.

**[00012]** It has surprisingly been found that patients respond better to treatment with a CRTh2 inhibitor when those patients have a baseline $FE_{NO}$ level greater than 48 ppb.

**[00013]** In one embodiment, patients with mild to moderate Th2-driven allergic asthma having a baseline $FE_{NO}$ level greater than 48 ppb had an average improvement in pre-bronchodilator FEV1 of about 7.7% after 2 weeks of treatment with ARRY-502 and an average improvement in pre-bronchodilator FEV1 of about 6.8% after 4 weeks of treatment with ARRY-502.

**[00014]** In addition, patients with mild to moderate Th2-driven allergic asthma having a baseline $FE_{NO}$ level greater than 48 ppb had a reduced $FE_{NO}$ level of about 30% (from baseline) after 4 weeks of treatment with ARRY-502.

**[00015]** In addition, treatment with ARRY-502 resulted in about a 30% decrease in the use of a SABA by patients with mild to moderate Th2-driven allergic asthma after treatment with ARRY-502, wherein the patients had a baseline $FE_{NO}$ level greater than 48 ppb.

**[00016]** It has further surprisingly been found that patients with mild to moderate Th2-driven allergic asthma respond better to treatment with a CRTh2 inhibitor when those patients have a baseline eosinophil level blood greater than 5% of the total lymphocyte population in peripheral blood.

**[00017]** In one embodiment, patients with mild to moderate Th2-driven allergic asthma

having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood had an average improvement in pre-bronchodilator FEV1 of about 9.2% after 2 weeks of treatment with ARRY-502 and an average improvement in pre-bronchodilator FEV1 of about 5.4% after 4 weeks of treatment with ARRY-502.

**[00018]** In one embodiment, patients with mild to moderate Th2-driven allergic asthma having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood had an average decrease in eosinophil levels of about 18% from their baseline level after 4 weeks of treatment with ARRY-502.

**[00019]** In contrast, baseline levels of other biomarkers which have been associated with Th2-driven inflammation such as serum levels of TARC, SCCA1, SCCA2 and periostin, levels of CRTh2 expression on eosinophils, and levels of urinary tPGDM (a marker of CRTh2 pathway activation) were not predictive of a patient's responsiveness to CRTh2 antagonists. Accordingly, it was unexpectedly discovered that $FE_{NO}$ levels and the percentage of peripheral blood eosinophils represent unique predictors of responsiveness to CRTh2 antagonists such as ARRY-502.

**[00020]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) analyzing a patient sample for baseline $FE_{NO}$ levels, wherein the sample is exhaled breath, wherein the patient is diagnosed with mild to moderate Th2-driven allergic asthma if the $FE_{NO}$ levels are greater than 48 ppb; and (b) administering a CRTh2 antagonist to the diagnosed patient.

**[00021]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of a CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00022]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of a CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00023]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00024]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00025]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00026]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) assaying the sample to measure the baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00027]** In one embodiment, provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven

allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00028]** In one embodiment, provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) measuring the baseline $FE_{NO}$ level in the sample; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00029]** In one embodiment of any of the above methods, the CRTh2 antagonist is ARRY-502.

**[00030]** In one embodiment, provided herein is a method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[00031]** In one embodiment, provided herein is a method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering to the patient a therapeutically effective amount of ARRY-502.

**[00032]** In one embodiment of any of the above methods, 200 mg of ARRY-502 is administered every 12 hours.

**[00033]** In one embodiment, provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00034]** In one embodiment, provided herein is a pharmaceutical composition for treating a patient with mild to moderate Th2-driven allergic asthma having a baseline $FE_{NO}$ level greater than 48 ppb, comprising ARRY-502.

**[00035]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00036]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof having a baseline $FE_{NO}$ level greater than 48 ppb, comprising (a) assaying a biological sample from the patient for a baseline $FE_{NO}$ level, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[00037]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a biological sample from the patient wherein the biological sample is exhaled breath; (b) assaying the biological sample for a baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[00038]** In one embodiment of any of the above methods, uses, composition or compounds, an inhaled corticosteroid is administered in combination with said CRTh2 antagonist.

**[00039]** In one embodiment of any of the above methods, uses, composition or compounds, a leukotriene receptor antagonist is administered in combination with said CRTh2 antagonist. In one embodiment, the leukotriene receptor antagonist is Montelukast.

**[00040]** In one embodiment of any of the above methods, uses, composition or compounds, a mast cell stabilizer is administered in combination with said CRTh2 antagonist.

**[00041]** In one embodiment of any of the above methods, uses, compositions or compounds, an antibody against immunoglobulin E is administered in combination with said CRTh2 antagonist.

**[00042]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) analyzing a patient sample for baseline eosinophil levels, wherein the sample is peripheral blood, wherein the patient is diagnosed with mild to moderate Th2-driven allergic asthma if the eosinophil levels are greater than 5% of the total lymphocyte population in peripheral blood; and (b) administering a CRTh2 antagonist to the diagnosed patient.

**[00043]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

**[00044]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said sample by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

**[00045]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient identified as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

**[00046]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient identified as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

**[00047]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline

eosinophil level greater than 5% of the total lymphocyte population; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00048]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample to measure the baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00049]** In one embodiment, provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

**[00050]** In one embodiment, provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a peripheral blood sample from the patient; (b) measuring the baseline eosinophil level in the sample; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (d) classifying the patient as having an increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (e) administering a therapeutically effective amount of the CRTh2 antagonist

to the patient classified as having an increased likelihood of response.

**[00051]** In one embodiment, the CRTh2 antagonist in any of the above methods is ARRY-502.

**[00052]** In one embodiment, provided herein is a method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[00053]** In one embodiment, provided herein is a method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering to the patient a therapeutically effective amount of ARRY-502.

**[00054]** In one embodiment of any of the above methods, 200 mg of ARRY-502 is administered every 12 hours.

**[00055]** In one embodiment, provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

**[00056]** In one embodiment, provided herein is a pharmaceutical composition for treating a patient with mild to moderate Th2-driven allergic asthma having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising ARRY-502.

**[00057]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

**[00058]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, comprising (a) assaying a peripheral blood sample from the patient for a baseline eosinophil level; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[00059]** In one embodiment, provided herein is the compound ARRY-502 for use in

treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample for a baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[00060]** In one embodiment of any of the above methods, uses, compositions or compounds, an inhaled corticosteroid is administered in combination with said CRTh2 antagonist.

**[00061]** In one embodiment of any of the above methods, uses, compositions or compounds, a leukotriene receptor antagonist is administered in combination with said CRTh2 antagonist. In one embodiment, the leukotriene receptor antagonist is Montelukast.

**[00062]** In one embodiment of any of the above methods, uses, compositions or compounds, a mast cell stabilizer is administered in combination with said CRTh2 antagonist.

**[00063]** In one embodiment of any of the above methods, uses, compositions or compounds, an antibody against immunoglobulin E is administered in combination with said CRTh2 antagonist.

**[00064]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[00065]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to

the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

## BRIEF DESCRIPTION OF THE FIGURES

**[00066]** The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate non-limiting embodiments of this invention, and together with the description, serve to explain the principles of the invention.

**[00067]** Figure 1 shows the percent change in pre-bronchodilator FEV1 in patients having a baseline $FE_{NO}$ greater than 48 ppb receiving ARRY-502 (solid line) and in patients having a baseline $FE_{NO}$ greater than 48 ppb receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

**[00068]** Figure 2 shows the percent change in pre-bronchodilator FEV1 in patients having a baseline $FE_{NO}$ less than or equal to 48 ppb receiving ARRY-502 (solid line) with patients having a baseline $FE_{NO}$ less than or equal to 48 ppb receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

**[00069]** Figure 3 shows the percent change in pre-bronchodilator FEV1 in patients having a baseline eosinophil level greater than 5 receiving ARRY-502 (solid line) and in patients having a baseline eosinophil level greater than 5% receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

**[00070]** Figure 4 shows the percent change in pre-bronchodilator FEV1 in patients having a baseline eosinophil level less than or equal to 5% receiving ARRY-502 (solid line) and in patients having a baseline eosinophil level less than or equal to 5 receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

**[00071]** Figure 5 shows the number of SABA puffs per week in patients receiving ARRY-502 (solid line) and in patients receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

**[00072]** Figure 6 shows the number of SABA puffs per week in patients having a baseline $FE_{NO}$ greater than 48 ppb receiving ARRY-502 (solid line) and in patients having a baseline $FE_{NO}$ greater than 48 ppb receiving placebo (dashed line), measured at weeks 1, 2, 3 and 4.

## DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

**[00073]** The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set

forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

**[00074]** "ACQ7" refers to the Asthma Control Questionnaire©, which is a validated 7-item questionnaire that measures asthma control and is one of the recommended composite scores to assess asthma control per the 2009 American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Statement. Patients were asked to recall their symptoms during the previous week and to respond to the 6 questions (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting medication use) on a 7-point scale from 0 (no impairment) to 6 (maximum impairment). After completion of the spirometry assessment, the site was to complete question 7 (associated with FEV1 % predicted). The items were equally weighted, with the final score being a mean of the 7 items.

**[00075]** "Allergic asthma" is the commonest form of asthma in which the patients are atopic (as indicated by a positive skin-prick test and the presence of IgE to common inhalant allergens, such as house-dust mites) and have allergic inflammation of the airways. Asthma is classified as "mild" if a patient has an $FEV_1$ of between 60% to 79% of predicted, and is classified as "moderate" if a patient has an $FEV_1$ of between 40% to 59% of predicted.

**[00076]** " AQLQ " refers to the Juniper Asthma Quality of Life Questionnaire©, which is a validated 32-item asthma-specific quality of life questionnaire and a recommended quality of life instrument per the 2009 ATS/ERS Joint Statement. Patients were asked to score their experiences during the previous 2 weeks on a 7-point scale from 1 (severe impairment) to 7 (no impairment). The overall AQLQ score and mean scores for the 4 domains (symptoms, activities, emotions, and environment) were calculated.

**[00077]** "Th2-driven allergic asthma" refers to eosinophilic-driven asthma and is a subset of allergic asthma (the other two subsets being neutrophilic- and paucigranulocytic-driven asthma). Th2-driven allergic asthma accounts for about 50% of allergic asthma.

**[00078]** "$FEV_1$" (forced expiratory volume in 1 second) refers to the amount of air that can be forcibly exhaled in one second, measured in liters. It is automatically calculated during spirometry or pulmonary function testing, and is used as a measurement of airway obstruction in asthma. "Prebronchodilator $FEV_1$" refers to an $FEV_1$ measurement prior to use of an inhaled bronchodilator by the patient.

**[00079]** "$FE_{NO}$" refers to the fractional NO (nitric oxide) concentration in exhalate from an $FEV_1$ measurement. NO is produced by the human lung and is present in the exhaled breath. It has been implicated in the pathophysiology of lung diseases, including asthma. The

measurement of the $FE_{NO}$ is a convenient, noninvasive, point-of-service office test for airway inflammation and is useful biomarker in the diagnosis of asthma. In comparison to normal individuals, $FE_{NO}$ levels are elevated in subjects with asthma. The $FE_{NO}$ is expressed in parts per billion, which is equivalent to nanoliters per liter.

**[00080]** "Baseline $FE_{NO}$ level" as used herein refers to a $FE_{NO}$ measurement taken at least 4 weeks after the last dosage taken by the patient of any type of treatment for mild to moderate Th2-driven allergic asthma, such as, but not limited to, inhaled corticosteroids, ARRY-502, and "rescue" medications.

**[00081]** "Baseline eosinophil levels" as used herein refers to a eosinophil measurement taken at least 4 weeks after the last dosage taken by the patient of any type of treatment for mild to moderate Th2-driven allergic asthma, such as, but not limited to, inhaled corticosteroids, ARRY-502, and "rescue" medications.

**[00082]** "FVC" (Forced vital capacity) is the volume of air that can forcibly be blown out after full inspiration during an FEV spirometry test, measured in liters.

**[00083]** "PEF" refers to peak expiratory flow, that is, a person's maximum speed of expiration, which is measured with a peak flow meter.

**[00084]** "Pre BD PEF" refers to a prebronchodilator PEF spirometry measurement.

**[00085]** "Pre BD FVC" refers to a prebronchodilator FVC spirometry measurement.

**[00086]** The phrase "pharmaceutically acceptable" is used herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a mammal such as a human (e.g., does not produce an adverse, allergic or other unwanted reaction when administered to a mammal).

**[00087]** "SFD" means symptom-free day.

**[00088]** "SABA" refers to a short-acting beta (β)-2 agonist. SABAs are typically used as "rescue" medications to provide quick relieve of asthma symptoms. Short-acting beta agonists act within minutes to temporarily relieve these symptoms. They do this by relaxing the tightening (bronchospasm) of the muscle bands around the airways, and are very effective in opening the airways. SABA therapies do not relieve the swelling or inflammation of the breathing tubes that occurs in individuals with asthma. Examples of SABAs include Albuterol, Proventil®, Ventolin®, Xopenex®, Maxair®, and ProAir.

**[00089]** The phrases "therapeutically effective amount" or "effective amount" mean an amount of a compound or composition described herein that, when administered to a patient in need of such treatment, is sufficient to (i) treat the particular disease, condition, or

disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound that will correspond to such an amount will vary depending upon factors such as the particular compound or composition, disease condition and its severity, and the identity (*e.g.*, weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

**[00090]** The terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

**[00091]** It has been surprisingly found that patients having mild to moderate Th2-driven allergic asthma have an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist such as ARRY-502 when those patients have a $FE_{NO}$ level greater than 48 ppb.

**[00092]** In one embodiment, patients having a baseline $FE_{NO}$ level greater than 48 ppb had an average improvement in pre-bronchodilator FEV1 of about 7.7% after 2 weeks of treatment with ARRY-502 and an average improvement in pre-bronchodilator FEV1 of about 6.8% after 4 weeks of treatment with ARRY-502.

**[00093]** In one embodiment, patients having a baseline $FE_{NO}$ level greater than 48 ppb had a reduced $FE_{NO}$ level of about 30% (from baseline) after treatment with ARRY-502.

**[00094]** In one embodiment, treatment with ARRY-502 resulted in about a 30% decrease in the use of a SABA by a patient after treatment with ARRY-502, wherein the patient had mild to moderate Th2-driven allergic asthma and had a baseline $FE_{NO}$ level greater than 48 ppb.

**[00095]** Accordingly, one embodiment provides ARRY-502 for use in treating Th2-driven allergic mild to moderate asthma.

**[00096]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) analyzing a patient sample for baseline $FE_{NO}$ levels, wherein the sample is exhaled breath, wherein the patient is diagnosed with mild to moderate Th2-driven allergic

asthma if the $FE_{NO}$ levels are greater than 48 ppb; and (b) administering a CRTh2 antagonist to the diagnosed patient.

**[00097]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[00098]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[00099]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000100]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering ARRY-502 to said patient, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000101]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic

treatment with a CRTh2 antagonist, comprising (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000102]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) assaying the sample to measure the baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the patient has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000103]** In one embodiment, provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000104]** In one embodiment, provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) measuring the baseline $FE_{NO}$ level in the sample of the patient; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an

increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000105]** In one embodiment, provided herein is a method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[000106]** In one embodiment, provided herein is a method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering to the patient a therapeutically effective amount of ARRY-502.

**[000107]** In one embodiment of any of the above methods, 200 mg of ARRY-502 is administered every 12 hours.

**[000108]** In one embodiment, provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[000109]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

**[000110]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, comprising (a) assaying a biological sample from the patient for a baseline $FE_{NO}$ level, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[000111]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a biological sample from the patient wherein the biological sample is exhaled breath; (b) assaying the biological sample for a baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[000112]** It has further surprisingly been found that patients having mild to moderate Th2-driven allergic asthma have an increased likelihood of a therapeutic response to treatment with a CRTh2 inhibitor such as ARRY-502 when those patients have a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

**[000113]** For example, in one embodiment, patients having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood had an average improvement in pre-bronchodilator FEV1 of about 9.2% after 2 weeks of treatment with ARRY-502 and an average improvement in pre-bronchodilator FEV1 of about 5.4% after 4 weeks of treatment with ARRY-502.

**[000114]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) analyzing a patient sample for baseline eosinophil levels, wherein the sample is peripheral blood, wherein the patient is diagnosed with mild to moderate Th2-driven allergic asthma if the eosinophil levels are greater than 5% of the total lymphocyte population in peripheral blood; and (b) administering a CRTh2 antagonist to the diagnosed patient.

**[000115]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000116]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000117]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising

administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000118]** In one embodiment, provided herein is a method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering ARRY-502 to said patient, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000119]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000120]** In one embodiment, provided herein is a method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample to measure the baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the patient has a baseline eosinophil level greater than 5% of the total lymphocyte population in said

peripheral blood; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000121]** In one embodiment, provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000122]** In one embodiment, provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a peripheral blood sample from the patient; (b) measuring the baseline eosinophil level in the sample of the patient; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (d) classifying the patient as having an increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000123]** In one embodiment, provided herein is a method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[000124]** In one embodiment, provided herein is a method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering to

the patient a therapeutically effective amount of ARRY-502.

**[000125]** In one embodiment of any of the above methods, 200 mg of ARRY-502 is administered every 12 hours.

**[000126]** In one embodiment, the baseline eosinophil level in a patient's peripheral blood is determined by requesting a test providing the results of an analysis to determine the baseline eosinophil level. In one embodiment, the test is performed by a party other than the party requesting the test.

**[000127]** In one embodiment, provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

**[000128]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

**[000129]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, comprising (a) assaying a peripheral blood sample from the patient for a baseline eosinophil level; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[000130]** In one embodiment, provided herein is the compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample for a baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[000131]** Pharmaceutical compositions described herein may be administered in any convenient administrative form, e.g., tablets, powders, capsules, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc.

**[000132]** Pharmaceutical compositions described herein may be administered by any convenient route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), ocular, vaginal, intraperitoneal, intrapulmonary and intranasal. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion.

**[000133]** Pharmaceutical compositions described herein are typically administered orally. Pharmaceutical compositions described herein for oral administration may be administered as a tablet, caplet, hard or soft gelatin capsule, hydroxypropylmethyl cellulose (HPMC) capsule, pill, granules or a suspension.

**[000134]** Accordingly, further provided is a pharmaceutical composition described herein comprising a CRTh2 antagonist, wherein the composition is formulated for oral administration. In one embodiment, the pharmaceutical composition described herein is formulated as a hard gelatin, soft gelatin or HPMC capsule.

**[000135]** In one embodiment, a pharmaceutical composition described herein comprises ARRY-502. A pharmaceutical composition comprising ARRY-502 is generally provided as a tablet or capsule for oral administration use. In one embodiment, the tablet or capsule comprises 100 mg of ARRY-502.

**[000136]** In one embodiment, provided herein is a pharmaceutical composition for treating a patient with mild to moderate asthma having a baseline $FE_{NO}$ greater than 48 ppb, comprising a CRTh2 antagonist. In one embodiment, the CRTh2 antagonist is ARRY-502. A further embodiment provides a pharmaceutical composition for treating a patient with Th2-driven mild to moderate asthma having a baseline $FE_{NO}$ greater than 48 ppb, comprising a CRTh2 antagonist together with a pharmaceutically acceptable carrier or excipient. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000137]** In one embodiment, provided herein is a pharmaceutical composition for treating a patient with mild to moderate asthma having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, comprising a CRTh2 antagonist. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000138]** A further embodiment provides a pharmaceutical composition for treating a patient with Th2-driven mild to moderate asthma having baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, comprising a CRTh2

antagonist together with a pharmaceutically acceptable carrier or excipient. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000139]** In one embodiment, ARRY-502 is administered orally every 12 hours. In one embodiment, the dosage of ARRY-502 is 200 mg. In one embodiment, ARRY-502 is supplied as powder in capsule. In one embodiment, the capsule is a size "00" Swedish Orange opaque gelatin capsule containing 100 mg of ARRY-502. In this embodiment, a 200 mg dose of ARRY-502 is administered orally as two 100 mg capsules.

**[000140]** The Th2 phenotype is not restricted to asthma. Several other allergic diseases, such as but not limited to atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, also express Th2 characteristics.

**[000141]** Accordingly, also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000142]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000143]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof comprising administering a CRTh2 antagonist to said

patient, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000144]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof comprising administering ARRY-502 to said patient, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000145]** Also provided herein is a method for increasing the likelihood of response in a patient in need thereof having an allergic disease to therapeutic treatment with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000146]** Also provided herein is a method for increasing the likelihood of response in a patient having an allergic disease to therapeutic treatment with a CRTh2 antagonist, wherein

the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) assaying the sample to measure the baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000147]** Also provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating an allergic disease with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000148]** Also provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating an allergic disease with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, the method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) measuring the baseline $FE_{NO}$ level in the sample; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline

$FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000149]** Also provided herein is a method of using ARRY-502 to treat a patient with an allergic disease selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, wherein the patient has been diagnosed as having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[000150]** Also provided herein is a method of treating an allergic disease in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising administering to the patient a therapeutically effective amount of ARRY-502.

**[000151]** Also provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of an allergic disease in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000152]** Also provided herein is a pharmaceutical composition for treating a patient with an allergic disease having a baseline $FE_{NO}$ level greater than 48 ppb comprising ARRY-502, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000153]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000154]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) assaying a biological sample from the patient for a baseline $FE_{NO}$ level, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[000155]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) obtaining a biological sample from the patient wherein the biological sample is exhaled breath; (b) assaying the biological sample for a baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

**[000156]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000157]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) obtaining

a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said sample by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000158]** Also provided herein is a method for identifying and treating an allergic disease in a patient in need thereof comprising administering ARRY-502 to said patient, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000159]** Also provided herein is a method for increasing the likelihood of response in a patient having an allergic disease to therapeutic treatment with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient identified as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

**[000160]** Also provided herein is a method for increasing the likelihood of response in a patient having an allergic disease to therapeutic treatment with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) measuring the baseline eosinophil level in a peripheral blood sample of the

patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000161]** Also provided herein is a method for predicting the likelihood a patient will respond therapeutically to a method of treating an allergic disease with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising: (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample to measure the baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000162]** Also provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating an allergic disease with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, said method comprising: (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient

classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000163]** Also provided herein is a method for predicting an increased likelihood a patient will respond therapeutically to a method of treating an allergic disease with a CRTh2 antagonist, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, the method comprising: (a) obtaining a peripheral blood sample from the patient; (b) measuring the baseline eosinophil level in the sample; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (d) classifying the patient as having an increased likelihood of responding therapeutically to the method of treating mild to moderate asthma if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000164]** Also provided herein is a method of using ARRY-502 to treat a patient with an allergic disease selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, wherein the patient has been diagnosed as having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

**[000165]** Also provided herein is a method of treating an allergic disease in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising administering to the patient a therapeutically effective amount of ARRY-502.

**[000166]** Also provided herein is the use of ARRY-502 in the manufacture of a medicament for the treatment of an allergic disease in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis,

urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000167]** Also provided herein is a pharmaceutical composition for treating a patient with an allergic disease having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising ARRY-502, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000168]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome.

**[000169]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) assaying a peripheral blood sample from the patient for a baseline eosinophil level; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[000170]** Also provided herein is the compound ARRY-502 for use in treating an allergic disease in a patient in need thereof, wherein the disease is selected from atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, urticaria (for example chronic idiopathic urticarial), and eosinophilic disorders such as eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis and hypereosinophilic syndrome, comprising (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample for a baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of ARRY-

502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

**[000171]** COMBINATION THERAPY

**[000172]** The CRTh2 antagonist may be employed alone or in combination with other therapeutic agents for treatment. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000173]** Accordingly, provided herein is a pharmaceutical combination for treating Th2-driven allergic asthma, which comprises (a) a CRTh2 antagonist, (b) an additional therapeutic agent for treating mild to moderate Th2-driven allergic asthma, and (c) optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use for the treatment of mild to moderate Th2-driven allergic asthma; a pharmaceutical combination comprising such a combination; the use of such a combination for the preparation of a medicament for the treatment of Th2-driven allergic asthma; a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of a warm-blooded animal, especially a human. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000174]** The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a CRTh2 antagonist and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a CRTh2 antagonist and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two active ingredients in the body of the patient.

**[000175]** Examples of additional therapeutic agents that may be used in combination with a CRTh2 antagonist as disclosed herein include steroids (including inhaled corticosteroids such as dexamethasone, cortisone and fluticasone), leukotriene receptor antagonists such as Montelukast (Singulair®), anti-inflammatory compounds, NSAIDs (e.g., ibuprofen, indomethacin and ketoprofen), antibodies against immunoglobulin E, anti-histamines, aspirin, anti-bodies (such as anti-IL-4, anti-IL-13, anti-IL-5, anti-TSLP), muscarinic antagonists/anticholinergics, long acting beta agonists and ultra-long acting beta agonists.

**[000176]** In one embodiment of any of the methods, uses, compositions or compounds

disclosed herein, an inhaled corticosteroid is administered in combination with said CRTh2 antagonist. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000177]** In one embodiment of any of the methods, uses, compositions or compounds disclosed herein, a leukotriene receptor antagonist is administered in combination with said CRTh2 antagonist. In one embodiment, the leukotriene receptor antagonist is Montelukast. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000178]** In one embodiment of any of the methods, uses, compositions or compounds disclosed herein, a mast cell stabilizer is administered in combination with said CRTh2 antagonist. In one embodiment, the CRTh2 antagonist is ARRY-502.

**[000179]** In one embodiment of any of the methods, uses, compositions or compounds disclosed herein, an antibody against immunoglobulin E is administered in combination with said CRTh2 antagonist. In one embodiment, the CRTh2 antagonist is ARRY-502.

## EXAMPLES

**[000180]** For illustrative purposes, the following Examples are included. However, it is to be understood that these Examples do not limit the invention and are only meant to suggest a method of practicing the invention.

### Example 1

Efficacy and safety study of ARRY-502 in adults with mild to moderate persistent asthma

**[000181]** **Methodology:**

**[000182]** This study was a randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of ARRY-502 in adults with mild to moderate persistent asthma. Asthmatic patients with active disease were consented at the Prescreening Visit and initiated washout of medications as prohibited by the protocol, as necessary. Patients were screened for eligibility within 10 to 35 days prior to the Baseline Visit. Patients must have met washout criteria for asthma medications at the Screening Visit and were permitted to use only the protocol-specified short-acting beta (β)-2 agonist (SABA; albuterol) for treatment of their asthma from the Prescreening Visit through the end of the study. At the Day -7 Visit (± 2 days), patients initiated a 7-day single-blind run-in period with placebo every 12 hours (Q12h), as well as underwent training on twice daily (BID) peak expiratory flow (PEF) assessments, diary completion and proper SABA metered-dose inhaler (MDI) use. Patients were required to fast (no food or drink except water) for at least 8 hours prior to their scheduled clinic visits from the Screening Visit onwards. Patients were not permitted any SABA therapy within 6 hours prior to their scheduled clinic visits from the Screening Visit onwards.

**[000183]** Upon enrollment at Baseline (Day 1), eligible patients were stratified by site and by the presence of allergic rhinitis and randomized in a 1:1 ratio to receive oral (PO) 200 mg ARRY-502 or matching placebo every 12 hours for 28 days. The dose of ARRY-502 selected for evaluation in this study (200 mg every 12 hours) was based on results of Phase 1 clinical studies of ARRY-502 in which optimal pharmacodynamics coverage (concentration resulting in 90% inhibition for eosinophil shape change (ESC)) was achieved throughout the dosing interval with 200 mg twice daily (BID). Patients were required to take their morning dose in the clinic at the visits on Days -7 (i.e., 7 days prior to start of study), Day 1 (start of study), and Days 8, 15, 22 and 29, but otherwise were discharged home with sufficient study medication until their next visit. Patients were required to take their morning dose in the clinic at the visits on Days -7, 1, 8, 15, 22 and 29, but otherwise were discharged home with sufficient study drug until their next visit. All patients were to take study drug as single-blind placebo run-in every 12 hours from Day -7 to Day -1 (i.e. the 7 days prior to the start of the study), then either placebo or ARRY-502 every 12 hours from the morning dose at Baseline (Day 1) through their evening dose on Day 28 (this portion of the study was double-blinded), and then single-blind placebo washout every 12 hours from the morning dose on Day 29 through the evening dose on Day 35. Efficacy assessments were obtained at visits on Days 1, 8, 15, 22 and 29 (± 1 day), and at the Follow-up Visit (Day 36 ± 2 days). Scheduled safety assessments occurred throughout the study. All study visits were to be in the morning and when possible, all visits were to occur at approximately the same time of day with spirometry assessments occurring ± 2 hours from the time of the initial Baseline Visit spirometry assessment. Patients were permitted to use only SABAs as rescue treatment for their asthma from the Prescreening Visit through Day 36. They were not permitted to be on any other medications for control of their asthma symptoms from the Prescreening Visit through Day 36.

**[000184]** A total of 184 patients were enrolled and randomized to treatment (93 on ARRY-502, 91 on placebo).

**[000185]** **Diagnosis and Main Criteria for Inclusion:**

**[000186]** Patients were to be male or female 18 to 70 years of age inclusive with documented history of bronchial asthma which must have been diagnosed at least 6 months prior to the Screening Visit and prior to the age of 40 years. Patients must also have met the criteria of an Asthma Control Questionnaire© (ACQ) score of ≥ 1.5 at the Screening and Baseline Visits; a mean fractional exhaled nitric oxide ($FE_{NO}$) level of ≥ 26 parts per billion (ppb) at the Screening Visit; a best prebronchodilator forced expiratory volume in 1 second

(FEV1) of 60% to 85% of the predicted normal value at the Screening and Baseline Visits; a change in best postbronchodilator FEV1 of ≥ 12% and ≥ 200 mL at the Screening Visit; and a positive Phadiatop® inhalant atopy screen at the Screening Visit or a positive skin prick test within 1 year prior to enrollment.

**[000187]** **Criteria for Evaluation:**

**[000188]** **Efficacy:** Efficacy assessments included pulmonary function testing via spirometry (pre- and postbronchodilator, FEV1, FVC, FEV1/FVC, forced expiratory flow [FEF] 25-75% and PEF assessments); $FE_{NO}$ measurements; patient completion of the ACQ, the Juniper Asthma Quality of Life Questionnaire© (AQLQ) and the Rhinasthma Questionnaire; and at-home patient completion of an asthma diary and PEF assessments.

**[000189]** **Biomarkers:** Venous blood samples were drawn and urine collected at specified time points for measurement of specified exploratory biomarkers of prostaglandin D2 (PGD2) biosynthesis, Th2-mediated inflammation and eosinophilic inflammation. $FE_{NO}$ levels were measured in exhaled breath.

**[000190]** Venous blood for whole blood biomarker analysis was withdrawn in vacuum blood collection tubes containing K2EDTA. Whole blood samples were maintained on wet ice or in a refrigerator until same-day shipment to the Sponsor for final whole blood biomarker analysis.

**[000191]** Venous blood for serum biomarker analysis was withdrawn in vacuum blood collection serum-separating tubes. The blood was allowed to clot undisturbed for 30 minutes to 60 minutes and then processed at the site within 1 hour of blood collection to isolate plasma samples. Plasma samples were frozen on dry ice or in a -20 °C or -80 °C freezer, stored at -20 °C or -80 °C until shipment on dry ice to LabConnect for sample coordination and then sent to the Sponsor for final serum biomarker analysis. A portion of the serum biomarker sample was sent by the Sponsor to Shino-Test Corporation for analysis of periostin. The remainder of the analyses were performed at the Sponsor.

**[000192]** Urine for urine biomarker analysis was collected and immediately frozen on dry ice or in a -20°C freezer, stored at -20°C until shipment on dry ice to LabConnect for sample coordination and then sent to the Sponsor for final bioanalytical analysis.

**[000193]** Fractional exhaled nitric oxide levels were measured utilizing a portable device (NIOX MINO®, Aerocrine, Solna, Sweden) in accordance with the Spirometry Manual (Am. J. Respir. Crit. Care Med. 2005; 171:912-30). At visits where $FE_{NO}$ and spirometry were to be obtained, the $FE_{NO}$ was performed first. Repeated, reproducible exhalations were performed to obtain at least two $FE_{NO}$ values that agreed within 10% of

each other. Exhaled nitric oxide was then calculated as the mean of two values. Results with decimal places were rounded to the nearest whole number.

**[000194]** **Biomarker Analysis:**

**[000195]** Observed value, change from Baseline and/or percentage change from Baseline of biomarkers were summarized using descriptive statistics by treatment group and week, as appropriate. The following biomarkers were evaluated in patient samples:

| Patient sample | Biomarker measured |
|---|---|
| Serum | Levels of serum biomarkers of Th2-mediated eosinophilic airway inflammation:<br>• squamous cell carcinoma antigen 1 (SCCA1)<br>• squamous cell carcinoma antigen 2 (SCCA2)<br>• periostin<br>• thymus and activation regulated chemokine (TARC)<br>• chemokine (C-C motif) ligand 17 (CCL17) |
| Serum | • levels of total immunoglobulin E (IgE) |
| Peripheral blood | Blood biomarkers of Th2-mediated eosinophilic airway inflammation:<br><br>Percentage of the following expressed as a proportion of the total lymphocyte population:<br>• eosinophils<br>• basophils<br>• CRTh2-expressing CD4+ cells |
| Urine | • tetranor prostaglandin D2 metabolite (tPGDM; 9α-hydroxy-11,15-dioxo-13,14-dihydro-2,3,4,5-tetranor-prostan-1,20-dioic acid) |
| Exhaled breath | $FE_{NO}$ levels |

**[000196]** **Results:**

**[000197]** Serum levels of SCCA1, SCCA2, periostin and TARC were evaluated by ELISA as potential serum biomarkers of Th2-mediated eosinophilic airway inflammation for patients in the Serum Biomarker Population (N = 183) and are summarized by treatment group in Table 1.

**Table 1**

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) | Percent of Baseline<br>Placebo<br>(N=90) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|---|---|
| ARRY-502 Outsourced SCCA1 Result | | | | |
| Baseline | | | | |
| n | 90 | 93 | | |
| Mean | 0.98 | 1.08 | | |
| SD | 0.447 | 0.984 | | |
| Median | 0.90 | 0.90 | | |
| Min, Max | 0.20, 2.90 | 0.20, 9.30 | | |
| Week 2 (Day 15) | | | | |
| n | 82 | 90 | 82 | 90 |
| Mean | 1.03 | 1.06 | 111.28 | 101.37 |
| SD | 0.493 | 0.978 | 34.115 | 30.525 |
| Median | 0.90 | 0.80 | 109.31 | 100.00 |
| Min, Max | 0.20, 3.10 | 0.30, 8.90 | 63.64, 280.00 | 46.67, 262.50 |
| Week 4 (Day 29) | | | | |
| n | 80 | 90 | 80 | 90 |
| Mean | 1.04 | 1.06 | 113.15 | 103.41 |
| SD | 0.499 | 0.948 | 46.832 | 32.015 |
| Median | 1.00 | 0.90 | 100.00 | 100.00 |
| Min, Max | 0.20, 3.00 | 0.30, 8.80 | 54.55, 366.67 | 50.00, 233.33 |
| Early Termination | | | | |
| n | 10 | 4 | 10 | 4 |
| Mean | 1.92 | 0.90 | 157.23 | 108.48 |
| SD | 2.164 | 0.082 | 101.040 | 38.231 |
| Median | 1.30 | 0.90 | 137.50 | 101.25 |
| Min, Max | 0.80, 8.00 | 0.80, 1.00 | 58.82, 421.05 | 71.43, 160.00 |
| Follow-Up (Day 36) | | | | |
| n | 80 | 88 | 80 | 88 |
| Mean | 1.18 | 1.12 | 135.91 | 107.87 |
| SD | 0.853 | 1.038 | 149.933 | 61.104 |
| Median | 1.00 | 0.90 | 110.10 | 100.00 |
| Min, Max | 0.20, 7.00 | 0.30, 7.60 | 62.50, 1400.00 | 42.86, 572.73 |
| ARRY-502 Outsourced SCCA2 Result | | | | |
| Baseline | | | | |
| n | 90 | 93 | | |
| Mean | 0.82 | 0.91 | | |
| SD | 0.520 | 1.223 | | |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) | Percent of Baseline<br>Placebo<br>(N=90) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|---|---|
| Median | 0.70 | 0.70 | | |
| Min, Max | 0.00, 3.20 | 0.10, 11.30 | | |
| Week 2 (Day 15) | | | | |
| n | 82 | 90 | 81 | 90 |
| Mean | 0.83 | 0.85 | 105.92 | 102.06 |
| SD | 0.579 | 1.042 | 40.257 | 41.186 |
| Median | 0.70 | 0.60 | 100.00 | 100.00 |
| Min, Max | 0.00, 3.40 | 0.20, 9.00 | 50.00, 350.00 | 27.27, 350.00 |
| Week 4 (Day 29) | | | | |
| n | 80 | 90 | 79 | 90 |
| Mean | 0.82 | 0.86 | 105.67 | 101.54 |
| SD | 0.544 | 1.033 | 35.413 | 29.267 |
| Median | 0.65 | 0.60 | 100.00 | 100.00 |
| Min, Max | 0.10, 3.30 | 0.20, 9.00 | 41.67, 300.00 | 50.00, 200.00 |
| Early Termination | | | | |
| n | 10 | 4 | 10 | 4 |
| Mean | 0.72 | 0.80 | 90.00 | 86.25 |
| SD | 0.278 | 0.356 | 25.005 | 11.893 |
| Median | 0.75 | 0.85 | 95.83 | 85.83 |
| Min, Max | 0.40, 1.10 | 0.40, 1.10 | 36.36, 125.00 | 73.33, 100.00 |
| Follow-Up (Day 36) | | | | |
| n | 80 | 88 | 79 | 88 |
| Mean | 0.87 | 0.88 | 118.27 | 101.50 |
| SD | 0.553 | 1.020 | 87.405 | 32.726 |
| Median | 0.70 | 0.65 | 100.00 | 100.00 |
| Min, Max | 0.00, 2.70 | 0.10, 8.30 | 57.14, 800.00 | 27.27, 211.11 |
| ARRY-502 Periostin 18Ax17B Result | | | | |
| Baseline | | | | |
| n | 90 | 93 | | |
| Mean | 60.34 | 58.26 | | |
| SD | 19.041 | 19.600 | | |
| Median | 56.00 | 55.00 | | |
| Min, Max | 23.00, 129.00 | 20.00, 121.00 | | |
| Week 2 (Day 15) | | | | |
| n | 82 | 90 | 82 | 90 |
| Mean | 60.15 | 56.78 | 100.76 | 99.03 |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) | Percent of Baseline<br>Placebo<br>(N=90) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|---|---|
| SD | 18.200 | 18.253 | 13.191 | 19.362 |
| Median | 55.00 | 54.50 | 100.00 | 97.37 |
| Min, Max | 23.00, 105.00 | 29.00, 150.00 | 69.81, 148.00 | 63.03, 185.00 |
| Week 4 (Day 29) | | | | |
| n | 80 | 90 | 80 | 90 |
| Mean | 62.76 | 55.40 | 105.48 | 96.75 |
| SD | 20.497 | 17.062 | 21.203 | 18.537 |
| Median | 58.50 | 53.00 | 101.34 | 94.18 |
| Min, Max | 26.00, 127.00 | 27.00, 135.00 | 59.65, 202.08 | 53.23, 190.00 |
| Early Termination | | | | |
| n | 10 | 4 | 10 | 4 |
| Mean | 55.40 | 40.00 | 93.02 | 103.52 |
| SD | 22.441 | 13.491 | 18.045 | 10.827 |
| Median | 48.00 | 34.50 | 87.14 | 102.37 |
| Min, Max | 29.00, 108.00 | 31.00, 60.00 | 70.91, 126.32 | 93.94, 115.38 |
| Follow-Up (Day 36) | | | | |
| n | 80 | 88 | 80 | 88 |
| Mean | 62.34 | 58.20 | 105.36 | 100.61 |
| SD | 18.596 | 17.287 | 21.005 | 16.999 |
| Median | 59.50 | 55.50 | 101.55 | 98.45 |
| Min, Max | 24.00, 114.00 | 27.00, 125.00 | 66.67, 168.75 | 69.01, 180.00 |
| ARRY-502 TARC Result Mean | | | | |
| Baseline | | | | |
| n | 91 | 88 | | |
| Mean | 368.87 | 383.20 | | |
| SD | 242.235 | 271.160 | | |
| Median | 318.53 | 312.82 | | |
| Min, Max | 28.58, 1369.43 | 41.21, 1320.08 | | |
| Week 2 (Day 15) | | | | |
| n | 80 | 84 | 80 | 81 |
| Mean | 367.87 | 377.47 | 116.24 | 122.15 |
| SD | 215.981 | 248.624 | 85.609 | 148.642 |
| Median | 315.57 | 324.24 | 101.24 | 100.90 |
| Min, Max | 57.64, 1283.43 | 30.51, 1183.66 | 12.55, 708.87 | 11.92, 1365.68 |
| Week 4 (Day 29) | | | | |
| n | 77 | 89 | 77 | 83 |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) | Percent of Baseline<br>Placebo<br>(N=90) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|---|---|
| Mean | 389.48 | 379.39 | 121.16 | 115.39 |
| SD | 236.543 | 277.085 | 82.814 | 91.079 |
| Median | 344.52 | 291.56 | 104.77 | 101.97 |
| Min, Max | 57.83, 1238.17 | 0.00, 1665.03 | 16.63, 567.96 | 0.00, 768.23 |
| Early Termination | | | | |
| n | 9 | 4 | 9 | 3 |
| Mean | 442.55 | 354.93 | 167.25 | 108.17 |
| SD | 310.667 | 103.383 | 129.484 | 25.282 |
| Median | 295.10 | 332.10 | 123.29 | 98.08 |
| Min, Max | 121.87, 939.91 | 259.52, 496.02 | 90.93, 506.88 | 89.49, 136.94 |
| Follow-Up (Day 36) | | | | |
| n | 75 | 83 | 75 | 78 |
| Mean | 318.94 | 388.34 | 100.18 | 120.97 |
| SD | 239.314 | 280.027 | 90.828 | 111.401 |
| Median | 279.67 | 321.58 | 91.58 | 110.94 |
| Min, Max | 0.00, 1270.59 | 0.00, 1442.09 | 0.00, 655.57 | 0.00, 948.46 |

**[000198]** The serum biomarker IgE was analyzed by ELISA as a potential serum biomarker of Th2-mediated eosinophilic airway inflammation for patients in the Safety Population (N = 183) and is summarized by treatment group in Table 2.

**Table 2**

| Visit<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) | Change from Baseline<br>Placebo<br>(N=90) | Change from Baseline<br>ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|---|---|
| Screening | | | | |
| n | 83 | 90 | | |
| Mean | 421.3 | 334.6 | | |
| SD | 936.65 | 446.68 | | |
| Median | 138 | 164 | | |
| Min, Max | 5, 7484 | 5, 2360 | | |
| Baseline | | | | |
| n | 90 | 93 | | |

| Visit Statistic | Placebo (N=90) | ARRY-502 200 mg (N=93) | Change from Baseline: Placebo (N=90) | Change from Baseline: ARRY-502 200 mg (N=93) |
|---|---|---|---|---|
| Mean | 418.1 | 361.0 | | |
| SD | 953.66 | 505.35 | | |
| Median | 133 | 170 | | |
| Min, Max | 7, 8000 | 7, 3431 | | |
| Week 2 (Day 15) | | | | |
| n | 81 | 89 | 81 | 89 |
| Mean | 301.9 | 328.4 | -20.3 | -10.6 |
| SD | 433.22 | 503.51 | 183.10 | 92.08 |
| Median | 136 | 153 | -1 | -3 |
| Min, Max | 7, 2757 | 5, 4008 | -1030, 1010 | -303, 577 |
| Week 4 (Day 29) | | | | |
| n | 80 | 89 | 80 | 89 |
| Mean | 434.6 | 331.9 | 11.5 | -6.1 |
| SD | 1060.35 | 484.66 | 159.22 | 77.96 |
| Median | 147 | 144 | -1 | -4 |
| Min, Max | 7, 8742 | 5, 3562 | -534, 890 | -260, 306 |
| Early Termination | | | | |
| n | 9 | 4 | 9 | 4 |
| Mean | 336.3 | 924.5 | 40.3 | 81.0 |
| SD | 419.48 | 1199.41 | 72.97 | 384.64 |
| Median | 110 | 542 | 8 | 5 |
| Min, Max | 10, 1094 | 29, 2586 | -8, 220 | -301, 616 |
| Follow-Up (Day 36) | | | | |
| n | 80 | 85 | 80 | 85 |
| Mean | 440.0 | 338.5 | 16.9 | -5.1 |
| SD | 1067.28 | 447.76 | 168.41 | 98.16 |
| Median | 146 | 155 | 0 | 3 |
| Min, Max | 7, 8819 | 5, 3024 | -492, 863 | -470, 273 |

**[000199]** Percentage of basophils, CD4+ lymphocytes and eosinophils present in peripheral blood were determined by flow cytometry according to the following procedure. Blood was collected into 4 mL Vacutainer collection tubes containing EDTA (BD, San Jose, CA). 400 microliters of blood were transferred from the collection tube to each of two 12 X 75 mm test tubes. Fc receptor blocking solution (Miltenyi Biotec, Auburn, CA) was added to each tube, followed by a 15 minute incubation at ambient temperature. Next, one sample was stained with FITC anti-CD4 alone and the other with a cocktail of antibodies containing FITC anti-CD4 (eBioscience, San Diego, CA), APC anti-FcεRI (eBioscience) and PE anti-CRTh2 (Miltenyi Biotec) for 15 minutes at ambient temperature. 4 mL of pre-warmed hypotonic formaldehyde solution (Phosflow Lyse/Fix buffer, BD Biosciences) were then added to each sample tube and the tube was incubated for 10 minutes at 37 °C. Samples were then centrifuged for 3 minutes at 1500 rpm. After aspiration of supernatants, cell pellets were resuspended in 2 mL of FACS buffer (1X PBS with 1% BSA and 0.9% sodium azide, BD Biosciences Pharmingen) and subjected to an additional centrifugation step. After resuspension of cell pellets in 0.4 mL FACS buffer, samples were analyzed by flow cytometry on a BD FACS Canto II using pre-determined instrument settings. The sample stained with FITC anti-CD4 alone was used to determine quadrant boundaries for analysis of CRTh2 expression on CD4-positive lymphocytes. Eosinophils were identified according to their unique position in the light scatter plot, with a secondary histogram gate to ensure that only CRTh2-positive events were included in the analysis. Basophils were identified by their high level of expression of both FcεRI and CRTh2. The percentages of these cell types present in peripheral blood are summarized by treatment group in Table 3.

**Table 3**

| | | | Percent of Baseline | |
|---|---|---|---|---|
| **Biomarker**<br>**Visit**<br>**Statistic** | **Placebo**<br>**(N=50)** | **ARRY-502**<br>**200 mg**<br>**(N=57)** | **Placebo**<br>**(N=50)** | **ARRY-502**<br>**200 mg**<br>**(N=57)** |
| CRTh2 Expression CRTh2+ Basophils gMFI | | | | |
| Baseline | | | | |
| n | 50 | 57 | | |
| Mean | 15997.20 | 14066.65 | | |
| SD | 4190.786 | 3716.762 | | |
| Median | 15865.00 | 14026.00 | | |
| Min, Max | 7453.00, 25963.00 | 2724.00, 23583.00 | | |
| Week 4 (Day 29) | | | | |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) | Percent of Baseline<br>Placebo<br>(N=50) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|---|---|
| n | 48 | 55 | 48 | 55 |
| Mean | 15797.60 | 22733.44 | 102.94 | 173.58 |
| SD | 3770.464 | 6248.423 | 23.431 | 66.730 |
| Median | 15728.00 | 22179.00 | 102.57 | 161.89 |
| Min, Max | 5808.00, 22679.00 | 7867.00, 38331.00 | 34.72, 163.18 | 69.70, 441.58 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 18048.00 | 24370.00 | 79.76 | 154.15 |
| SD | | | | |
| Median | 18048.00 | 24370.00 | 79.76 | 154.15 |
| Min, Max | 18048.00, 18048.00 | 24370.00, 24370.00 | 79.76, 79.76 | 154.15, 154.15 |
| CRTh2 Expression CRTh2+ Basophils, % of total | | | | |
| Baseline | | | | |
| n | 50 | 57 | | |
| Mean | 0.61 | 0.72 | | |
| SD | 0.263 | 0.366 | | |
| Median | 0.58 | 0.63 | | |
| Min, Max | 0.14, 1.23 | 0.17, 1.98 | | |
| Week 4 (Day 29) | | | | |
| n | 48 | 55 | 48 | 55 |
| Mean | 0.67 | 0.81 | 123.18 | 113.68 |
| SD | 0.328 | 0.523 | 91.154 | 30.974 |
| Median | 0.60 | 0.61 | 98.91 | 109.62 |
| Min, Max | 0.12, 1.97 | 0.18, 2.85 | 30.00, 678.26 | 30.88, 200.00 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 0.38 | 0.51 | 102.70 | 70.83 |
| SD | | | | |
| Median | 0.38 | 0.51 | 102.70 | 70.83 |
| Min, Max | 0.38, 0.38 | 0.51, 0.51 | 102.70, 102.70 | 70.83, 70.83 |
| CRTh2 Expression CRTh2+ CD4+ T cell gMFI | | | | |
| Baseline | | | | |
| n | 50 | 57 | | |
| Mean | 4292.42 | 4118.93 | | |
| SD | 1276.478 | 1022.724 | | |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) | Percent of Baseline<br>Placebo<br>(N=50) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|---|---|
| Median | 4099.50 | 4150.00 | | |
| Min, Max | 2043.00, 9565.00 | 1120.00, 7041.00 | | |
| Week 4 (Day 29) | | | | |
| n | 48 | 55 | 48 | 55 |
| Mean | 4462.60 | 6089.11 | 107.98 | 150.25 |
| SD | 1466.892 | 1979.642 | 30.698 | 55.179 |
| Median | 4100.50 | 5985.00 | 104.69 | 147.79 |
| Min, Max | 2060.00, 9726.00 | 1071.00, 10949.00 | 57.32, 212.77 | 51.65, 428.53 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 5245.00 | 5716.00 | 93.85 | 203.27 |
| SD | | | | |
| Median | 5245.00 | 5716.00 | 93.85 | 203.27 |
| Min, Max | 5245.00, 5245.00 | 5716.00, 5716.00 | 93.85, 93.85 | 203.27, 203.27 |
| CRTh2 Expression CRTh2+ CD4+ T cells, %of total | | | | |
| Baseline | | | | |
| n | 50 | 57 | | |
| Mean | 0.29 | 0.32 | | |
| SD | 0.299 | 0.869 | | |
| Median | 0.24 | 0.18 | | |
| Min, Max | 0.06, 2.08 | 0.04, 6.73 | | |
| Week 4 (Day 29) | | | | |
| n | 48 | 55 | 48 | 55 |
| Mean | 0.26 | 0.31 | 100.84 | 132.19 |
| SD | 0.138 | 0.394 | 34.232 | 46.599 |
| Median | 0.23 | 0.24 | 99.00 | 123.81 |
| Min, Max | 0.06, 0.72 | 0.05, 3.06 | 26.92, 205.00 | 45.47, 269.23 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 0.08 | 0.32 | 100.00 | 139.13 |
| SD | | | | |
| Median | 0.08 | 0.32 | 100.00 | 139.13 |
| Min, Max | 0.08, 0.08 | 0.32, 0.32 | 100.00, 100.00 | 139.13, 139.13 |
| CRTh2 Expression CRTh2+ Eosinophils gMFI | | | | |
| Baseline | | | | |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) | Percent of Baseline<br>Placebo<br>(N=50) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|---|---|
| n | 50 | 57 | | |
| Mean | 14579.88 | 12767.47 | | |
| SD | 3623.899 | 3395.098 | | |
| Median | 14049.50 | 12312.00 | | |
| Min, Max | 8148.00, 23279.00 | 4149.00, 21403.00 | | |
| Week 4 (Day 29) | | | | |
| n | 48 | 55 | 48 | 55 |
| Mean | 14236.63 | 21306.71 | 101.63 | 176.00 |
| SD | 3409.678 | 5946.948 | 23.594 | 64.397 |
| Median | 13807.00 | 22035.00 | 98.04 | 172.16 |
| Min, Max | 6690.00, 21662.00 | 5194.00, 34376.00 | 36.62, 161.44 | 69.89, 368.14 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 15848.00 | 18242.00 | 78.18 | 148.16 |
| SD | | | | |
| Median | 15848.00 | 18242.00 | 78.18 | 148.16 |
| Min, Max | 15848.00, 15848.00 | 18242.00, 18242.00 | 78.18, 78.18 | 148.16, 148.16 |
| CRTh2 Expression CRTh2+ Eosinophils, % of total | | | | |
| Baseline | | | | |
| n | 50 | 57 | | |
| Mean | 5.55 | 5.76 | | |
| SD | 3.493 | 3.128 | | |
| Median | 5.32 | 4.97 | | |
| Min, Max | 0.14, 13.96 | 1.30, 14.45 | | |
| Week 4 (Day 29) | | | | |
| n | 48 | 55 | 48 | 55 |
| Mean | 6.46 | 5.65 | 141.74 | 105.94 |
| SD | 4.156 | 3.149 | 120.117 | 48.007 |
| Median | 5.26 | 5.26 | 113.43 | 96.75 |
| Min, Max | 0.06, 18.24 | 1.42, 17.32 | 40.00, 821.31 | 31.79, 272.66 |
| Early Termination | | | | |
| n | 1 | 1 | 1 | 1 |
| Mean | 4.33 | 6.77 | 125.51 | 164.72 |
| SD | | | | |
| Median | 4.33 | 6.77 | 125.51 | 164.72 |

| Biomarker<br>Visit<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) | Percent of Baseline<br>Placebo<br>(N=50) | Percent of Baseline<br>ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|---|---|
| Min, Max | 4.33, 4.33 | 6.77, 6.77 | 125.51, 125.51 | 164.72, 164.72 |

**[000200] Relationships Between Biomarkers and Clinical Efficacy Assessments**

**[000201]** Relationships between Baseline biomarker values and clinical efficacy assessments were investigated by displaying percentage change in prebronchodilator FEV1 by treatment and Baseline level of biomarker, where the Baseline level of biomarker was categorized as either "above the median" or "at or below the median" for that biomarker. Descriptive statistics were displayed for the following 4 groups: (1) Placebo with biomarker value below the median; (2) Placebo with biomarker value above the median; (3) ARRY-502 with biomarker value below the median; and (4) ARRY-502 with biomarker value above the median.

**[000202]** These displays were repeated for the subset of patients with Baseline $FE_{NO}$ > 48 ppb and for the subset of patients with Baseline $FE_{NO} \leq 48$ ppb.

**[000203] Examination of Subgroups**

**[000204]** Relationships between Baseline biomarker values and the efficacy endpoint of percent change from Baseline at Week 4 in prebronchodilator FEV1 are presented in Table 4 (serum biomarkers), Table 5 (whole blood biomarkers), Table 6 (urine biomarker), Table 7 ($FE_{NO}$) and Table 8 (IgE). These analyses were repeated in patients with a Baseline $FE_{NO}$ level > 48 ppb, and data at Week 4 are presented in Table 9 (serum biomarkers), Table 10 (whole blood biomarkers), Table 11 (urine biomarker) and Table 12 (IgE). These analyses were also repeated in patients with a Baseline $FE_{NO}$ level $\leq$ 48 ppb, and data at Week 4 are presented in Table 13 (serum biomarkers), Table 14 (whole blood biomarkers), Table 15 (urine biomarker) and Table 16 (IgE).

## Table 4

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=90) | ARRY-502 200 mg (N=93) |
|---|---|---|
| ARRY-502 Outsourced SCCA1 Result [(Median) 0.90 ng/ml] | | |
| Above Cutoff | | |
| n | 36 | 41 |
| Mean | 2.02 | 3.64 |
| SD | 9.297 | 11.926 |
| Median | 0.52 | 1.14 |
| Min, Max | -11.87, 27.72 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 44 | 49 |
| Mean | 1.69 | 4.81 |
| SD | 11.939 | 11.889 |
| Median | 1.55 | 4.17 |
| Min, Max | -24.51, 30.56 | -19.51, 31.58 |
| ARRY-502 Outsourced SCCA2 Result [(Median) 0.70 ng/ml] | | |
| Above Cutoff | | |
| n | 35 | 36 |
| Mean | 3.03 | 4.95 |
| SD | 9.511 | 12.247 |
| Median | 2.03 | 2.82 |
| Min, Max | -11.87, 27.72 | -12.30, 40.89 |
| At or Below Cutoff | | |
| n | 45 | 54 |
| Mean | 0.91 | 3.83 |
| SD | 11.670 | 11.677 |
| Median | 0.43 | 3.35 |
| Min, Max | -24.51, 30.56 | -19.51, 31.58 |
| ARRY 502 Periostin 18Ax17B Result [(Median) 55.00 ng/ml] | | |
| Above Cutoff | | |
| n | 43 | 45 |
| Mean | 2.61 | 4.85 |
| SD | 11.108 | 13.340 |
| Median | 2.03 | 2.90 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|
| Min, Max | -24.51, 27.72 | -19.51, 40.89 |
| At or Below Cutoff | | |
| n | 37 | 45 |
| Mean | 0.94 | 3.70 |
| SD | 10.433 | 10.273 |
| Median | 0.19 | 3.26 |
| Min, Max | -19.56, 30.56 | -13.43, 30.90 |
| ARRY-502 TARC Result Mean [(Median) 317.43 pg/mL] | | |
| Above Cutoff | | |
| n | 43 | 41 |
| Mean | 2.62 | 2.09 |
| SD | 11.627 | 11.769 |
| Median | 0.71 | 1.14 |
| Min, Max | -20.80, 30.56 | -19.51, 40.89 |
| At or Below Cutoff | | |
| n | 37 | 43 |
| Mean | 0.93 | 4.98 |
| SD | 9.748 | 11.181 |
| Median | 2.03 | 3.84 |
| Min, Max | -24.51, 19.21 | -12.35, 31.58 |

## Table 5

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|
| CRTh2 Expression CRTh2+ Basophils gMFI [(Median) 15000.00] | | |
| Above Cutoff | | |
| n | 29 | 22 |
| Mean | 2.73 | 2.53 |
| SD | 11.547 | 10.547 |
| Median | 2.03 | 1.11 |
| Min, Max | -24.51, 27.72 | -19.51, 26.96 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|
| At or Below Cutoff | | |
| n | 20 | 34 |
| Mean | 2.34 | 3.88 |
| SD | 10.069 | 11.078 |
| Median | 0.30 | 3.85 |
| Min, Max | -19.56, 22.45 | -13.89, 30.80 |
| CRTh2 Expression CRTh2+ Basophils, % of total [(Median) 0.62] | | |
| Above Cutoff | | |
| n | 22 | 30 |
| Mean | 3.34 | 4.74 |
| SD | 11.393 | 11.623 |
| Median | 0.32 | 3.85 |
| Min, Max | -19.56, 24.43 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 27 | 26 |
| Mean | 1.94 | 1.75 |
| SD | 10.582 | 9.732 |
| Median | 2.36 | 1.95 |
| Min, Max | -24.51, 27.72 | -14.14, 26.96 |
| CRTh2 Expression CRTh2+ CD4+ T cell gMFI [(Median) 4127.00] | | |
| Above Cutoff | | |
| n | 23 | 29 |
| Mean | 1.12 | 2.78 |
| SD | 11.165 | 12.180 |
| Median | 2.36 | 1.61 |
| Min, Max | -24.51, 22.45 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 26 | 27 |
| Mean | 3.85 | 3.96 |
| SD | 10.636 | 9.276 |
| Median | 0.32 | 4.34 |
| Min, Max | -19.56, 27.72 | -10.62, 26.96 |
| CRTh2 Expression CRTh2+ CD4+ T cells, % of total [(Median) 0.20] | | |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=50) | ARRY-502<br>200 mg<br>(N=57) |
|---|---|---|
| Above Cutoff | | |
| n | 27 | 24 |
| Mean | 1.82 | 0.01 |
| SD | 9.483 | 11.232 |
| Median | 0.37 | 0.50 |
| Min, Max | -19.56, 19.21 | -19.51, 24.79 |
| At or Below Cutoff | | |
| n | 22 | 32 |
| Mean | 3.48 | 5.85 |
| SD | 12.516 | 9.905 |
| Median | 2.26 | 4.41 |
| Min, Max | -24.51, 27.72 | -13.89, 30.80 |
| CRTh2 Expression CRTh2+ Eosinophils gMFI [(Median) 12899.00] | | |
| Above Cutoff | | |
| n | 27 | 25 |
| Mean | 4.31 | 2.67 |
| SD | 11.923 | 9.095 |
| Median | 4.99 | 2.30 |
| Min, Max | -24.51, 27.72 | -14.14, 20.81 |
| At or Below Cutoff | | |
| n | 22 | 31 |
| Mean | 0.42 | 3.90 |
| SD | 9.211 | 12.116 |
| Median | 0.15 | 3.09 |
| Min, Max | -19.56, 22.45 | -19.51, 30.80 |
| CRTh2 Expression CRTh2+ Eosinophils, % of total [(Median) 5.29] | | |
| Above Cutoff | | |
| n | 24 | 27 |
| Mean | 5.66 | 6.09 |
| SD | 10.473 | 11.285 |
| Median | 4.26 | 4.34 |
| Min, Max | -19.56, 27.72 | -12.23, 30.80 |
| At or Below Cutoff | | |

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=50) | ARRY-502 200 mg (N=57) |
|---|---|---|
| n | 25 | 29 |
| Mean | -0.41 | 0.80 |
| SD | 10.582 | 9.835 |
| Median | -0.62 | 0.56 |
| Min, Max | -24.51, 24.43 | -19.51, 26.96 |

**Table 6**

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=89) | ARRY-502 200 mg (N=90) |
|---|---|---|
| Tetranor-PGDM Tetranor-PGDM conc. [(Median) 1.38 ng/ml creatinine] | | |
| Above Cutoff | | |
| n | 33 | 47 |
| Mean | 0.52 | 4.61 |
| SD | 11.086 | 13.061 |
| Median | 0.28 | 3.26 |
| Min, Max | -24.51, 27.72 | -19.51, 40.89 |
| At or Below Cutoff | | |
| n | 46 | 40 |
| Mean | 2.16 | 4.48 |
| SD | 9.817 | 10.595 |
| Median | 0.84 | 3.27 |
| Min, Max | -20.80, 24.43 | -14.14, 28.65 |

## Table 7

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|
| Fractional Exhaled Nitric Oxide[(Median) 48 ppb] | | |
| Above Cutoff | | |
| n | 40 | 44 |
| Mean | 2.45 | 7.03 |
| SD | 10.779 | 12.608 |
| Median | 1.37 | 4.32 |
| Min, Max | -20.80, 30.56 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 40 | 46 |
| Mean | 1.22 | 1.64 |
| SD | 10.854 | 10.558 |
| Median | 0.82 | 1.72 |
| Min, Max | -24.51, 27.72 | -19.51, 30.80 |

## Table 8

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=90) | ARRY-502<br>200 mg<br>(N=93) |
|---|---|---|
| Immunoglobulin E[(Median) 145.00 kU/L] | | |
| Above Cutoff | | |
| n | 37 | 48 |
| Mean | 3.52 | 4.11 |
| SD | 11.274 | 12.888 |
| Median | 2.33 | 1.95 |
| Min, Max | -24.51, 30.56 | -14.14, 40.89 |
| At or Below Cutoff | | |
| n | 43 | 42 |
| Mean | 0.39 | 4.46 |
| SD | 10.218 | 10.700 |
| Median | 0.28 | 3.54 |
| Min, Max | -20.80, 24.43 | -19.51, 31.58 |

## Table 9

## Patients with a Baseline $FE_{NO}$ level > 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=47) | ARRY-502<br>200 mg<br>(N=44) |
|---|---|---|
| ARRY-502 Outsourced SCCA1 Result [(Median) 1.00 ng/ml] | | |
| Above Cutoff | | |
| n | 17 | 18 |
| Mean | 2.34 | 8.23 |
| SD | 9.870 | 14.760 |
| Median | 2.03 | 6.50 |
| Min, Max | -11.65, 22.45 | -10.57, 40.89 |
| At or Below Cutoff | | |
| n | 23 | 26 |
| Mean | 2.54 | 6.19 |
| SD | 11.624 | 11.114 |
| Median | 0.71 | 4.32 |
| Min, Max | -20.80, 30.56 | -13.89, 31.58 |
| ARRY-502 Outsourced SCCA2 Result [(Median) 0.70 ng/ml] | | |
| Above Cutoff | | |
| n | 22 | 18 |
| Mean | 3.02 | 7.31 |
| SD | 9.818 | 14.475 |
| Median | 2.10 | 2.33 |
| Min, Max | -11.65, 24.43 | -10.57, 40.89 |
| At or Below Cutoff | | |
| n | 18 | 26 |
| Mean | 1.76 | 6.83 |
| SD | 12.107 | 11.439 |
| Median | 0.57 | 4.51 |
| Min, Max | -20.80, 30.56 | -13.89, 31.58 |
| ARRY-502 Periostin 18Ax17B Result [(Median) 58.00 ng/ml] | | |
| Above Cutoff | | |
| n | 20 | 22 |

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=47) | ARRY-502 200 mg (N=44) |
|---|---|---|
| Mean | 2.88 | 7.73 |
| SD | 11.143 | 14.969 |
| Median | 2.28 | 3.54 |
| Min, Max | -20.80, 24.43 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 20 | 22 |
| Mean | 2.03 | 6.33 |
| SD | 10.675 | 10.020 |
| Median | 0.57 | 4.51 |
| Min, Max | -12.29, 30.56 | -10.45, 30.90 |
| ARRY-502 TARC Result Mean [(Median) 328.34 pg/mL] | | |
| Above Cutoff | | |
| n | 23 | 17 |
| Mean | 2.95 | 5.25 |
| SD | 12.457 | 13.144 |
| Median | 0.71 | 3.05 |
| Min, Max | -20.80, 30.56 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 17 | 22 |
| Mean | 1.77 | 7.03 |
| SD | 8.307 | 11.895 |
| Median | 2.03 | 6.17 |
| Min, Max | -12.29, 17.83 | -10.45, 31.58 |

## Table 10

## Patients with a Baseline $FE_{NO}$ level > 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=24) | ARRY-502<br>200 mg<br>(N=27) |
|---|---|---|
| CRTh2 Expression CRTh2+ Basophils gMFI [(Median) 15262.00] | | |
| Above Cutoff | | |
| n | 15 | 10 |
| Mean | 1.89 | 4.94 |
| SD | 10.650 | 7.304 |
| Median | 2.03 | 4.32 |
| Min, Max | -11.65, 24.43 | -4.31, 20.81 |
| At or Below Cutoff | | |
| n | 9 | 17 |
| Mean | 4.98 | 3.06 |
| SD | 8.890 | 11.576 |
| Median | 2.16 | 0.43 |
| Min, Max | -4.79, 22.45 | -13.89, 24.79 |
| CRTh2 Expression CRTh2+ Basophils, % of total [(Median) 0.63] | | |
| Above Cutoff | | |
| n | 11 | 13 |
| Mean | 5.16 | 6.51 |
| SD | 11.850 | 11.693 |
| Median | 2.03 | 10.29 |
| Min, Max | -7.61, 24.43 | -13.89, 24.79 |
| At or Below Cutoff | | |
| n | 13 | 14 |
| Mean | 1.26 | 1.20 |
| SD | 8.057 | 7.923 |
| Median | 2.16 | 1.02 |
| Min, Max | -11.65, 15.58 | -10.45, 20.81 |
| CRTh2 Expression CRTh2+ CD4+ T cell gMFI [(Median) 3983.00] | | |
| Above Cutoff | | |
| n | 11 | 14 |
| Mean | 0.66 | 5.10 |
| SD | 10.661 | 10.582 |
| Median | 2.16 | 3.61 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=24) | ARRY-502<br>200 mg<br>(N=27) |
|---|---|---|
| Min, Max | -11.65, 22.45 | -13.89, 24.79 |
| | | |
| At or Below Cutoff | | |
| n | 13 | 13 |
| Mean | 5.08 | 2.31 |
| SD | 9.224 | 9.739 |
| Median | 2.03 | 0.43 |
| Min, Max | -4.79, 24.43 | -10.45, 20.47 |
| | | |
| CRTh2 Expression CRTh2+ CD4+ T cells, %of total [(Median) 0.20] | | |
| Above Cutoff | | |
| n | 13 | 11 |
| Mean | 2.29 | 1.97 |
| SD | 7.724 | 11.193 |
| Median | 2.03 | 1.61 |
| Min, Max | -7.61, 13.79 | -10.45, 24.79 |
| | | |
| At or Below Cutoff | | |
| n | 11 | 16 |
| Mean | 3.94 | 4.99 |
| SD | 12.417 | 9.430 |
| Median | 2.16 | 4.51 |
| Min, Max | -11.65, 24.43 | -13.89, 20.81 |
| | | |
| CRTh2 Expression CRTh2+ Eosinophils gMFI [(Median) 13337.00] | | |
| Above Cutoff | | |
| n | 14 | 11 |
| Mean | 2.86 | 2.27 |
| SD | 10.347 | 9.358 |
| Median | 3.05 | 1.61 |
| Min, Max | -11.59, 24.43 | -13.89, 20.81 |
| | | |
| At or Below Cutoff | | |
| n | 10 | 16 |
| Mean | 3.32 | 4.78 |
| SD | 9.894 | 10.738 |
| Median | 1.26 | 3.77 |
| Min, Max | -11.65, 22.45 | -10.45, 24.79 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=24) | ARRY-502<br>200 mg<br>(N=27) |
|---|---|---|
| CRTh2 Expression CRTh2+ Eosinophils, % of total [(Median) 5.81] | | |
| Above Cutoff | | |
| n | 12 | 13 |
| Mean | 5.71 | 6.65 |
| SD | 8.968 | 12.096 |
| Median | 4.26 | 7.80 |
| Min, Max | -6.48, 22.45 | -10.45, 24.79 |
| At or Below Cutoff | | |
| n | 12 | 14 |
| Mean | 0.39 | 1.07 |
| SD | 10.528 | 7.237 |
| Median | -1.82 | 0.50 |
| Min, Max | -11.65, 24.43 | -13.89, 13.99 |

## Table 11

## Patients with a Baseline $FE_{NO}$ level > 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=46) | ARRY-502<br>200 mg<br>(N=41) |
|---|---|---|
| Tetranor-PGDM Tetranor-PGDM conc. [(Median) 1.38 ng/ml creatinine] | | |
| Above Cutoff | | |
| n | 17 | 22 |
| Mean | 0.17 | 8.28 |
| SD | 8.915 | 14.248 |
| Median | 0.23 | 4.51 |
| Min, Max | -11.65, 22.45 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 22 | 19 |
| Mean | 2.94 | 7.27 |
| SD | 10.638 | 10.827 |
| Median | 1.37 | 5.73 |
| Min, Max | -20.80, 24.43 | -10.57, 28.65 |

## Table 12

## Patients with a Baseline $FE_{NO}$ level > 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=47) | ARRY-502<br>200 mg<br>(N=44) |
|---|---|---|
| Immunoglobulin E[(Median) 229.00 kU/L] | | |
| Above Cutoff | | |
| n | 21 | 21 |
| Mean | 3.61 | 7.98 |
| SD | 10.189 | 15.686 |
| Median | 2.16 | 4.17 |
| Min, Max | -10.27, 30.56 | -13.89, 40.89 |
| At or Below Cutoff | | |
| n | 19 | 23 |
| Mean | 1.17 | 6.16 |
| SD | 11.538 | 9.240 |
| Median | 0.71 | 4.48 |
| Min, Max | -20.80, 24.43 | -5.99, 31.58 |

## Table 13

## Patients with a Baseline $FE_{NO}$ level ≤ 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=43) | ARRY-502<br>200 mg<br>(N=49) |
|---|---|---|
| ARRY-502 Outsourced SCCA1 Result [(Median) 0.90 ng/ml] | | |
| Above Cutoff | | |
| n | 15 | 19 |
| Mean | 2.08 | 0.77 |
| SD | 9.313 | 7.780 |
| Median | 0.28 | 1.14 |
| Min, Max | -11.87, 27.72 | -12.35, 14.03 |
| At or Below Cutoff | | |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=43) | ARRY-502<br>200 mg<br>(N=49) |
|---|---|---|
| n | 25 | 27 |
| Mean | 0.71 | 2.26 |
| SD | 11.836 | 12.251 |
| Median | 1.96 | 2.30 |
| Min, Max | -24.51, 19.21 | -19.51, 30.80 |
| ARRY-502 Outsourced SCCA2 Result [(Median) 0.65 ng/ml] | | |
| Above Cutoff | | |
| n | 17 | 25 |
| Mean | 1.66 | 1.68 |
| SD | 8.794 | 9.153 |
| Median | 0.97 | 1.14 |
| Min, Max | -11.87, 27.72 | -13.43, 26.96 |
| At or Below Cutoff | | |
| n | 23 | 21 |
| Mean | 0.90 | 1.61 |
| SD | 12.342 | 12.259 |
| Median | 0.19 | 2.30 |
| Min, Max | -24.51, 19.21 | -19.51, 30.80 |
| ARRY-502 Periostin 18Ax17B Result [(Median) 54.00 ng/ml] | | |
| Above Cutoff | | |
| n | 22 | 23 |
| Mean | 2.67 | 1.44 |
| SD | 11.238 | 11.509 |
| Median | 1.06 | 2.30 |
| Min, Max | -24.51, 27.72 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 18 | 23 |
| Mean | -0.55 | 1.85 |
| SD | 10.402 | 9.772 |
| Median | 0.21 | 1.14 |
| Min, Max | -19.56, 17.81 | -13.43, 26.96 |
| ARRY-502 TARC Result Mean [(Median) 309.29 pg/mL] | | |
| Above Cutoff | | |

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=43) | ARRY-502 200 mg (N=49) |
|---|---|---|
| n | 20 | 24 |
| Mean | 2.24 | -0.48 |
| SD | 10.902 | 10.114 |
| Median | 0.63 | 0.67 |
| Min, Max | -19.56, 27.72 | -19.51, 26.96 |
| At or Below Cutoff | | |
| n | 20 | 21 |
| Mean | 0.21 | 3.20 |
| SD | 10.989 | 10.417 |
| Median | 1.50 | 3.64 |
| Min, Max | -24.51, 19.21 | -12.35, 30.80 |

## Table 14

## Patients with a Baseline $FE_{NO}$ level ≤ 48 ppb

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=26) | ARRY-502 200 mg (N=30) |
|---|---|---|
| CRTh2 Expression CRTh2+ Basophils gMFI [(Median) 14957.00] | | |
| Above Cutoff | | |
| n | 13 | 13 |
| Mean | 3.88 | 0.55 |
| SD | 13.263 | 12.077 |
| Median | 2.36 | -0.34 |
| Min, Max | -24.51, 27.72 | -19.51, 26.96 |
| At or Below Cutoff | | |
| n | 12 | 16 |
| Mean | 0.18 | 4.94 |
| SD | 10.355 | 11.156 |
| Median | -0.28 | 4.43 |
| Min, Max | -19.56, 19.21 | -12.30, 30.80 |
| CRTh2 Expression CRTh2+ Basophils, % of total [(Median) 0.59] | | |
| Above Cutoff | | |
| n | 11 | 15 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=26) | ARRY-502<br>200 mg<br>(N=30) |
|---|---|---|
| Mean | 1.52 | 3.47 |
| SD | 11.174 | 12.403 |
| Median | 0.23 | 3.44 |
| Min, Max | -19.56, 19.21 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 14 | 14 |
| Mean | 2.56 | 2.43 |
| SD | 12.773 | 11.073 |
| Median | 3.04 | 2.69 |
| Min, Max | -24.51, 27.72 | -14.14, 26.96 |
| CRTh2 Expression CRTh2+ CD4+ T cell gMFI [(Median) 4143.00] | | |
| Above Cutoff | | |
| n | 11 | 16 |
| Mean | 1.60 | 0.78 |
| SD | 12.652 | 13.060 |
| Median | 3.71 | 0.67 |
| Min, Max | -24.51, 17.30 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 14 | 13 |
| Mean | 2.50 | 5.67 |
| SD | 11.670 | 9.243 |
| Median | 0.25 | 4.53 |
| Min, Max | -19.56, 27.72 | -10.62, 26.96 |
| CRTh2 Expression CRTh2+ CD4+ T cells, % of total [(Median) 0.21] | | |
| Above Cutoff | | |
| n | 14 | 13 |
| Mean | 1.38 | -1.64 |
| SD | 11.151 | 11.443 |
| Median | -0.28 | -0.60 |
| Min, Max | -19.56, 19.21 | -19.51, 19.94 |
| At or Below Cutoff | | |
| n | 11 | 16 |
| Mean | 3.02 | 6.72 |

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=26) | ARRY-502<br>200 mg<br>(N=30) |
|---|---|---|
| SD | 13.203 | 10.593 |
| Median | 2.36 | 4.30 |
| Min, Max | -24.51, 27.72 | -10.62, 30.80 |
| CRTh2 Expression CRTh2+ Eosinophils gMFI [(Median) 12713.50] | | |
| Above Cutoff | | |
| n | 15 | 12 |
| Mean | 5.12 | 2.24 |
| SD | 12.817 | 9.743 |
| Median | 4.99 | 1.51 |
| Min, Max | -24.51, 27.72 | -14.14, 19.94 |
| At or Below Cutoff | | |
| n | 10 | 17 |
| Mean | -2.41 | 3.49 |
| SD | 9.044 | 12.991 |
| Median | -1.21 | 3.44 |
| Min, Max | -19.56, 14.79 | -19.51, 30.80 |
| CRTh2 Expression CRTh2+ Eosinophils, % of total [(Median) 4.14] | | |
| Above Cutoff | | |
| n | 11 | 16 |
| Mean | 5.60 | 6.85 |
| SD | 12.682 | 11.363 |
| Median | 1.14 | 6.69 |
| Min, Max | -19.56, 27.72 | -12.23, 30.80 |
| At or Below Cutoff | | |
| n | 14 | 13 |
| Mean | -0.64 | -1.81 |
| SD | 10.841 | 10.333 |
| Median | -0.17 | -0.34 |
| Min, Max | -24.51, 17.30 | -19.51, 19.94 |

## Table 15

## Patients with a Baseline $FE_{NO}$ level ≤ 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=43) | ARRY-502<br>200 mg<br>(N=49) |
|---|---|---|
| Tetranor-PGDM Tetranor-PGDM conc. [(Median) 1.38 ng/ml creatinine] | | |
| Above Cutoff | | |
| n | 16 | 27 |
| Mean | 0.89 | 2.18 |
| SD | 13.308 | 11.371 |
| Median | 0.71 | 2.30 |
| Min, Max | -24.51, 27.72 | -19.51, 30.80 |
| At or Below Cutoff | | |
| n | 24 | 19 |
| Mean | 1.44 | 0.89 |
| SD | 9.172 | 9.535 |
| Median | 0.82 | 1.14 |
| Min, Max | -19.56, 17.81 | -14.14, 26.96 |

## Table 16

## Patients with a Baseline $FE_{NO}$ level ≤ 48 ppb

| Biomarker<br>Level at Baseline [cutoff]<br>Statistic | Placebo<br>(N=43) | ARRY-502<br>200 mg<br>(N=49) |
|---|---|---|
| Immunoglobulin E[(Median) 113.50 kU/L] | | |
| Above Cutoff | | |
| n | 18 | 24 |
| Mean | 3.90 | 0.16 |
| SD | 13.126 | 9.703 |
| Median | 4.35 | -0.20 |
| Min, Max | -24.51, 27.72 | -14.14, 19.94 |
| At or Below Cutoff | | |
| n | 22 | 22 |
| Mean | -0.97 | 3.26 |
| SD | 8.253 | 11.425 |
| Median | 0.13 | 3.27 |

| Biomarker Level at Baseline [cutoff] Statistic | Placebo (N=43) | ARRY-502 200 mg (N=49) |
|---|---|---|
| Min, Max | -16.16, 17.30 | -19.51, 30.80 |

**[000205]** **Summary of results**

**[000206]** As part of this study, a variety of Th2–associated biomarkers were evaluated in patient serum, whole blood, urine and exhaled breath in relation to the efficacy endpoint of percent change from Baseline in prebronchodilator FEV1. A statistically significant difference in response to ARRY-502 was observed with 2 biomarkers; the biomarker of Baseline $FE_{NO}$ level and the whole blood biomarker of baseline percentage of CRTh2-expressing eosinophils present in the total leukocyte population both predicted response to ARRY-502.

**[000207]** Adult patients with mild to moderate persistent asthma receiving ARRY-502 administered at a dose of 200 mg (every 12 hours) for 28 days demonstrated statistically significant improvements compared with placebo in measures of lung function, asthma control and patient reported outcomes. The primary endpoint of this clinical study evaluated prebronchodilator FEV1 on Day 29 as an objective spirometric measure of lung function. At Day 29, patients receiving ARRY-502 demonstrated an improvement of 4.5% in prebronchodilator FEV1, a statistically significant difference compared with the improvement observed in the placebo group (0.6%) as shown in Table 17.

**Table 17**

| | Placebo (N = 91) | ARRY-502 (N = 93) | Difference (LS means) | Absolute Difference (mL) | P-value (two-tailed) |
|---|---|---|---|---|---|
| Baseline (Liters) | 2.75 | 2.67 | | | |
| % Δ Week 1 | -0.22 | 5.73 | 5.95 | 159.0 | <0.001 |
| % Δ Week 2 | 0.42 | 5.69 | 5.28 | 140.4 | 0.001 |
| % Δ Week 3 | 0.51 | 5.45 | 4.94 | 131.5 | 0.003 |

| | | | | | |
|---|---|---|---|---|---|
| % Δ Week 4 | 0.62 | 4.49 | 3.87 | 102.8 | 0.020 |

**[000208]** Accordingly, it was discovered that $FE_{NO}$ levels and the percentage of peripheral blood eosinophils represent unique predictors of responsiveness to CRTh2 antagonists such as ARRY-502.

**[000209]** As demonstrated herein, it was surprisingly observed that improvements in FEV1 were maintained in patients with a high $FE_{NO}$ level at Baseline (i.e., $FE_{NO}$ level above the median Baseline value of 48 ppb). At Day 29, patients receiving ARRY-502 with high $FE_{NO}$ at Baseline demonstrated an improvement of 7.0% in prebronchodilator FEV1, a statistically significant difference compared with the improvement observed in the placebo group (0.2%) (See Figure 1). Conversely, the "low $FE_{NO}$" subset (i.e., $FE_{NO}$ level at or below the median Baseline value of 48 ppb) had little or no benefit from ARRY-502 (See Figure 2). These results verify that this subset analysis may be effective for selecting responders to ARRY-502.

**[000210]** As further demonstrated herein, improvements in FEV1 were also surprisingly maintained in patients with a high percentage of CRTh2-expressing eosinophils at Baseline (i.e., percentage of CRTh2-expressing eosinophils above the median Baseline value of 5.06% of total leukocytes). Patients with a high percentage of CRTh2-expressing eosinophils at Baseline receiving ARRY-502 demonstrated an improvement of 8.5% in prebronchodilator FEV1, a statistically significant difference compared with the improvement observed in the placebo group (2.7%) (See Figure 3). Conversely, the "low eosinophil" subset (i.e., patients with percentage of CRTh2-expressing eosinophils at or below the median Baseline value of 5.06% of total leukocytes) had little or no benefit from ARRY-502 (See Figure 4). These results verify that this subset analysis may also be effective for selecting responders to ARRY-502.

**[000211]** A statistically significant difference was also observed in the change from Baseline in the number of weekly short-acting beta-2 antagonist metered-dose inhaler (SABA MDI) actuations at Day 29 between the ARRY-502 group and the placebo group. A mean decrease from Baseline in the number of weekly SABA MDI actuations at Day 36 of 2.48 (SD = 13.537) was observed for the ARRY-502 group (See Figure 5), compared with a mean increase of 1.00 (SD = 12.437) for the placebo group (see Figure 6). Within the high $FE_{NO}$ subset of the ARRY-502 group, the number of weekly SABA MDI actuations at Day 29 was reduced by 7.3,

and within the high eosinophil subset of the ARRY-502 group, the number of weekly SABA MDI actuations at Day 29 was also reduced by 7.3.

**[000212]** Analysis of the other Th2-associated biomarkers (serum periostin, SCCA1, SCCA2, serum IgE, urinary PGDM and serum TARC) showed that levels of these markers were not associated with increased responsiveness to ARRY-502.

**[000213]** Taking into account all cohorts, mean $FE_{NO}$ levels in the ARRY-502 group decreased by 12.8 ppb at Day 29. In contrast, mean $FE_{NO}$ levels increased in the placebo group by 4.6 ppb.

**[000214]** Additional key secondary endpoints for which statistically significant differences between treatment groups were observed at Day 29 included improvements in prebronchodilator FVC, number of symptom-free days (SFD) during the Treatment Period and patient questionnaires relating to asthma symptom severity and quality of life (see Table 18). For example, in patients with elevated $FE_{NO}$ levels at baseline (i.e., baseline $FE_{NO}$ levels greater than 48 ppb) or elevated blood eosinophil levels at baseline (i.e., baseline eosinophil level greater than 5% of the total lymphocyte population peripheral blood), there were significant improvements in spirometric outcomes, measures of asthma control and quality of life. The fact that patients with elevated $FE_{NO}$ levels at baseline or elevated blood eosinophil levels at baseline receiving ARRY-502 showed improvements relative to placebo in measures of lung function, asthma control and patient reported outcome suggests a clinically meaningful benefit to patients.

**Table 18**

| Secondary Endpoint | Placebo (N=91) | ARRY-502 (N=93) [a] | LS difference | P-value | High $FE_{NO}$ (> 48 ppb) subset [b]: LS-difference | High $FE_{NO}$ subset [b] (> 48 ppb): P-value | High EOS[c] subset [b] LS-difference | P-value High EOS[c] subset [b] |
|---|---|---|---|---|---|---|---|---|
| Pre BD FVC | -0.86% | 2.43% | 3.29% | 0.006 | 4.9% | 0.004 | 4.6% | 0.003 |
| Pre BD PEF | 2.57% | 6.29% | 3.73% | 0.081 | 8.3% | 0.011 | 3.1% | 0.368 |
| ACQ7 Δ Week 4 | -0.31 pts | -0.68 pts | -0.37 pts | <0.001 | -0.52 pts | <0.001 | -0.48 pts | 0.003 |
| SFD Δ Week 4 | 22 subjects | 35 subjects | 13 subjects (14%) | 0.072 | 7 subjects (17%) | 0.123 | 3 subjects (8%) | 0.712 |
| AQLQ Δ Week 4 | 0.31 pts | 0.58 pts | 0.27 pts | 0.012 | 0.36 pts | 0.023 | 0.40 pts | 0.017 |
| Rhinasthma Δ Week 4 | -5.53 pts | -9.76 pts | -3.47 pts | 0.007 | -4.0 pts | 0.086 | -5.8 pts | 0.020 |

[a] includes the high and low $FE_{NO}$ and EOS groups
[b] ARRY-502 treated group
[c] EOS = eosinophils; 5% of the total lymphocyte population in peripheral blood

**[000215]** In addition, the low baseline $FE_{NO}$ ($\leq$ 48 ppb) and low baseline eosinophil (less than 5% of the total lymphocyte population in peripheral blood) groups experienced more exacerbations during treatment with ARRY-502 versus other groups (see Table 19).

**Table 19**

| | **Patient ID** | **Exacerbations during Treatment Phase** | **Corticosteroid Route of Administration during treatment phase** |
|---|---|---|---|
| ARRY-502 – treated group | 1 [a, b] | Severe (discontinued) | Oral/Inhaled |
| | 2 [a, b] | Mild | Inhaled |
| | 3 | Moderate | Inhaled |

[a] Low $FE_{NO}$
[b] Low eosinophils

**[000216]** It will be understood that the enumerated embodiments are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications and equivalents, which may be included within the scope of the present invention as defined by the claims. Thus, the foregoing description is considered as illustrative only of the principles of the invention.

**[000217]** The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

What is claimed is:

1. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of a CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

2. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of a CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

3. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying a biological sample from the patient, wherein the biological sample is exhaled breath; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

4. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) identifying the patient as having a baseline $FE_{NO}$ level greater than 48 ppb by assaying the biological sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline $FE_{NO}$ level greater than 48 ppb.

5. A method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist,

comprising (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

6. A method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) assaying the sample to measure the baseline $FE_{NO}$ level; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the patient has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

7. A method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline $FE_{NO}$ level in a biological sample of the patient, wherein the biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

8. A method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a biological sample from the patient, wherein the biological sample is exhaled breath; (b) measuring the baseline $FE_{NO}$ level in the sample; (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; (d) classifying the patient as having an increased likelihood of responding

therapeutically to the method of treating mild to moderate asthma if the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

9. The method according to any one of claims 1-8, wherein the CRTh2 antagonist is ARRY-502.

10. A method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

11. A method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, comprising administering to the patient a therapeutically effective amount of ARRY-502.

12. The method according to any one of claims 9-11, wherein 200 mg of ARRY-502 is administered every 12 hours.

13. Use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

14. A pharmaceutical composition for treating a patient with mild to moderate Th2-driven allergic asthma having a baseline $FE_{NO}$ level greater than 48 ppb, comprising ARRY-502.

15. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb.

16. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline $FE_{NO}$ level greater than 48 ppb, comprising (a) assaying a biological sample from the patient for a baseline $FE_{NO}$ level, wherein the

biological sample is exhaled breath; (b) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

17. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a biological sample from the patient wherein the biological sample is exhaled breath; (b) assaying the biological sample for a baseline $FE_{NO}$ level, (c) determining whether the sample has a baseline $FE_{NO}$ level greater than 48 ppb, and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline $FE_{NO}$ level is greater than 48 ppb.

18. The compound, method, use or composition according to any one of claims 1 to 17, wherein an inhaled corticosteroid is administered in combination with said CRTh2 antagonist.

19. The compound, method, use or composition according to any one of claims 1 to 17, wherein a leukotriene receptor antagonist is administered in combination with said CRTh2 antagonist.

20. The compound, method, use or composition according to claim 19, wherein said leukotriene receptor antagonist is Montelukast.

21. The compound, method, use or composition according to any one of claims 1 to 17, wherein a mast cell stabilizer is administered in combination with said CRTh2 antagonist.

22. The compound, method, use or composition according to any one of claims 1 to 17, wherein an antibody against immunoglobulin E is administered in combination with said CRTh2 antagonist.

23. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b)

administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

24. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said sample by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

25. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood by assaying a peripheral blood sample from the patient; and (b) administering a therapeutically effective amount of the CRTh2 antagonist to the patient identified as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

26. A method for identifying and treating mild to moderate Th2-driven allergic asthma in a patient in need thereof comprising administering a CRTh2 antagonist to said patient, said method comprising: (a) obtaining a peripheral blood sample from the patient; (b) identifying the patient as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood by assaying the sample; and (c) administering a therapeutically effective amount of the CRTh2 antagonist to the patient identified as having a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood.

27. A method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than

5% of the total lymphocyte population; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

28. A method for increasing the likelihood of response in a patient having mild to moderate Th2-driven allergic asthma to therapeutic treatment with a CRTh2 antagonist, comprising: (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample to measure the baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (d) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population in said peripheral blood; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

29. A method for predicting the likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, said method comprising: (a) measuring the baseline eosinophil level in a peripheral blood sample of the patient; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (c) classifying the patient as having an increased likelihood of a therapeutic response to treatment with a CRTh2 antagonist if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

30. A method for predicting an increased likelihood a patient will respond therapeutically to a method of treating mild to moderate Th2-driven allergic asthma with a CRTh2 antagonist, the method comprising: (a) obtaining a peripheral blood sample from the patient; (b) measuring the baseline eosinophil level in the sample; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; (d) classifying the patient as having an increased likelihood of responding

therapeutically to the method of treating mild to moderate asthma if the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (e) administering a therapeutically effective amount of the CRTh2 antagonist to the patient classified as having an increased likelihood of response.

31. The method according to any one of claims 23-30 wherein the CRTh2 antagonist is ARRY-502.

32. A method of using ARRY-502 to treat a patient with mild to moderate Th2-driven allergic asthma wherein the patient has been diagnosed as having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering a therapeutically effective amount of ARRY-502 to said patient.

33. A method of treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising administering to the patient a therapeutically effective amount of ARRY-502.

34. The method according to any one of claims 31-33, wherein 200 mg of ARRY-502 is administered every 12 hours.

35. Use of ARRY-502 in the manufacture of a medicament for the treatment of mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

36. A pharmaceutical composition for treating a patient with mild to moderate Th2-driven allergic asthma having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood, comprising ARRY-502.

37. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in the patient's peripheral blood.

38. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient having a baseline eosinophil level greater than 5% of the total lymphocyte population in peripheral blood, comprising (a) assaying a peripheral blood sample from the patient for a baseline eosinophil level; (b) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (c) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

39. The compound ARRY-502 for use in treating mild to moderate Th2-driven allergic asthma in a patient in need thereof, comprising (a) obtaining a peripheral blood sample from the patient; (b) assaying the sample for a baseline eosinophil level; (c) determining whether the sample has a baseline eosinophil level greater than 5% of the total lymphocyte population; and (d) administering a therapeutically effective amount of ARRY-502 to the patient if the baseline eosinophil level is greater than 5% of the total lymphocyte population in said peripheral blood.

40. The method, use, composition or compound according to any one of claims 23-39, wherein an inhaled corticosteroid is administered in combination with said CRTh2 antagonist.

41. The method, use, composition or compound according to any one of claims 23-39, wherein a leukotriene receptor antagonist is administered in combination with said CRTh2 antagonist.

42. The method, use, composition or compound according to claim 41, wherein said leukotriene receptor antagonist is Montelukast.

43. The method, use, composition or compound according to any one of claims 23-39, wherein a mast cell stabilizer is administered in combination with said CRTh2 antagonist.

44. The method, use, composition or compound according to any one of claims 23-39, wherein an antibody against immunoglobulin E is administered in combination with said CRTh2 antagonist.

45. The method according to any of claims 23-39, wherein the baseline eosinophil level in a patient's peripheral blood is determined by requesting a test providing the results of an analysis to determine the baseline eosinophil level.

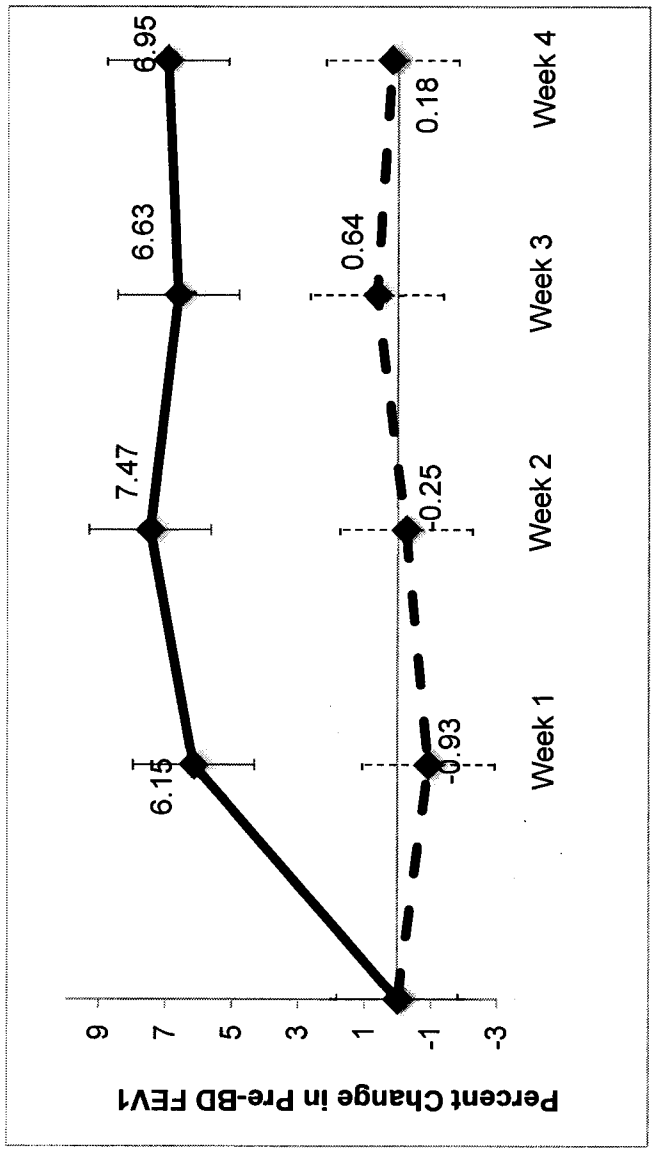

Percent Change in Pre-BD FEV1
9
7
5
3
1
-1
-3
6.15
7.47
6.63
6.95
-0.93
-0.25
0.64
0.18
Week 1
Week 2
Week 3
Week 4

FIG. 1

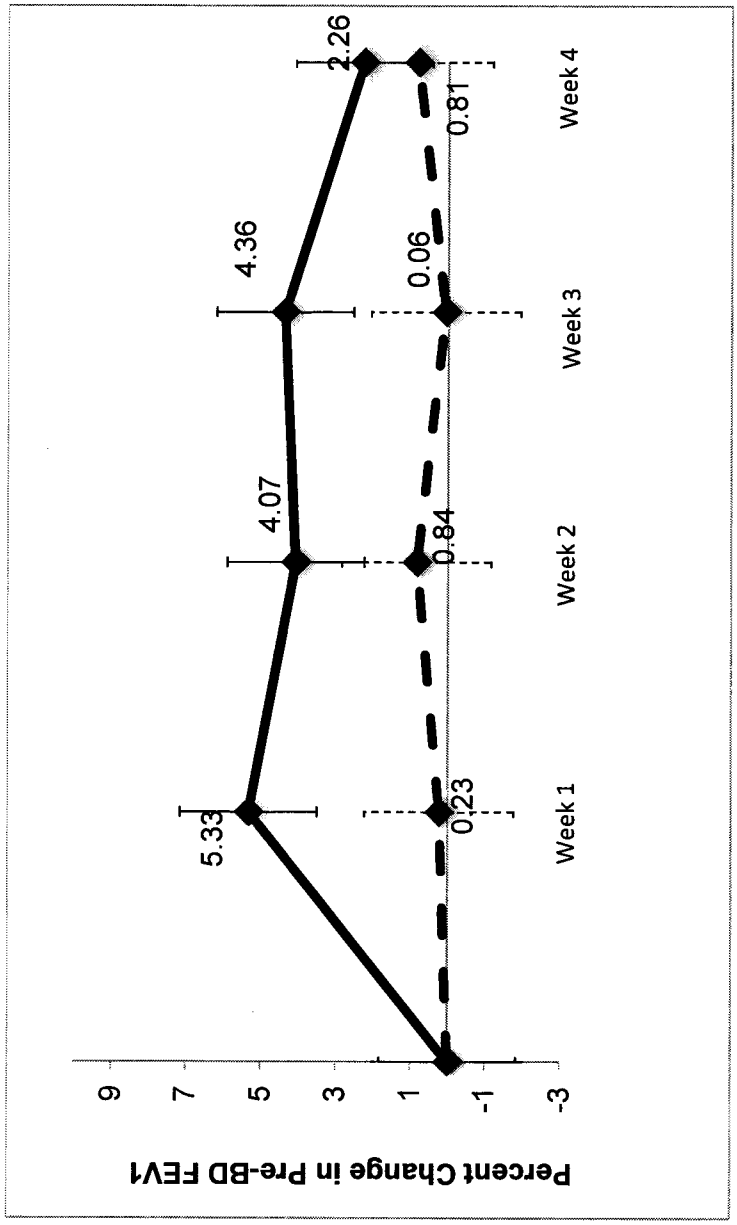

Percent Change in Pre-BD FEV1
9
7
5
3
1
-1
-3
Week 1
Week 2
Week 3
Week 4
5.33
4.07
4.36
2.26
0.23
0.84
0.06
0.81

FIG. 2

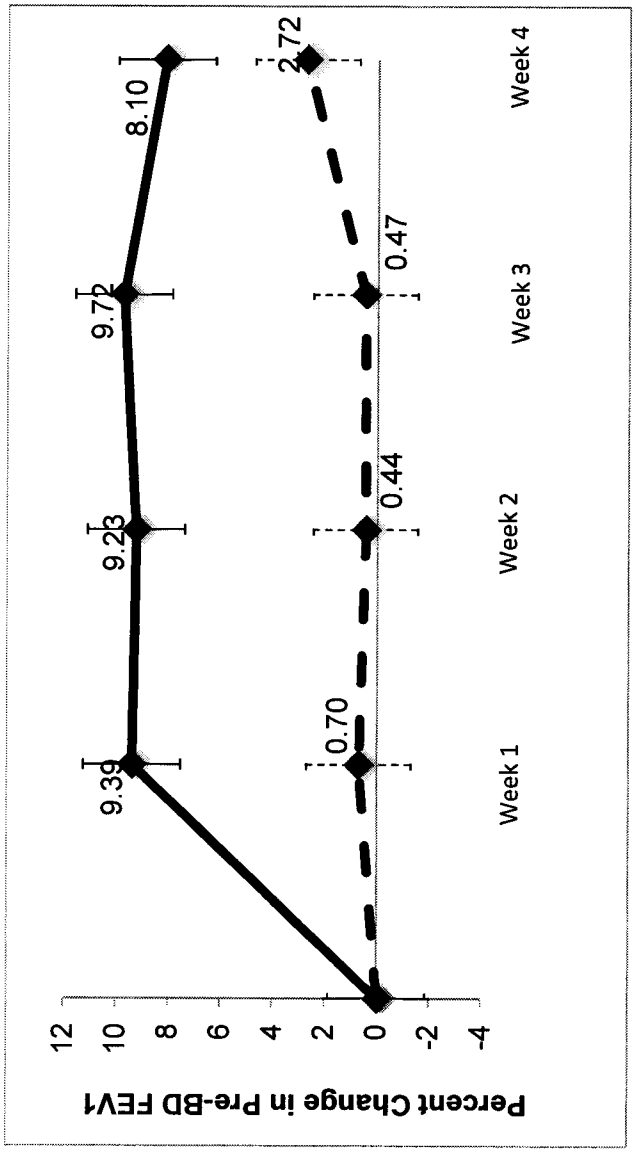

Percent Change in Pre-BD FEV1
12
10
8
6
4
2
0
-2
-4
9.39
9.23
9.72
8.10
0.70
0.44
0.47
2.72
Week 1
Week 2
Week 3
Week 4

FIG. 3

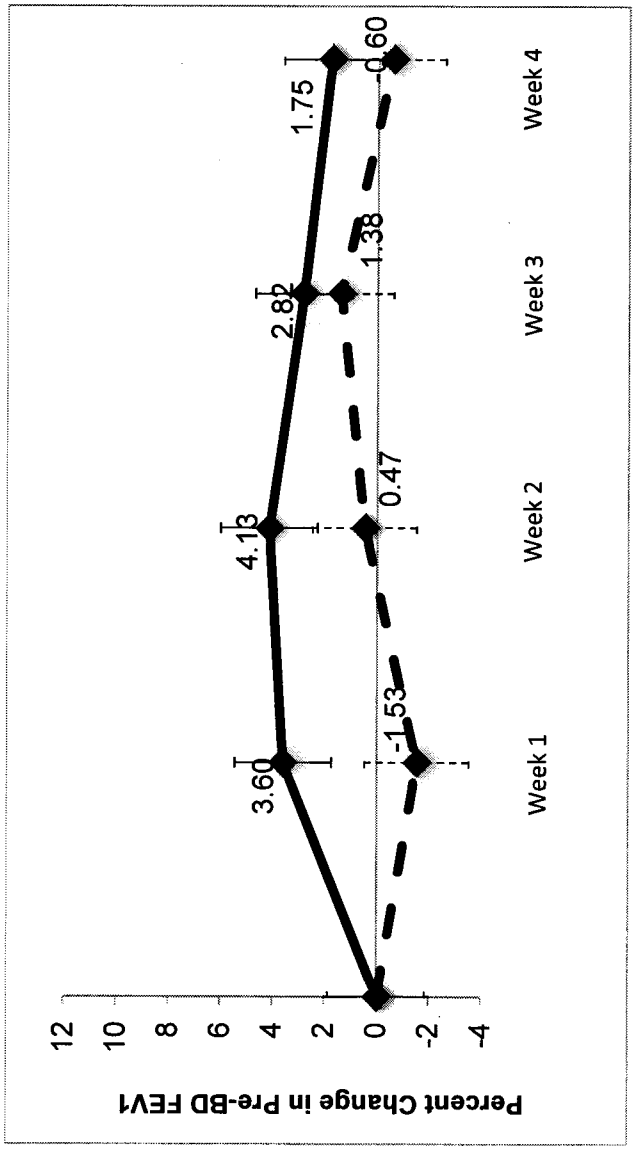

Percent Change in Pre-BD FEV1
12
10
8
6
4
2
0
-2
-4
3.60
4.13
2.82
1.75
-1.53
0.47
1.38
-0.60
Week 1
Week 2
Week 3
Week 4

FIG. 4

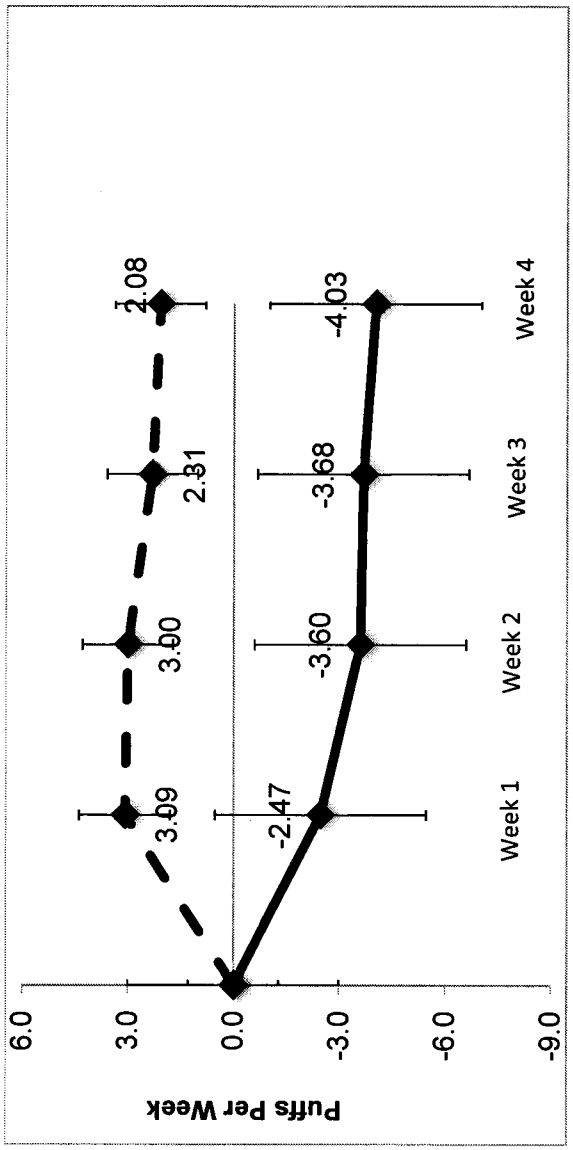

Puffs Per Week
6.0
3.0
0.0
-3.0
-6.0
-9.0
Week 1
Week 2
Week 3
Week 4
3.09
3.00
2.31
2.08
-2.47
-3.60
-3.68
-4.03

FIG. 5

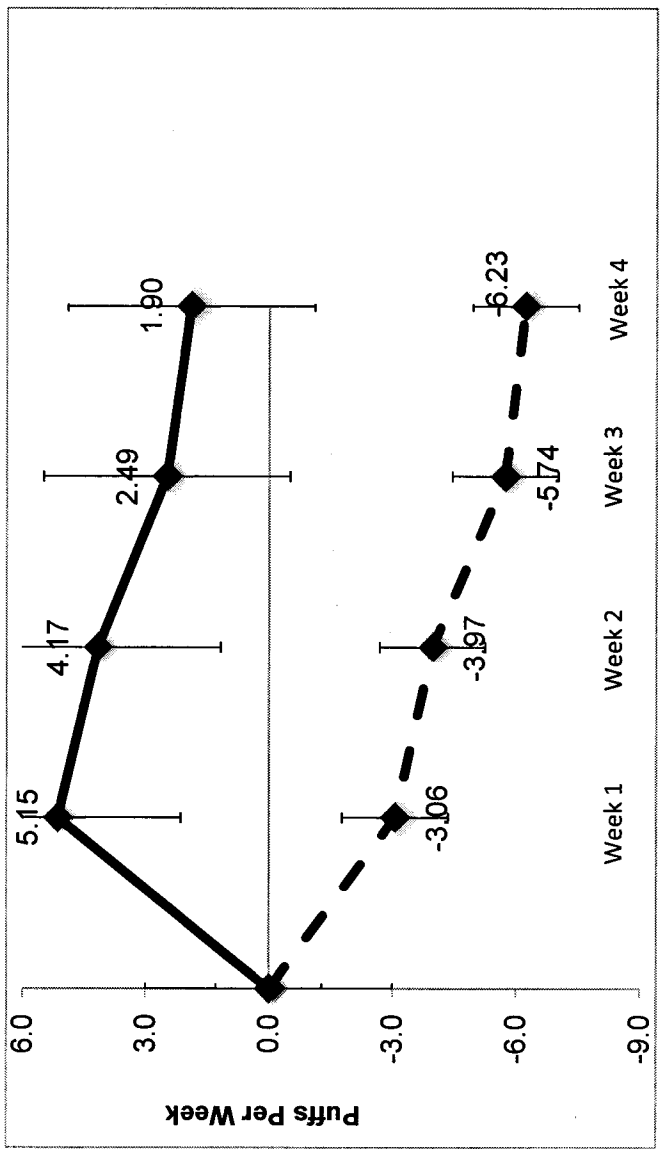

Puffs Per Week
6.0
3.0
0.0
-3.0
-6.0
-9.0
5.15
4.17
2.49
1.90
-3.06
-3.97
-5.74
-6.23
Week 1
Week 2
Week 3
Week 4

FIG. 6

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/015806

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/497 G01N33/50 G01N33/88
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2009/158426 A1 (ARRAY BIOPHARMA INC [US]; BURGESS LAURENCE E [US]; CLARK CHRISTOPHER T) 30 December 2009 (2009-12-30) This document is cited for non-compliance with the requirements of unity. abstract paragraph [0002] - paragraph [0003] ----- | 1-22 |
| A | WO 2009/124090 A1 (GENENTECH INC [US]; UNIV CALIFORNIA [US]; ARRON JOSEPH R [US]; FAHY JO) 8 October 2009 (2009-10-08) This document is cited for non-compliance with the requirements of unity. abstract; claims 13,19,21 ----- | 1-22 |

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 July 2015 | 13/07/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Mulder, Lonneke |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/015806

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | HIRAI H ET AL: "PROSTAGLANDIN D2 SELECTIVELY INDUCES CHEMOTAXIS IN T HELPER TYPE 2 CELLS, EOSINOPHILS, AND BASOPHILS VIA SEVEN-TRANSMEMBRANE RECEPTOR CRTH2", THE JOURNAL OF EXPERIMENTAL MEDICINE, ROCKEFELLER UNIVERSITY PRESS, US, vol. 193, no. 2, 15 January 2001 (2001-01-15), pages 255-261, XP008050257, ISSN: 0022-1007, DOI: 10.1084/JEM.193.2.255 This document is cited for non-compliance with the requirements of unity. abstract page 260 sentence bridging the two columns<br>----- | 1-22 |
| X | David Chantry ET AL: "Th2 Signature Selection Strategies for CRTh2 Antagonists: Baseline Characteristics of a Mild to Moderate Persistent Asthma Population", Available at www.arraybiopharma.com, 13 May 2013 (2013-05-13), XP055188070, Retrieved from the Internet: URL:http://www.arraybiopharma.com/files/8113/9810/8031/PubAttachment567.pdf [retrieved on 2015-05-07] | 1-17 |
| Y | abstract; figure 3 section 'methods' Retrieved at www.arraybiopharma.com, select 'publications', select by 'programme': ARRY-502 / Asthma. Second entry in the list. The poster was presented at the American Thoracic Society International Conference, which took place in May 2013. The document can also be retrieved at the website of the conference (http://conference.thoracic.org/2013/program).<br>----- | 18-45 |
| X | WO 2012/083132 A2 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]; ARRON JOSEPH R [US]; ERICK) 21 June 2012 (2012-06-21) | 1-8, 23-30 |
| Y | abstract; claims 1,21,23, paragraph [0070] paragraph [0323] - paragraph [0324] figures 4, 6, 13, 15; claims 1, 3, 4; paragraph 56, 292, 296-297; 346-350<br>----- | 18-22 |
| Y | WO 2012/158954 A1 (MEDIMMUNE LLC [US]; GOSSAGE DAVID [US]; KHATRY DEEPAK B [US]; GEBA GRE) 22 November 2012 (2012-11-22) abstract; claims 12-16, 25, 45, 72, 82; figures 6,8 paragraph [0194]<br>----- | 18-45 |

-/--

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/015806

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| T | Ian E Pavord: "Non-eosinophilic asthma and the innate immune response", Thorax, 1 March 2007 (2007-03-01), pages 193-194, XP055188188, DOI: 10.1136/thx.2006.065805 Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117160/?report=reader [retrieved on 2015-05-07] the whole document | 1-22 |
| X,P | Sally Wenzel ET AL: "Safety and Efficacy of ARRY-502, a Potent, Selective, Oral CRTh2 Antagonist, in Patients with Mild to Moderate Th2-Driven Asthma", , 1 March 2014 (2014-03-01), XP055188225, AAAAI Meeting, March 1, 2014; Abstract # 13 Retrieved from the Internet: URL:http://www.arraybiopharma.com/files/8013/9810/8036/PubAttachment596.pdf [retrieved on 2015-05-08] the whole document column to the right (4th column) Retrieved at www.arraybiopharma.com, select 'publications', select by 'programme': ARRY-502 / Asthma. First entry in the list. The poster was presented at the AAAAI Meeting, March 1, 2014; Abstract # 13. The document can also be retrieved at the website of the conference http://aaaai.confex.com/aaaai/2014/webprogram/Paper11265.html). | 1-22 |
| Y | ULVEN TROND ET AL: "Novel CRTH2 antagonists: a review of patents from 2006 to 2009", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 20, no. 11, 1 November 2010 (2010-11-01), pages 1505-1530, XP009142666, ISSN: 1354-3776 abstract; table 3 | 23-45 |

-/--

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/015806

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CHEVALIER E ET AL: "Cutting Edge: Chemoattractant Receptor-Homologous Molecule Expressed on TH2 Cells Play a Restricting Role on IL-5 Production and Eosinophil Recruitment", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 175, no. 4, 15 August 2005 (2005-08-15), pages 2056-2060, XP003008946, ISSN: 0022-1767 abstract<br>----- | 23-45 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/015806

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-45(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/** 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-22

   Methods involving Th2-driven allergic asthma by determining baseline FENO to be > 48 ppb in exhaled breath samples and administering a CRTh2 antagonist.

   ---

2. claims: 23-45

   Methods involving Th2-driven allergic asthma by determining the % eosinophil in a lymphocyte population to be > 5% in a peripheral blood sample, and administering a CRTh2 antagonist.

   ---

Continuation of Box II.2

Claims Nos.: 1-45(partially)

The present application contains 45 claims, of which 30 are independent. Group of inventions 1 contains 22 claims, 15 of which are independent. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25).

The search was based on the subject-matter that, as far as can be understood, could reasonably be expected to be claimed later in the procedure, and the corresponding claims, namely:

- method of selecting patients that would benefit from treatment with a CRth2 antagonist.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/015806

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2009158426 A1 | 30-12-2009 | AR 072301 A1 | 18-08-2010 |
| | | AU 2009262274 A1 | 30-12-2009 |
| | | CA 2729217 A1 | 30-12-2009 |
| | | CN 102131794 A | 20-07-2011 |
| | | CN 103450138 A | 18-12-2013 |
| | | CO 6362002 A2 | 20-01-2012 |
| | | CR 20110037 A | 14-03-2011 |
| | | DK 2307397 T3 | 03-11-2014 |
| | | EP 2307397 A1 | 13-04-2011 |
| | | EP 2826774 A1 | 21-01-2015 |
| | | ES 2524314 T3 | 05-12-2014 |
| | | HK 1155735 A1 | 09-01-2015 |
| | | HR P20140988 T1 | 05-12-2014 |
| | | JP 2011526290 A | 06-10-2011 |
| | | JP 2014122241 A | 03-07-2014 |
| | | KR 20110027798 A | 16-03-2011 |
| | | NZ 590437 A | 27-07-2012 |
| | | PH 12014500079 A1 | 09-02-2015 |
| | | PT 2307397 E | 29-10-2014 |
| | | RU 2011102595 A | 27-07-2012 |
| | | SI 2307397 T1 | 28-11-2014 |
| | | TW 201022222 A | 16-06-2010 |
| | | TW 201427965 A | 16-07-2014 |
| | | US 2011105463 A1 | 05-05-2011 |
| | | US 2014005418 A1 | 02-01-2014 |
| | | US 2014221342 A1 | 07-08-2014 |
| | | UY 31938 A | 31-01-2011 |
| | | WO 2009158426 A1 | 30-12-2009 |
| WO 2009124090 A1 | 08-10-2009 | AU 2009231733 A1 | 08-10-2009 |
| | | CA 2718120 A1 | 08-10-2009 |
| | | CN 102232113 A | 02-11-2011 |
| | | EP 2271770 A1 | 12-01-2011 |
| | | EP 2631302 A2 | 28-08-2013 |
| | | JP 2011523350 A | 11-08-2011 |
| | | JP 2014204725 A | 30-10-2014 |
| | | KR 20100131003 A | 14-12-2010 |
| | | NZ 588853 A | 26-07-2013 |
| | | NZ 601815 A | 31-10-2014 |
| | | US 2011123530 A1 | 26-05-2011 |
| | | WO 2009124090 A1 | 08-10-2009 |
| WO 2012083132 A2 | 21-06-2012 | AR 084342 A1 | 08-05-2013 |
| | | AU 2011343570 A1 | 02-05-2013 |
| | | CA 2817380 A1 | 21-06-2012 |
| | | CN 103688171 A | 26-03-2014 |
| | | EP 2652498 A2 | 23-10-2013 |
| | | JP 2014506321 A | 13-03-2014 |
| | | JP 2015091812 A | 14-05-2015 |
| | | KR 20130082508 A | 19-07-2013 |
| | | KR 20150008919 A | 23-01-2015 |
| | | KR 20150014985 A | 09-02-2015 |
| | | RU 2013132733 A | 27-01-2015 |
| | | SG 190885 A1 | 31-07-2013 |
| | | TW 201250244 A | 16-12-2012 |
| | | US 2012156194 A1 | 21-06-2012 |
| | | US 2014044645 A1 | 13-02-2014 |
| | | US 2014044702 A1 | 13-02-2014 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/015806

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| | | WO 2012083132 A2 | 21-06-2012 |
| WO 2012158954 A1 | 22-11-2012 | EP 2710370 A1 | 26-03-2014 |
| | | US 2012328606 A1 | 27-12-2012 |
| | | WO 2012158954 A1 | 22-11-2012 |