Abstract: The present patent application relates to a pharmaceutical composition comprising a benzofuropyridine PDE4 enzyme inhibitor and a leukotriene receptor antagonist; a process for preparing such composition; and its use in treating a respiratory disorder in a subject.
TECHNICAL FIELD

The present patent application relates to a pharmaceutical composition comprising a benzofuropyridine phosphodiesterase-4 ("PDE4") enzyme inhibitor and a leukotriene receptor antagonist. Particularly, the application relates to a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt (as a PDE4 enzyme inhibitor) and a leukotriene receptor antagonist; a process for preparing such composition; and its use in treating a respiratory disorder in a subject.

BACKGROUND

Many individuals suffer from respiratory disorders related to airway inflammation, including a number of severe lung diseases such as asthma and chronic obstructive pulmonary disease ("COPD"). Leukotriene receptor antagonists are believed to act at the leukotriene receptors in tissues such as the bronchial smooth muscles and block the actions of leukotrienes at the receptor site. Leukotriene receptor antagonists (such as montelukast and zafirlukast) are used to treat certain respiratory disorders.

Montelukast sodium is chemically \( [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethyl]phenyl] -3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl]thio]methyl] cyclopropaneacetic acid, monosodium salt.\) Montelukast sodium is commercially available as SINGULAIR® as 10mg tablets, 4mg and 5mg chewable tablets and as 4mg oral granules (marketed by Merck and Co., Inc.) in the United States. Montelukast sodium is indicated for the prophylaxis and chronic treatment of
asthma, for prevention of exercise-induced bronchoconstriction and for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis and perennial allergic rhinitis).

Zafirlukast is chemically 4-(5-cyclopentyloxy-carbonylamino-l-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. Zafirlukast is commercially available as ACCOLATE® as 10mg and 20mg oral tablets (marketed by AstraZeneca Pharmaceuticals LP) in the United States. Zafirlukast is indicated for the prophylaxis and chronic treatment of asthma.

EP 1429843B1 discloses a combination of roflumilast with montelukast sodium, where the inhibitory effects of roflumilast and montelukast sodium on bronchoconstriction are found to be merely additive.

US 6528527 discloses a composition comprising N-(3,5-dichloropyrid-4-yl)-cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound and a leukotriene antagonist.

WO 2009052624 discloses a medicinal preparation comprising montelukast acid and a second active agent selected from a PDE4 enzyme inhibitor (specifically N-cyclopropyl-1-[3-(1-oxido-3-pyridinylethynyl)phenyl]-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxamide) and an inhaled corticosteroid.

There still exists a need for an improved therapeutic treatment for respiratory disorders like asthma, COPD and rhinitis.

SUMMARY

The present invention relates to use of a benzofuropyridine PDE4 enzyme inhibitor and a leukotriene receptor antagonist. A preferred PDE4 enzyme inhibitor is 3,5-dichloro-4-(6-difluoromethoxybenzo [4,5]furo[3,2-c]pyridin-9-ylcarboxamido)-l-pyridiniumlate) [INN: Revamilast] or its pharmaceutically acceptable salt. The inventors have surprisingly found that revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist (particularly, montelukast or its pharmaceutically acceptable salt) act synergistically in the treatment of respiratory disorders, and are more effective and provide better therapeutic value than treatment with either active ingredient alone.
In an embodiment, the present invention relates to a pharmaceutical composition comprising a synergistic effective amount revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist. Preferably, the pharmaceutical composition comprises a synergistic effective amount of (a) revamilast or its pharmaceutically acceptable salt and (b) a leukotriene receptor antagonist selected from montelukast, zafirlukast, and pharmaceutically acceptable salts thereof (e.g., for the treatment of a respiratory disorder). The pharmaceutical composition may be administered to improve lung function, reduce airway hyper-reactivity/resistance, or reduce airway exacerbations in a subject having a respiratory disorder.

In another embodiment, the weight ratio of revamilast or its pharmaceutically acceptable salt to the leukotriene receptor antagonist may range from about 1:0.1 to about 1:30, or from about 1:0.5 to about 1:20. Alternatively, the weight ratio is from about 1:0.5 to about 1:15, from about 1:0.67 to about 1:10, from about 1:1 to about 1:8, from about 1:1.5 to about 1:6, from about 1:1 to about 1:5, from about 1:2 to about 1:5, or from about 1:2 to about 1:4.

In a preferred embodiment, the pharmaceutical composition of the present invention is suitable for oral administration to a subject, and may optionally comprise one or more pharmaceutically acceptable excipients.

In the context of present invention, the effective amount of revamilast or its pharmaceutically acceptable salt may range from about 0.1 mg to about 30 mg, and preferably from about 1 mg to about 20 mg, such as from about 2 mg to about 10 mg.

In one embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt. The weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may range from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5. The composition can comprise from about 1 mg to about 20 mg, or from about 2 mg to about 10 mg of revamilast or its
pharmaceutically acceptable salt, and from about 1 mg to 30 mg of montelukast or its pharmaceutically acceptable salt. Preferably, such composition comprises about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg or 7mg or 8mg or 9mg or 10mg of revamilast or its pharmaceutically acceptable salt. In one aspect of this embodiment, the composition is a fixed dose combination formulation. In yet another aspect, the amounts of revamilast and montelukast in the composition are sufficient to exhibit synergy for the treatment of a respiratory disorder, for example, by improvement in declined lung function in a subject.

In a specific embodiment, the present invention relates to a fixed dose pharmaceutical composition for oral administration comprising about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg, or 8 mg, or 10 mg of montelukast or its pharmaceutically acceptable salt.

In another embodiment, the invention relates to a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to zafirlukast or its pharmaceutically acceptable salt ranges from about 1:1 to about 1:30, or from about 1:1.6 to about 1:20. The composition comprises from about 1 mg to about 20 mg, or from about 2 mg to about 10 mg of revamilast or its pharmaceutically acceptable salt, and from about 1 mg to 50 mg of zafirlukast or its pharmaceutically acceptable salt. Preferably, the composition comprises about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg or 7mg or 8mg or 9mg or 10mg of revamilast or its pharmaceutically acceptable salt. In one aspect of this embodiment, the composition is a fixed dose combination formulation. In yet another aspect, the amounts of revamilast and zafirlukast in the composition are sufficient to exhibit synergy for the treatment of a respiratory disorder by improvement in declined lung function in a subject.

In a specific embodiment, the present invention relates to a fixed dose pharmaceutical composition for oral administration comprising about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and
about 5mg or 10mg or 15mg or 20mg of zafirlukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of a respiratory disorder by improvement in declined lung function in a subject. Preferably, the respiratory disorder is asthma, COPD, or exercise-induced bronchoconstriction.

The present invention also provides a method of treating a respiratory disorder in a subject, comprising administering to the subject a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist. Preferably, a synergistic effective amount of the revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist are administered orally. In one embodiment, the revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist are incorporated into a single pharmaceutical composition (e.g., an oral dosage form). The combination of revamilast and the leukotriene receptor antagonist preferably exhibits synergy for the treatment of the respiratory disorder by improvement in declined lung function in a subject.

Another embodiment is a method of treating a respiratory disorder in a subject, comprising administering to the subject one or more pharmaceutical compositions of the present invention. In one preferred embodiment, the pharmaceutical composition is orally administered.

The present invention also provides a method of treating a respiratory disorder in a subject, comprising orally administering to the subject a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt. The weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may range from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5. The combination of revamilast and montelukast preferably exhibits synergy for the treatment of the respiratory disorder by improvement in declined lung function in a subject. Preferably, the respiratory disorder is asthma, COPD, exercise-induced bronchoconstriction or allergic rhinitis. In one embodiment, the revamilast or its pharmaceutically acceptable salt and the
montelukast or its pharmaceutically acceptable salt are incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

The present invention also provides a method of improving lung function in a subject having a respiratory disorder, comprising orally administering to the subject a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt. The weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may range from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5. In one embodiment, the revamilast or its pharmaceutically acceptable salt and the montelukast or its pharmaceutically acceptable salt are incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

The present invention also provides a method of treating a respiratory disorder in a subject, comprising orally administering to the subject a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to zafirlukast or its pharmaceutically acceptable salt ranges from about 1:1 to about 1:30, or from about 1:1.6 to about 1:20, or from about 1:2 to about 1:10. The combination of revamilast and zafirlukast preferably exhibits synergy for the treatment of the respiratory disorder by improvement in declined lung function. Preferably, the respiratory disorder is asthma, COPD, or exercise-induced bronchoconstriction. In one embodiment, the revamilast or its pharmaceutically acceptable salt and the zafirlukast or its pharmaceutically acceptable salt are incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

In a specific embodiment, the present invention relates to a method of treating asthma, COPD, or exercise-induced bronchoconstriction in a subject, comprising administering to the subject about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg or 8mg, or 10mg of montelukast or its pharmaceutically acceptable salt, wherein the combination exhibits synergy in terms of improvement
in declined lung function in a subject. The revamilast and montelukast may be incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

In a preferred embodiment, the present invention relates to a method of treating asthma, or COPD in a subject, comprising administering to the subject about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 5mg or 10mg or 15mg or 20mg of zafirlukast or its pharmaceutically acceptable salt, wherein the combination exhibits synergy in terms of improvement in declined lung function in a subject. The revamilast and zafirlukast may be incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

Another embodiment is a kit containing a unit dose formulation comprising revamilast or its pharmaceutically acceptable salt and another unit dose formulation comprising montelukast or its pharmaceutically acceptable salt. Preferably, the amounts of revamilast and montelukast are sufficient to exhibit synergy for the treatment of a respiratory disorder, for example, by improvement in declined lung function in a subject.

Yet another embodiment of this invention is a kit containing a unit dose formulation comprising revamilast or its pharmaceutically acceptable salt and another unit dose formulation comprising zafirlukast or its pharmaceutically acceptable salt. The amounts of revamilast and zafirlukast can be those mentioned above. Preferably, the amounts of revamilast and zafirlukast are sufficient to exhibit synergy for the treatment of a respiratory disorder, for example, by improvement in declined lung function in a subject.

The present invention also relates to use of revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist in the preparation of a pharmaceutical composition of the present invention, for example, for treating a respiratory disorder, such as asthma or COPD.

The present invention also relates to use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt
and montelukast or its pharmaceutically acceptable salt for treatment of a respiratory disorder (such as asthma, COPD, exercise-induced bronchoconstriction or allergic rhinitis) in a subject. In one preferred embodiment, the pharmaceutical composition is for improving lung function in a subject. The weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may range from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5, for treatment of a respiratory disorder (such as asthma, COPD, exercise-induced bronchoconstriction or allergic rhinitis) in a subject. The composition may exhibit synergy for the treatment of the respiratory disorder by improvement in declined lung function in a subject.

The present invention also relates to use of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt for treatment of a respiratory disorder (such as asthma, COPD, or exercise-induced bronchoconstriction) in a subject. The weight ratio of revamilast or its pharmaceutically acceptable salt to zafirlukast or its pharmaceutically acceptable salt may range from about 1:1 to about 1:30, or from about 1:1.6 to about 1:20, or from about 1:2 to about 1:10. The composition may exhibit synergy for the treatment of the respiratory disorder by improvement in declined lung function in a subject.

In a specific embodiment, the present invention relates to a fixed dose pharmaceutical composition for oral administration comprising about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 5mg or 10mg or 15mg or 20mg of zafirlukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of a respiratory disorder by improvement in declined lung function in a subject. Preferably, the respiratory disorder is asthma, COPD, or exercise-induced bronchoconstriction.
In the context of present invention, the effective amount of the active ingredients can be administered as a single dose or in divided doses, either once daily or two, three, or four times a day.

Revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist (such as montelukast, zafirlukast or a pharmaceutically acceptable salt thereof) may be administered in a single dosage form or in separate dosage forms. Revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist may be administered by the same or different routes and either separately, simultaneously, or sequentially. In one preferred embodiment, both, revamilast (or its pharmaceutically acceptable salt) and the leukotriene receptor antagonist are administered orally.

The respiratory disorder may be airway inflammation, asthma, emphysema, bronchitis, COPD, exercise induced bronchoconstriction, sinusitis, rhinitis, or cough. Preferably, the respiratory disorder is asthma, COPD or allergic rhinitis.

In a specific embodiment, the present invention relates to a method of treating asthma, COPD, or exercise-induced bronchoconstriction in a subject, comprising administering to the subject a pharmaceutical composition comprising about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg, or 8mg, or 10mg of montelukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy in terms of improvement in declined lung function in a subject.

In a preferred embodiment, the present invention relates to a method of treating asthma, or COPD in a subject, said method comprising administering to the subject about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 5mg or 10mg or 15mg or 20mg of zafirlukast or its pharmaceutically acceptable salt, wherein the combination of revamilast and zafirlukast exhibits synergy in terms of improvement in declined lung function in a subject.

In another embodiment, the present invention provides a process for preparing a pharmaceutical composition comprising revamilast or its
pharmaceutically acceptable salt, a leukotriene receptor antagonist and, optionally, a pharmaceutically acceptable excipient, wherein the composition is in the form of a fixed dose combination formulation. The process comprises admixing revamilast or its pharmaceutically acceptable salt with the leukotriene receptor antagonist and, optionally, a pharmaceutically acceptable excipient. In one embodiment, the revamilast and leukotriene receptor antagonist are in intimate contact with each other in the composition.

Alternately, the process comprises formulating revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist in a pharmaceutical composition (such as an oral dosage form) in such a way that revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist are not in intimate contact with each other.

**BRIEF DESCRIPTION OF FIGURE**

Figure 1 is a bar graph showing the effect of revamilast and montelukast on allergen induced decline in lung function in ovalbumin sensitized guinea pigs.

**DETAILED DESCRIPTION**

**Definitions:**

The terms used herein are defined as follows. If a definition set forth in the present application and a definition set forth earlier in a provisional application from which priority is claimed are in conflict, the definition in the present application shall control the meaning of the terms.

The term "effective amount" or "therapeutically effective amount" denotes an amount of an active ingredient or active ingredients that, when administered to a subject for treating a respiratory disorder, produces an intended therapeutic benefit in the subject. The therapeutically effective amount of revamilast or its pharmaceutically acceptable salt may range from about 0.1 mg to about 30 mg, or from about 1 mg to about 20 mg, and preferably from about 2 mg to about 10 mg.

The therapeutically effective amount of montelukast or its pharmaceutically acceptable salt (e.g., montelukast sodium) may range from about 0.1 mg to about 50
mg, and preferably from about 1 mg to about 30 mg. The therapeutically effective amount of zafirlukast or its pharmaceutically acceptable salt to be administered may range from about 1 mg to about 100 mg and preferably from about 5 mg to about 50 mg.

The term "active ingredient" (used interchangeably with "active" or "active substance" or "drug") as used herein includes revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist (such as montelukast, zafirlukast or a pharmaceutically acceptable salt thereof).

By "pharmaceutically acceptable salt", it is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit to risk ratio, and effective for their intended use. Representative acid addition salts include hydrochloride, hydrobromide, sulphate, bisulphate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, mesylate, citrate, malate, fumarate, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, and lauryl sulphate salts. Representative alkali or alkaline earth metal salts include sodium, calcium, potassium and magnesium salts.

The term "treating" or "treatment" as used herein includes the prophylaxis, mitigation, prevention, amelioration, control, relief or suppression of a disorder or its symptoms.

The term "synergistic" or "synergy", as used herein, refers to a combination exhibiting an effect greater than would be expected from the sum of the effects of the individual components of the combination alone. The term "synergistic" or "synergy" with regard to the combination of revamilast or its pharmaceutically acceptable salt with a leukotriene receptor antagonist (preferably montelukast, zafirlukast or a pharmaceutically acceptable salt thereof) which is used in the treatment of a respiratory disorder (for example, in the form of a pharmaceutical composition, a combination product or a kit according to the invention) refers to an efficacy for the treatment of the respiratory disorder that is greater than would be expected from the sum of their individuals effects. The advantages for the
synergistic combinations of the present invention include, but are not limited to,
lowering the required dose of one or more of the active compounds of the
combination, reducing the side effects of one or more of the active compounds of the
combination and/or rendering one or more of the active compounds more tolerable
to the subject in need of treatment of the respiratory disorder.

The term "respiratory disorder" includes any condition or disease related to
respiration or the respiratory system and includes, but is not limited to, airway
inflammation, asthma, emphysema, bronchitis, COPD, exercise induced
bronchoconstriction, sinusitis, rhinitis (including allergic rhinitis) and cough.

Preferably, the respiratory disorder is asthma, COPD, exercise-induced
bronchoconstriction or rhinitis.

It is believed that in a subject who has a respiratory disorder (e.g., asthma or
COPD), the lung function is declined or compromised. The decline in lung function
is influenced by age, gender, disease duration and disease severity. Progressive
decline in lung function of such subject is well recognized, but not fully explained.

In the context of present invention, the term "improving lung function" or
"improvement in lung function" refers to enhancing or improving the declined lung
function in a subject having a respiratory disorder by one or more of the following
mechanisms, but not limited to, - inhibiting bronchoconstriction, preventing
bronchoconstriction, inducing bronchodilation, reducing airway hyper-
reactivity/responsiveness by suppression of airway inflammation , or reducing
airway exacerbations - in said subject.

Lung function generally means how well one's lungs work. Various tests are
used to assess the lung function in human. For example, spirometry, which is the
most commonly used lung function test, measures specifically the amount (volume)
and/or speed (flow) of air that can be inhaled and exhaled. Typically, spirometric
measurements involve determination on certain functional parameters such as forced
expiratory volume (FEV), forced vital capacity (FVC), forced expiratory flow, peak
expiratory flow, and the like.

Asthma and COPD are major chronic diseases related to airway obstruction.
The Global Initiative for Chronic Obstructive Lung Disease provides guidelines for
the distinction between asthma and COPD. Asthma is believed to be a chronic inflammatory disease wherein the airflow limitation is more or less reversible while it is more or less irreversible in the case of COPD. Asthma among other things is believed to be triggered by inhalation of sensitizing agents (like allergens) unlike noxious agents (like particles and certain gases) in the case of COPD.

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEVi), peak expiratory flow rate and severity (e.g., acute, intermittent, mild persistent, moderate persistent, and severe persistent). Asthma may also be classified as allergic (extrinsic) or non-allergic (intrinsic), based on whether symptoms are precipitated by allergens or not. Asthma can also be categorized according to following types viz., nocturnal asthma, bronchial asthma, exercise induced asthma, occupational asthma, seasonal asthma, silent asthma, and cough variant asthma.

Asthma in humans typically manifests as bronchoconstrictive responses namely early allergen response (EAR) and late asthmatic response (LAR). EAR occurs 15-30 minutes post allergen exposure whereas LAR occurs after 3-5 hours, reaches maximum at 6-12 hours and may persist up to 24 hours. (Clin. Allergy. 1977, 7:503-513; Clin Exp. Allergy. 1991, 21:3-7.) These bronchoconstrictive responses are believed to result in declined lung/pulmonary function. Such lung function decline can also be simulated in rodent models of allergic asthma and is measured as Penh (enhanced pause). These animal models are characterised by inflammatory infiltration and a biphasic bronchoconstrictor response (EAR and LAR) (Thorax 2012; 67:19-25). In conscious animals, an EAR is followed by LAR and both can be subjectively evidenced by audible (wheeze) and visual signs of respiratory distress associated with quantifiable changes in lung function that can be measured non-invasively as penh (Am. J. Respir. Crit. Care Med. 2005;172: 962 -71). Thus increased Penh is an indicator of decreased pulmonary/lung function during EAR and LAR and is a close correlate of lung resistance (Am. J. Respir.Crit. Care Med. 1997, 156:766-775). Generally, if the Penh is significantly reduced (p < 0.05 or less) in the drug treated animals as
compared to the vehicle treated animals, then the observed effect is considered as significant improvement in the lung function in animals.

It is believed that reduction of eosinophil count and increase in FEV1 are important components of the treatment of respiratory disorders such as asthma. Ulrik CS, 1995 (Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma; Clinical and Experimental Allergy; 1995, Volume 25, pages 820-827) discloses the relationship between eosinophil count and severity of asthmatic symptoms. It describes that in childhood and adulthood subjects, there exists an inverse correlation between number of eosinophils and FEV1% (r = -0.75, P < 0.001, and r = -0.80, P < 0.001, respectively).

COPD, also known as chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), or chronic obstructive respiratory disease (CORD), is believed to be the co-occurrence of chronic bronchitis (characterized by a long-term cough with mucus) and emphysema (characterized by destruction of the lungs over time), a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath. An acute exacerbation of COPD is a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically lasts for several days and is believed to be triggered by an infection with bacteria or viruses or by environmental pollutants. Based on the FEVi values, COPD can be classified as mild, moderate, severe and very severe.

The term "rhinitis" encompasses all types of rhinitis such as seasonal allergic rhinitis, perennial rhinitis, non-allergic (vasomotor) rhinitis, infectious rhinitis, persistent rhinitis and chronic rhinitis, including its associated symptoms like rhinorrhea, nasopharyngitis, nasal congestion, scratchy throat and sneezing.

Rhinitis as described herein is characterized by irritation and inflammation of some internal areas of the nose. It is caused by chronic or acute inflammation of the mucous membrane of the nose due to viruses, bacteria or irritants. The inflammation results in the generation of excessive amounts of mucous causing nasal congestion.

Rhinitis is categorized into three types: infective, non-allergic (vasomotor) and allergic rhinitis. Allergic rhinitis is caused by allergens such as dust or pollen which,
when inhaled by the sensitized individuals, trigger antibody production. The antibodies bind to mast cells (containing histamine), which upon stimulation cause itching (urticaria), swelling and mucous production. Thus, it leads to inflammation of the mucous membranes of the nose, eyes, eustachian tubes, middle ear, sinuses, and pharynx. Inflammation of the mucous membranes is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E (IgE)-mediated response to an extrinsic protein.

The term "subject" includes mammals, such as humans and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife). Preferably, the subject is a human.

By the term "pharmaceutically acceptable excipients", it is meant any of the components of a pharmaceutical composition other than the actives and which are approved by regulatory authorities or are generally regarded as safe for human or animal use.

PDE4 Enzyme Inhibitors:

Suitable PDE4 enzyme inhibitors include benzofuropyridine PDE4 enzyme inhibitors, such as those described in International Publication No. WO 2006/064355, which is incorporated herein by reference in its entirety.

In one embodiment, the compound is 3, 5-dichloro-4-(6 difluoromethoxy benzo [4, 5] furo [3, 2-c] pyridin-9-ylcarboxamido)-l-pyridiniumolate) [INN: REVAMILAST] or its pharmaceutically acceptable salt. All stereoisomers of the compound, including enantiomers and diastereomers are separately contemplated.

Revamilast has a molecular weight of 440.185 and molecular formula C_{18}H_{9}Cl_{2}F_{2}N_{3}O_{4} with the following structure:
In healthy volunteers, the median $t_{\text{max}}$ (time to reach maximum plasma concentration) of revamilast was from about 1 to about 3 hours following an oral administration. The mean terminal elimination half-life of revamilast was found to be ranging from about 28 to about 36 hours in healthy volunteers across the doses studied. The elimination pattern was consistent following repeat administration as well, indicating linear pharmacokinetics of revamilast. The terminal elimination half-life ranged from about 26 to about 46 hours in healthy volunteers across the studies including single and repeat dose administration of revamilast. The in-vitro human PDE4 IC$_{50}$ (quantity needed to inhibit PDE4 by half) of revamilast is 2.69 nM. The $t_{\text{PDE4i}}$ (total PDE4 inhibition) estimated at 0.5, 2, 4, 6 and 8 mg doses of revamilast were 0.55; 2.4; 4.4; 6.6 and 8.3, respectively at once daily dosing in healthy volunteers.

**Leukotriene receptor antagonists:**

Leukotrienes are a class of inflammatory mediators derived from arachidonic acid that are believed to act at the leukotriene receptors and bring about inflammatory and bronchoconstrictive events in the airway. The major leukotrienes are the cysteinyl leukotrienes (Cys-LTs) - LTC4, LTD4 and LTE4. Of these, LTE4 and LTD4 are believed to be the more potent mediators of airway inflammation. The receptors for these mediators have been identified as Cys-LT receptor Type-1 (Cys-LT1) and Cys-LT receptor Type-2 (Cys-LT2). The Cys-LT receptors are also believed to induce airway eosinophilia in patients with asthma. Antagonists to these receptors are thus believed to alleviate the airway inflammation and bronchoconstriction brought about by the activation of the receptors by the leukotrienes. These antagonists find use in indications like early and late response to allergen and exercise-induced asthma. Suitable leukotriene receptor antagonists include, but are not limited to, montelukast, zafirlukast, pranlukast, tipelukast, masilukast, iralukast, cinalukast, tomelukast, verlukast, ablukast, poblukast, sulukast, and their salts. Preferably, the leukotriene receptor antagonist is montelukast, zafirlukast or a pharmaceutically acceptable salt thereof. Preferred
leukotriene receptor antagonists include, but are not limited to, montelukast, zafirlukast or a pharmaceutically acceptable salt thereof.

**PDE4 enzyme inhibitor / Leukotriene receptor antagonist combination:**

The present invention relates to a pharmaceutical composition comprising a benzofuropyridine PDE4 enzyme inhibitor and a leukotriene receptor antagonist. A preferred PDE4 enzyme inhibitor is 3, 5-dichloro-4-(6-difluoromethoxybenzo [4, 5] furo [3, 2-c] pyridin-9-ylcarboxamido)-l-pyridiniumolate) [INN: Revamilast] or its pharmaceutically acceptable salt. The inventors have surprisingly found that revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist (such as montelukast or its pharmaceutically acceptable salt) act synergistically in the treatment of respiratory disorders, and are more effective and provide better therapeutic value than treatment with either active ingredient alone.

In another embodiment, the present invention relates to a pharmaceutical composition for improving declined lung function, reducing airway hyper-reactivity/resistance, or reducing airway exacerbations comprising a synergistic effective amount of (a) revamilast or its pharmaceutically acceptable salt and (b) a leukotriene receptor antagonist selected from montelukast, zafirlukast, and pharmaceutically acceptable salts thereof.

In another embodiment, the weight ratio of revamilast or its pharmaceutically acceptable salt to the leukotriene receptor antagonist ranges from about 1:0.1 to about 1:30, or from about 1:0.5 to about 1:20. Alternatively, the weight ratio is from about 1:0.5 to about 1:15, from about 1:0.67 to about 1:10, from about 1:1 to about 1:8, from about 1:1.5 to about 1:6, from about 1:1 to about 1:5, from about 1:2 to about 1:5, or from about 1:2 to about 1:4.

In a preferred embodiment, the pharmaceutical composition of the present invention is suitable for oral administration to a subject, and may optionally comprise one or more pharmaceutically acceptable excipients.

In the context of present invention, the effective amount of revamilast or its pharmaceutically acceptable salt may range from about 0.1 mg to about 30 mg, and preferably from about 1 mg to about 20 mg, such as from about 2 mg to about 10
mg. Preferably, the discrete dosage strengths of revamilast or its pharmaceutically acceptable salt may be about 0.1 mg, 0.2 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 12 mg, 15 mg and 20 mg.

In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt.

The therapeutically effective amount of montelukast or its pharmaceutically acceptable salt (e.g., montelukast sodium) to be administered may range from about 0.1 mg to about 50 mg, and preferably from about 1 mg to about 30 mg. Preferably, the discrete dosage strengths of montelukast or its salt may be 2 mg, 4 mg, 5 mg, or 10 mg.

In one embodiment, the present invention relates to a pharmaceutical composition comprising from about 0.1 mg to about 30 mg, or from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt and from about 0.1 mg to about 50 mg, or from about 1 mg to about 30 mg of montelukast or its pharmaceutically acceptable salt.

In an embodiment, the present invention relates to a pharmaceutical composition for oral administration, wherein the composition includes from about 1 mg to about 10 mg of revamilast or its pharmaceutically acceptable salt and about 2 mg to about 10 mg of montelukast or its pharmaceutically acceptable salt.

The present invention also provides a method of treating a respiratory disorder in a subject, comprising orally administering to the subject a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5, and wherein the combination of revamilast and montelukast exhibits synergy for the treatment of the respiratory disorder by improvement in declined lung function. Preferably, the
respiratory disorder is asthma, COPD, exercise-induced bronchoconstriction or allergic rhinitis. In one embodiment, the revamilast or its pharmaceutically acceptable salt and the montelukast or its pharmaceutically acceptable salt are incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

The present invention also provides a method of improving lung function in a subject having a respiratory disorder, said method comprising administering to the subject the pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5. The typical weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may be about 1:0.83, 1:1.25, 1:2.5, 1:1.67, or 1:3.3.

The present invention also relates to use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5, for treatment of a respiratory disorder (such as asthma, COPD, exercise-induced bronchoconstriction or allergic rhinitis) in a subject. The composition preferably exhibits synergy for the treatment of the respiratory disorder by improvement in declined lung function in a subject.

The present invention also relates to use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of
revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5, for improving lung function in a subject having a respiratory disorder.

In a specific embodiment, the present invention relates to a fixed dose pharmaceutical composition for oral administration comprising about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg, or 8mg, or 10 mg of montelukast or its pharmaceutically acceptable salt. The composition preferably exhibits synergy for the treatment of a respiratory disorder by improvement in declined lung function in a subject.

In another embodiment, the invention relates to a pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to zafirlukast or its pharmaceutically acceptable salt ranges from about 1:1 to about 1:30, or from about 1:1.6 to about 1:20. The composition may comprise from about 1 mg to about 20mg, or from about 2 mg to about 10 mg of revamilast or its pharmaceutically acceptable salt, and from about 1 mg to 50 mg of zafirlukast or its pharmaceutically acceptable salt. Preferably, the composition comprises about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg or 7mg or 8mg or 9mg or 10mg of revamilast or its pharmaceutically acceptable salt. In an aspect of this embodiment, the composition is a fixed dose combination formulation. In yet another aspect, the amounts of revamilast and zafirlukast in the composition are sufficient to exhibit synergy for the treatment of a respiratory disorder by improvement in declined lung function in a subject.

Another embodiment is a kit containing a unit dose formulation comprising revamilast or its pharmaceutically acceptable salt and another unit dose formulation comprising zafirlukast or its pharmaceutically acceptable salt. Preferably, the amounts of revamilast and zafirlukast are sufficient to exhibit synergy for the
treatment of a respiratory disorder, for example, by improvement in declined lung function in a subject.

The therapeutically effective amount of zafirlukast or its pharmaceutically acceptable salt to be administered may range from about 1 mg to about 100 mg, and preferably from about 5 mg to about 50 mg. Preferably the discrete dosage strengths of zafirlukast or its salt may be 10 mg or 20 mg or 40 mg.

The optimal dose of the active ingredients can vary as a function of the severity of the disease, route of administration, composition type, the patient body weight, the age and the general state of mind of the patient, and the response to the active ingredients.

In the context of present invention, the effective amount of the active ingredients can be administered as a single dose or in divided doses, either once daily or two, three, or four times a day.

Revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist (such as montelukast, zafirlukast or a pharmaceutically acceptable salt thereof) may be administered in a single dosage form or in separate dosage forms. Revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist may be administered by the same or different routes and either separately, simultaneously, or sequentially. In one preferred embodiment, the actives are administered orally.

In the pharmaceutical composition as described herein, the active ingredients may be in the form of a single dosage form (i.e., fixed-dose formulation in which both the active ingredients are present together) or they may be formulated separately. The fixed dose formulation may be administered as a single dose or as divided doses. Multiple dosage forms (either divided doses of a fixed dose combination or as dosage forms containing separate active ingredients) may be part of the same therapeutic treatment, program or regimen. The pharmaceutical compositions may be administered either once daily or two, three, or four times a day. In one embodiment, the pharmaceutical composition of the present invention is in the form of a fixed dose combination formulation of revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist.
In another specific embodiment, the present invention relates to a pharmaceutical composition in the form of a fixed dose combination formulation comprising about 0.5mg or 1mg or 1.5mg or 2mg or 2.5 mg or 3mg or 3.5 mg or 4 mg or 4.5 mg or 5mg or 5.5 mg or 6 mg or 6.5 mg or 7mg or 7.5 mg or 8mg or 8.5 mg or 9 mg or 9.5 mg or 10mg or 12mg or 15mg or 20mg of revamilast or its pharmaceutically acceptable salt, and about 2 mg or 4 mg or 5 mg or 10 mg of montelukast or its pharmaceutically acceptable salt.

In another embodiment, the present invention relates to a pharmaceutical composition in the form of a fixed dose combination formulation comprising about 0.5mg or 1mg or 1.5mg or 2mg or 2.5 mg or 3mg or 3.5 mg or 4 mg or 4.5 mg or 5mg or 5.5 mg or 6 mg or 6.5 mg or 7mg or 7.5 mg or 8mg or 8.5 mg or 9 mg or 9.5 mg or 10mg or 12mg or 15mg or 20mg of revamilast or its pharmaceutically acceptable salt, and about 10 mg or 20 mg or 40 mg of zafirlukast or its pharmaceutically acceptable salt.

The pharmaceutical compositions of the present invention, such as those including revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt may further include one or more additional active agents.

The additional active agent may be selected from beta-2 agonists (e.g. salmeterol, salbutamol, indacaterol, formoterol, bambuterol or a salt thereof), glucocorticoids (e.g., fluticasone, budesonide, beclomethasone, flunisolide, dexamethasone, ciclesonide, triamcinolone, mometasone, prednisone, prednisolone, methylprednisolone or a salt thereof), or histamine receptor antagonist (e.g., cetirizine, levocetirizine, azelastine, astemizole, loratadine, rupatadine, fexofenadine, desloratadine, terfenadine or a salt thereof).

The pharmaceutical composition of the present invention may be administered orally, nasally, intra-tracheally, parenterally, transdermally, transmucosal, inhalation or by any other route that a physician or a health-care provider may determine to be appropriate. Preferably, the pharmaceutical composition is administered by the oral or the inhalation route.
The pharmaceutical compositions of the invention include those for oral, parenteral, intra-tracheal, transdermal, transmucosal and nasal administration, or by inhalation route among others. Preferably, pharmaceutical composition of present invention is for oral administration or by inhalation administration. In a preferred embodiment, both the active ingredients, e.g., revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist, are formulated as a pharmaceutical composition suitable for oral administration.

The pharmaceutical compositions for oral administration may be in conventional forms, for example, tablets, capsules, granules (synonymously, "beads" or "particles" or "pellets"), suspensions, emulsions, powders, dry syrups, and the like. The capsules may contain granules, pellets, particles, mini-tablets, or mini-capsules containing the active ingredients.

The pharmaceutical compositions for parenteral administration include, but are not limited to, solutions for intravenous, subcutaneous or intramuscular injection/infusion, suspensions for intramuscular or subcutaneous injection, emulsions for intramuscular or subcutaneous injection and implants.

The pharmaceutical compositions for transdermal or transmucosal administration include, but are not limited to, patches, gels, creams, ointments and the like.

The amount of active ingredient that may be incorporated in the pharmaceutical composition may range from about 1% w/w to about 98% w/w; or from about 5% w/w to about 90% w/w.

As set forth above, the pharmaceutical composition may include at least one pharmaceutically acceptable excipient, which includes but is not limited to one or more of the following; diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents/viscosifying agents, surfactants, propellants, and solvents.

In one embodiment, the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist and, optionally, a pharmaceutically acceptable excipient. Preferably, the leukotriene
receptor antagonist is montelukast, zafirlukast, or its pharmaceutically acceptable salt.

In a specific embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising revamilast or its pharmaceutically acceptable salt, montelukast or its pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

In another specific embodiment, the present invention relates to a pharmaceutical composition for oral administration comprising a therapeutically effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable excipient.

In an embodiment, the present invention relates to a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist, wherein the combination exhibits synergy for the treatment of a respiratory disorder in a subject in need thereof.

Specifically, in an embodiment, the present invention relates to a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of a respiratory disorder in a subject in need thereof.

In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or a pharmaceutically acceptable salt and from about 2 mg to about 20 mg montelukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of respiratory disorder in a subject in need thereof.

In another specific embodiment, the present invention relates to a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of a respiratory disorder in a subject in need thereof.
In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising from about 1mg to about 20mg of revamilast or a pharmaceutically acceptable salt and from about 5 mg to about 40 mg zafirlukast or its pharmaceutically acceptable salt, wherein the composition exhibits synergy for the treatment of respiratory disorder in a subject in need thereof.

In another embodiment, the present invention relates to a pharmaceutical composition comprising an effective amount of revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist (such as monteleukast or a pharmaceutically acceptable salt thereof) for the treatment of a respiratory disorder in a subject in need thereof.

The respiratory disorder includes, but is not limited to, airway inflammation, asthma, emphysema, bronchitis, COPD, exercise induced bronchoconstriction, sinusitis, rhinitis (including allergic rhinitis), and cough. Preferably, the respiratory disorder is asthma COPD, exercise induced bronchoconstriction or rhinitis.

In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising from about 0.1mg to about 30mg of revamilast or its pharmaceutically acceptable salt and from about 1 mg to about 30 mg of montelukast or its pharmaceutically acceptable salt for the treatment of asthma, COPD, exercise-induced bronchoconstriction or rhinitis.

In a specific embodiment, the present invention relates to a pharmaceutical composition comprising from about 1mg to about 20mg of revamilast or its pharmaceutically acceptable salt and from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt for the treatment of asthma.

In another specific embodiment, the present invention relates to a pharmaceutical composition comprising from about 1mg to about 20mg of revamilast or its pharmaceutically acceptable salt and from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt for the treatment of COPD.

In yet another specific embodiment, the present invention relates to a pharmaceutical composition comprising from about 1mg to about 20mg of revamilast or its pharmaceutically acceptable salt and from about 2 mg to about 20
mg of montelukast or its pharmaceutically acceptable salt for the treatment of rhinitis (e.g., allergic rhinitis).

In a further specific embodiment, the present invention relates to a pharmaceutical composition comprising from about 1mg to about 20mg of revamilast or its pharmaceutically acceptable salt and from about 2mg to about 20mg of montelukast or its pharmaceutically acceptable salt for the treatment of exercise-induced bronchoconstriction.

In a specific embodiment, the present invention relates to a method of treating asthma, COPD, or exercise-induced bronchoconstriction in a subject, comprising administering to the subject about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg of revamilast or its pharmaceutically acceptable salt and about 1mg or 2mg or 3mg or 4mg or 5mg or 6mg, or 8mg, or 10mg of montelukast or its pharmaceutically acceptable salt, wherein the combination exhibits synergy in terms of improvement in declined lung function. The revamilast and montelukast may be incorporated into a single pharmaceutical composition (e.g., an oral dosage form).

In another embodiment, the present invention relates to a pharmaceutical composition comprising about 0.5mg or 1mg or 1.5mg or 2mg or 2.5 mg or 3mg or 3.5 mg or 4 mg or 4.5 mg or 5mg or 5.5 mg or 6 mg or 6.5 mg or 7mg or 7.5 mg or 8mg or 8.5 mg or 9 mg or 9.5 mg or 10mg or 12mg or 15mg or 20mg of revamilast or its pharmaceutically acceptable salt and about 2 mg, or 4 mg or 5 mg or 10 mg of montelukast or its pharmaceutically acceptable salt for the treatment of a respiratory disorder selected from asthma, COPD, exercise-induced bronchoconstriction or rhinitis in a subject in need thereof.

In yet another embodiment, the present invention relates to a pharmaceutical composition comprising about 0.5mg or 1mg or 1.5mg or 2mg or 2.5 mg or 3mg or 3.5 mg or 4 mg or 4.5 mg or 5mg or 5.5 mg or 6 mg or 6.5 mg or 7mg or 7.5 mg or 8mg or 8.5 mg or 9 mg or 9.5 mg or 10mg or 12mg or 15mg or 20mg of revamilast or its pharmaceutically acceptable salt to be administered orally and about 2 mg, or 4 mg or 5 mg or 10 mg of montelukast or its pharmaceutically acceptable salt to be administered orally for the treatment of a respiratory disorder selected from asthma, COPD, exercise-induced bronchoconstriction or rhinitis in a subject in need thereof.
In another embodiment, the present invention relates to a pharmaceutical composition comprising an effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt for the treatment of a respiratory disorder in a subject in need thereof.

Methods of Treatment:

The present invention also provides a method of treating a respiratory disorder in a subject, comprising administering to the subject a pharmaceutical composition of the present invention. Preferably, the pharmaceutical composition is orally administered. In one preferred embodiment, the composition includes a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist for the treatment of the respiratory disorder by improvement in declined lung function in a subject.

In another embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising an effective amount of revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist to a subject in need thereof. Preferably, the leukotriene receptor antagonist is montelukast or zafirlukast or its pharmaceutically acceptable salt.

In an embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, including administering to the subject a pharmaceutical composition comprising an effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt.

In a preferred embodiment, the present invention relates to a method of treating a respiratory disorder selected from asthma, COPD, exercise-induced bronchoconstriction or rhinitis in a subject, including administering to the subject a pharmaceutical composition comprising from about 0.1mg to about 30mg of revamilast or its pharmaceutically acceptable salt and from about 1mg to about 30mg montelukast or its pharmaceutically acceptable salt.
In a specific embodiment, the present invention relates to a method of treating asthma in a subject, including administering to the subject a pharmaceutical composition comprising from about 1 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt and from about 2 mg to about 20 mg of zafirlukast or its pharmaceutically acceptable salt.

In another specific embodiment, the present invention relates to a method of treating COPD in a subject, including administering to the subject a pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt and from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt.

In yet another specific embodiment, the present invention relates to a method of treating rhinitis in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt, from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt.

In a further specific embodiment, the present invention relates to a method of treating exercise-induced bronchoconstriction in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt, from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt.

In one embodiment, the present invention relates to a method of treating a respiratory disorder in a subject, including administering to the subject a pharmaceutical composition comprising an effective amount of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt.

In a preferred embodiment, the present invention relates to a method of treating a respiratory disorder selected from asthma, or COPD in a subject, including administering to the subject pharmaceutical composition comprising from about 0.1 mg to about 30 mg of revamilast or its pharmaceutically acceptable salt and from about 1 mg to about 50 mg of zafirlukast or its pharmaceutically acceptable salt.
In a specific embodiment, the present invention relates to a method of treating asthma in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt and from about 1 mg to about 40 mg of zafirlukast or its pharmaceutically acceptable salt.

In another specific embodiment, the present invention relates to a method of treating COPD in a subject, including administering to the subject pharmaceutical composition comprising from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt and from about 1 mg to about 40 mg of zafirlukast or its pharmaceutically acceptable salt.

The present invention also provides a method of improving lung function in a subject having a respiratory disorder, comprising administering to the subject the pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15, or from about 1:0.67 to about 1:10, or from about 1:1 to about 1:5. The weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt may be about 1:0.83, 1:1.25, 1:2.5, 1:1.67, or 1:3.3.

As contemplated herein, the active ingredients may be administered together in a single dosage form or they may be administered in different dosage forms. They may be administered at the same time or they may be administered either close in time or remotely, such as, where one drug is administered in the morning and the second drug is administered in the evening. The combination may be used prophylactically or after the onset of symptoms has occurred.

As discussed above, one or more additional active ingredients, such as beta-2 agonists, glucocorticoids, and histamine receptor antagonists can be administered with revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist.
Kits:
The present invention may be in the form of a kit comprising two or more separate formulations of revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist. The two or more separate formulations can be administered by the same or different routes, either separately, simultaneously, or sequentially, where the sequential administration is close in time or remote in time. For sequential administration, the period of time may be in the range from 10 minutes to 12 hours.

The two or more separate formulations may be administered in the same regimen or different regimen. For example one formulation may be administered once daily, whereas the second formulation may be administered either once or two, three, or four times a day.

In another embodiment, the present invention relates to a kit having a unit dose oral formulation comprising about 0.5 mg or 1 mg or 1.5 mg or 2 mg or 2.5 mg or 3 mg or 3.5 mg or 4 mg or 4.5 mg or 5 mg or 5.5 mg or 6 mg or 6.5 mg or 7 mg or 7.5 mg or 8 mg or 8.5 mg or 9 mg or 9.5 mg or 10 mg of revamilast or its pharmaceutically acceptable salt, and another unit dose oral formulation comprising about 2 mg or 4 mg or 5 mg or 10 mg of montelukast or its pharmaceutically acceptable salt.

In one embodiment, the present invention relates to a kit having a unit dose oral formulation comprising about 0.5 mg or 1 mg or 1.5 mg or 2 mg or 2.5 mg or 3 mg or 3.5 mg or 4 mg or 4.5 mg or 5 mg or 5.5 mg or 6 mg or 6.5 mg or 7 mg or 7.5 mg or 8 mg or 8.5 mg or 9 mg or 9.5 mg or 10 mg of revamilast or its pharmaceutically acceptable salt, and another unit dose oral formulation comprising about 10 mg or 20 mg or 40 mg of zafirlukast or its pharmaceutically acceptable salt.

Uses:
In another embodiment, the present invention relates to use of therapeutically effective amount of revamilast or its pharmaceutically acceptable salt and a leukotriene receptor antagonist in the preparation of a pharmaceutical composition for the treatment of a respiratory disorder in a subject in need thereof. Preferably,
the leukotriene receptor antagonist is montelukast or zafirlukast or its pharmaceutically acceptable salt.

Various animal models have been used for the evaluation of the therapeutic efficacy of drug candidates for respiratory disorders like asthma and COPD. For example, a commonly used strategy for evaluation of drug candidates in asthma is allergen sensitization and challenge method. The commonly used model is the ovalbumin (OVA) sensitization and challenge in mice. The model is believed to generate increased OVA-specific IgE and IgG1, eosinophilia (intraluminal, peribronchial, and perivascular). The model is also believed to increase recruitment of lymphocytes in the airways. The model may also generate Th2-type cytokines, and airway hyper-responsiveness is also observed many times.

A commonly used model for evaluation of drug candidates in COPD involves the chronic exposure of the animal (e.g., rats) to S02. Another model that can be used for evaluation of drug candidates in COPD involves the exposure of animals (e.g., rats) to lipopolysaccharide (LPS). Tobacco smoke is also used in animal models to induce conditions similar to COPD.

**Process of Preparing the Pharmaceutical Composition:**

In another embodiment, the present invention provides a process for preparing a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt, a leukotriene receptor antagonist and optionally a pharmaceutically acceptable excipient, wherein the composition is in the form of a fixed dose combination formulation. The process comprises admixing revamilast or its pharmaceutically acceptable salt with the leukotriene receptor antagonist and optionally a pharmaceutically acceptable excipient.

Alternately, the process comprises formulating revamilast or its pharmaceutically acceptable salt and the leukotriene receptor antagonist in such a way that they are not in intimate contact with each other.

In an embodiment, the present invention relates to a process for preparing a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt, montelukast or its salt and a pharmaceutically acceptable excipient.
In another specific embodiment, the present invention relates to a process for preparing a pharmaceutical composition comprising revamilast or its pharmaceutically acceptable salt, zafirlukast or its salt and a pharmaceutically acceptable excipient.

For example, the process for making the pharmaceutical composition may include (1) granulating either or both the active ingredients, combined or separately, along with pharmaceutically acceptable carriers so as to obtain granulates, and (2) converting these granulates into suitable dosage forms for oral administration. The typical processes involved in the preparation of the pharmaceutical compositions include various unit operations such as mixing, sifting, solubilizing, dispensing, granulating, lubricating, compressing, coating, and the like. These processes, as contemplated by a person skilled in the formulation art, have been incorporated herein for preparing the pharmaceutical compositions of the present invention.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

**EXAMPLES**

**EXAMPLE 1:** Effect of revamilast and montelukast on allergen induced decline in lung function (early allergen response) in ovalbumin (ova) induced bronchoconstriction in ova sensitized guinea pigs.

The effect of revamilast and montelukast on allergen induced decline in lung function during EAR was evaluated in ova sensitized male guinea pig. Guinea pigs (300-350g) were actively sensitized on Day 0 and Day 2 with intraperitonial (i.p.) injection of 5 mg and 10 mg respectively of Ovalbumin (OVA) per animal suspended in 0.1 ml saline + 0.1 ml 10% aluminum hydroxide. On day 21 the
animals were randomized based on bodyweight and grouped into five groups as mentioned in Table 1. Animals from group 2-5 were challenged with 1% ova nebulization (in normal saline) and those of group 1 with normal saline for 2 minutes using a non invasive Buxco apparatus. Revamilast (0.3mg/kg) and/or montelukast (1mg/kg) were administered orally 1.0 and 0.5 h respectively, prior to ova challenge. Control groups received 0.5% methyl cellulose. Exposure to inhaled OVA caused an increase in audible (wheeze) and visual signs of respiratory distress which were measured as Penh in all guinea pigs previously sensitised to the antigen. Ova induced bronchoconstriction during EAR was measured for a 30 minute period at each 5 minute interval. Each 5 minute average was recorded in the form of enhanced pause (penh). The effect of the treatment was expressed as percentage inhibition of penh with respect to the vehicle (ova-ova) control group taking into consideration the response of the ova-saline control group. Statistical analysis was performed using two way ANOVA followed by Bonferroni test. Graphpad Prism software was used for the analysis. Statistical significance was set at p <0.05.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment (n)</th>
<th>Montelukast (mg/kg, p.o.)</th>
<th>Revamilast (mg/kg, p.o.)</th>
<th>Exposure to 1% Ova</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ova-Sal control (5)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
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<td>2</td>
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<td>Revamilast (8)</td>
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The combination of revamilast and montelukast produced significantly superior inhibition of ovalbumin induced bronchoconstriction during EAR compared to the individual and sum of the activity of both treatments. The results are shown in Table 2 and Fig 1. Hence the combination of revamilast and montelukast produced significant improvement in declined lung function during the EAR compared to the individual and sum of the activity of both treatments.
Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and application of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments.

All publications, patents, and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated herein by reference.
CLAIMS

We claim:

1. A pharmaceutical composition comprising synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt.

2. The pharmaceutical composition according to claim 1, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15.

3. The pharmaceutical composition according to claim 1, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:1 to about 1:5.

4. The pharmaceutical composition according to any one of claims 1-3, wherein the composition is suitable for oral administration to a subject.

5. The pharmaceutical composition according to any one of claims 1-4, wherein the composition comprises from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt.

6. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 1-5.

7. A method of improving lung function in a subject having a respiratory disorder, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 1-5.

8. Use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical
composition according to any one of claims 1-5 for treatment of a respiratory disorder in a subject.

9. A pharmaceutical composition for oral administration comprising synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15.

10. The pharmaceutical composition according to claim 9, wherein the composition comprises from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt, and from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt.

11. The pharmaceutical composition according to any one of claims 9-10, wherein the composition is a fixed dose combination formulation.

12. The pharmaceutical composition according to any one of claims 9-11 for treatment of a respiratory disorder in a subject.

13. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 9-11.

14. The method according to claim 6 or 13, wherein the respiratory disorder is asthma or COPD.

15. Use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a pharmaceutical composition according to any one of claims 9-11 for treatment of a respiratory disorder in a subject.
16. A pharmaceutical composition for improving lung function in a subject having a respiratory disorder comprising a synergistic effective amount of (a) revamilast or its pharmaceutically acceptable salt and (b) a leukotriene receptor antagonist selected from montelukast, zafirlukast, and pharmaceutically acceptable salts thereof.

17. The pharmaceutical composition according to claim 16, wherein the weight ratio of (a):(b) ranges from about 1:0.5 to about 1:20.

18. The pharmaceutical composition according to claim 16, wherein the weight ratio of (a):(b) ranges from about 1:0.5 to about 1:15.

19. The pharmaceutical composition according to any one of claims 16-18, wherein the pharmaceutical composition comprises from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt.

20. The pharmaceutical composition according to any one of claims 16-19, wherein the pharmaceutical composition comprises from about 2 mg to about 10 mg of revamilast or its pharmaceutically acceptable salt.

21. The pharmaceutical composition according to any one of claims 16-20, wherein the pharmaceutical composition comprises from about 2 mg to about 20 mg of montelukast or its pharmaceutically acceptable salt.

22. A pharmaceutical composition for oral administration comprising revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to zafirlukast or its pharmaceutically acceptable salt ranges from about 1:1.6 to about 1:20.
23. The pharmaceutical composition according to claim 22, wherein the composition comprises from about 1 mg to about 20 mg of revamilast or its pharmaceutically acceptable salt, and from about 5 mg to about 50 mg of zafirlukast or its pharmaceutically acceptable salt.

24. The pharmaceutical composition according to any one of claims 22-23, wherein the composition is a fixed dose combination formulation.

25. The pharmaceutical composition according to any one of claims 22-24, for treatment of a respiratory disorder in a subject.

26. A method of treating a respiratory disorder in a subject, said method comprising administering to the subject the pharmaceutical composition according to any one of claims 22-24.

27. Use of revamilast or its pharmaceutically acceptable salt and zafirlukast or its pharmaceutically acceptable salt in the preparation of the pharmaceutical composition according to any one of claims 22-24 for treatment of a respiratory disorder in a subject.

28. A method of improving lung function in a subject having a respiratory disorder, said method comprising administering to the subject a fixed dose pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15.

29. The method according to claim 28, wherein the respiratory disorder is asthma or COPD.
30. Use of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt in the preparation of a fixed dose pharmaceutical composition for oral administration comprising a synergistic effective amount of revamilast or its pharmaceutically acceptable salt and montelukast or its pharmaceutically acceptable salt, wherein the weight ratio of revamilast or its pharmaceutically acceptable salt to montelukast or its pharmaceutically acceptable salt ranges from about 1:0.5 to about 1:15 for improving lung function in a subject having a respiratory disorder.
Figure 1

- Montelukast 1mg/kg p.o
- Revamilast 0.3mg/kg p.o
- Combination (Revamilast, 0.3mg/kg + Montelukast, 1 mg/kg) p.o.
INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052895

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/404 A61K31/4355 A61K31/47 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>1-21, 28-30</td>
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Date of the actual completion of the international search
9 October 2012

Date of mailing of the international search report
16/10/2012

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

Authorized officer
Albayrak, Timur
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