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(71) Applicant: PATARA PHARMA, LLC [US/US]; 11455 El Camino Real, Suite 460, San Diego, California 92130 (US).

(72) Inventors: GERHART, William; P.O. Box 1124, Del Mar, California 92014 (US). SONI, Pravin; 1320 Bedford Avenue, Sunnyvale, California 94087 (US). TUTUNCU, Ahmet; 1807 Seaview Avenue, Del Mar, California 92014 (US).

(74) Agents: YU, Wenhua et al.; Foley & Lardner LLP, 3000 K Street, NW, Sixth Floor, Washington, District of Columbia 20007-5109 (US).

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(54) Title: COMBINATION THERAPIES FOR THE TREATMENT OF LUNG DISEASES

(57) Abstract: Methods and compositions for treating lung diseases with cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition (comprising, for example, a P2X3 and/or a P2X2/3 receptor antagonist) are disclosed.



WO 2017/011729 A1

COMBINATION THERAPIES FOR THE TREATMENT OF LUNG DISEASES

RELATED APPLICATIONS

[0001] This application claims the benefit of provisional application USSN 62/193,386, filed July 16, 2015, the contents of which are herein incorporated by reference in their entirety.

FIELD OF THE DISCLOSURE

[0002] The disclosure is directed to fields of small molecules, medicine, inflammation, and respiratory /lung disease. Specifically, the disclosure is directed to the use of cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition (for example, comprising P2X3 and/or a P2X2/3 receptor antagonist), or a composition comprising cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition (for example, comprising P2X3 and/or a P2X2/3 receptor antagonist) for the treatment of lung diseases and conditions.

BACKGROUND OF THE INVENTION

[0003] Mast cells play a key role in the inflammatory process. They are found in the perivascular spaces of most tissues and contain pro-inflammatory and vasoactive mediators, such as serine proteases, tryptase, histamine, serotonin, proteoglycans, thromboxane, prostaglandin D2, leukotriene C4, platelet-activating factor, and eosinophil chemotactic factor. When activated, mast cells rapidly release granules and various hormone mediators into the interstitium, a process referred to as degranulation. Degranulation of mast cells can be caused by physical or chemical injury, crosslinking of immunoglobulin G receptors, or by activated complement proteins.

[0004] Mast cells are involved in the pathophysiology of a number of lung diseases and conditions. Sustained release of pro-inflammatory and vasoactive mediators from mast cells in lung tissues can result in diseases and conditions such as asthma, fibrotic lung disease, interstitial lung disease, and chronic obstructive pulmonary disease. Another lung condition in which mast cells play a role in the pathophysiology is chronic cough. Mast cells have been found in the airway smooth muscle bundles of patients with chronic cough.

[0005] Chronic cough also has neurological components. Afferent vagal activity of unmyelinated C-fibers, myelinated A δ -fibers, and stimulation of prostaglandin-sensitive nerve endings have been implicated in the pathophysiology of certain forms of cough. Vagal autonomic nerves in the respiratory

tract control smooth muscles of the tracheobronchial tree, and thus caliber of airways, as well as liberation and movement of secretions (mucus and fluid). Control is coordinated within brainstem nuclei, which regulate voluntary and autonomic outflow, relying on a rich input of vagal sensory signals from the airway tissues that in turn convey conscious sensation and trigger autonomic reflexes. Vagal sensory fibers arise mostly from cell bodies within jugular and nodose ganglia, and their activity is regulated by a range of chemical substances.

[0006] P2X3 and P2X2/3 are purinergic receptor-channels that modulate the function of the nodose and jugular afferent fibers of the respiratory tract. The overstimulation of these purinergic receptor-channels by ATP has been implicated in a variety of respiratory conditions. ATP stimulates and sensitizes sensory nerve endings resulting in intense sensations such as pain, discomfort, urgency, and itch, and urges a pronounced increase in sensory nerve discharge, largely via P2X3 receptor activation on afferent nerve fibers. Studies show that patients with airway disease associated with cough and breathlessness (such as asthma, COPD or pulmonary fibrosis) have excess ATP concentrations in their airway fluids, and that inhalation of nebulized ATP by asthmatic patients is able to activate airways sensations leading to urge to cough and precipitating cough itself.

[0007] Some lung diseases and conditions have been treated by the local delivery of active pharmaceutical agents, including mast cell stabilizers and P2X3 and/or P2X2/3 antagonists, to the lungs. However, a need still exists for improved methods of treating lung diseases and conditions, including cough and chronic cough.

SUMMARY OF THE INVENTION

[0008] The foregoing and further needs are satisfied by embodiments of the methods disclosed herein. Specifically, disclosed herein are methods of treating lung diseases and conditions in a patient in need thereof comprising administering to a patient cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition are administered in the same composition. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition are administered in different compositions. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition are each administered with one or more inhalation device(s). In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device and an antitussive composition is administered by a route of

administration selected from oral, rectal, nasal, topical, pulmonary, vaginal, and parenteral administration. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device and an antitussive composition is administered orally. An antitussive composition of the disclosure may comprise, consist essentially of or consist of an H₁-Receptor antagonist (also referred to as an H₁-antihistamine or a histamine H₁-receptor antagonist), dextromethorphan (including dextromethorphan hydrobromide and (+)-3-methoxy-17-methylmorphinan hydrobromide monohydrate), an opiate (including, but not limited to codeine and morphine), a local anesthetic (including, but not limited to, lidocaine and benzonatate), caramiphen (including caramiphen edisylate), carbetapentane (also known as pentoxyverine (2-[2-(diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate)), chlophedianol (including 1-phenyl-1-(o-chlorophenyl)-3-dimethylamino-propanol-1 hydrochloride), levodropropizine, menthol, a TRPM8 (Transient Receptor Potential Cation Channel Subfamily M Member 8) agonist, erdosteine, an antibiotic (including, but not limited to, erythromycin, amoxicillin, and doxycycline), a glucocorticosteroid, a β_2 -agonist (including, but not limited to, salbutamol (albuterol)), a muscarinic receptor antagonist, a mucolytic, an expectorant, an antacid, a proton pump inhibitor, a gastrointestinal motility drug, xanthine, levocloperastine, amitriptyline, an N-Methyl-D-aspartate (NMDA) receptor antagonist, glaucine, moguisteine, a phosphodiesterase inhibitor, a potassium (K⁺) channel opener, a chloride (Cl⁻) pump inhibitor, an ouabain-sensitive sodium-potassium (Na⁺-K⁺) ATPase inhibitor, a leukotriene receptor antagonist, interferon-alpha (interferon- α), a tropan derivative (preferably, a tropan with high affinity for the Nociceptin Opioid Receptor, including, but not limited to, nociceptin), a selective cannabinoid 2 receptor agonist, a neurokinin receptor antagonist, a transient receptor potential vanilloid 1 (TRPV1) receptor antagonist, a transient receptor potential A₁ (TRPA1) receptor antagonist, VRP700, a gamma-aminobutyric acid (GABA) receptor agonist, an enaminone (including, but not limited to, E121), gabapentin, thalidomide, Botulinum A Toxin, a voltage-gated sodium (Na_v) channel blocker, a P2X2/3 antagonist, or any combination thereof.

[0009] In certain embodiments, the disclosure provides methods of treating lung diseases and conditions comprising co-administering to a patient cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist are co-administered in the same composition. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist are co-administered in different compositions. In some

embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist are each co-administered with inhalation devices. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered with an inhalation device and a P2X3 and/or a P2X2/3 receptor antagonist is co-administered by a route of administration selected from oral, rectal, nasal, topical, pulmonary, vaginal, and parenteral administration. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered with an inhalation device and a P2X3 and/or the P2X2/3 receptor antagonist is co-administered orally.

[0010] In some embodiments of the methods disclosed herein, a composition comprising cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device. In some embodiments, the inhalation device produces a systemically effective amount of the cromolyn or the pharmaceutically acceptable salt thereof and/or a locally effective amount of the cromolyn or the pharmaceutically acceptable salt thereof to treat the lung disease or condition. In some embodiments, the pharmaceutically acceptable salt of cromolyn is selected from cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate. In some embodiments, the pharmaceutically acceptable salt of cromolyn is cromolyn sodium. In some embodiments, the inhalation device is a dry powder inhaler, metered dose inhaler, nebulizer, jet nebulizer, or soft mist inhaler. In some embodiments, the inhalation device is a high efficiency nebulizer.

[0011] In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%. In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL and/or an average C_{max} of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 55 ng/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%. In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 200 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%. In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 330 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%. In some embodiments, the

inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 525 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%. In some embodiments, a nominal dose of about 40 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the inhalation device. In some embodiments, a nominal dose of about 80 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the inhalation device.

[0012] In some embodiments, co-administration is with a jet nebulizer and co-administration with the jet nebulizer produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 5%. In some embodiments, co-administration is with a jet nebulizer and co-administration with the jet nebulizer produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 15 ng/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 5%. In some embodiments, a nominal dose of about 20 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the jet nebulizer.

[0013] In some embodiments, a composition co-administered with a high efficiency nebulizer comprises greater than about 2% of cromolyn or a pharmaceutically acceptable salt thereof. In some embodiments, a composition co-administered with a high efficiency nebulizer comprises about 4% of cromolyn or a pharmaceutically acceptable salt thereof. In some embodiments, a composition co-administered with a high efficiency nebulizer comprises one or more of purified water, sodium chloride, mannitol, and sodium EDTA. In some embodiments, about 1 mg to about 120 mg of cromolyn sodium is co-administered. In some embodiments, about 5 mg to about 80 mg of cromolyn sodium is co-administered. In some embodiments, about 20 mg to about 60 mg of cromolyn sodium is co-administered. In some embodiments, about 30 mg to about 50 mg of cromolyn sodium is co-administered. In some embodiments, about 40 mg of cromolyn sodium is co-administered.

[0014] In some embodiments, the composition co-administered with a high efficiency nebulizer has an osmolality greater than about 70 mOsm/kg. In some embodiments, the median particle size of the cromolyn or the pharmaceutically acceptable salt thereof aerosol is between about 3 μm and about 4 μm . In some embodiments, the high efficiency nebulizer emits droplets having an MMAD of about 4.1 μm

or less and a GSD of about 1.7. In some embodiments, the high efficiency nebulizer emits droplets having an MMAD of about 3.5 μm or less and a GSD of about 1.7. In some embodiments, the RF ($\leq 3.3 \mu\text{m}$) is at least about 30% and/or the RF ($\leq 5 \mu\text{m}$) is at least about 65%. In some embodiments, the RF ($\leq 3.3 \mu\text{m}$) is at least about 40%. In some embodiments, the RF ($\leq 3.3 \mu\text{m}$) is at least about 45% and/or the RF ($\leq 5 \mu\text{m}$) is at least about 75%.

[0015] In some embodiments, compositions of the disclosure comprising cromolyn sodium have an osmolality of between about 70 mOsm/kg to about 295 mOsm/kg (i.e., the compositions are hypotonic). In some embodiments, compositions of the disclosure comprising cromolyn sodium have an osmolality of between about 100 mOsm/kg to about 135 mOsm/kg. In certain embodiments, compositions of the disclosure comprising cromolyn sodium are formulated for administration by a nebulizer or a high-efficiency nebulizer. In certain embodiments, compositions of the disclosure comprising, consisting essentially of or consisting of cromolyn sodium, sodium chloride, EDTA, and water are formulated for administration by a nebulizer or a high-efficiency nebulizer and have an osmolality of between about 70 mOsm/kg to about 295 mOsm/kg (i.e., the compositions are hypotonic). Nonlimiting examples of compositions of the disclosure comprising, consisting essentially of or consisting of cromolyn sodium, sodium chloride, EDTA, and water are formulated for administration by a nebulizer or a high-efficiency nebulizer and have an osmolality of between about 70 mOsm/kg to about 295 mOsm/kg are provided below in Table 1.

[0016] Table 1

Ingredient	PA101B, 6%	PA101B, 4%	PA101B, 2%	PA101B, 1%	PA101B, 0.5%
Cromolyn sodium, USP/PhEur	6.0%	4%	2%	1%	0.5%
Sodium chloride, USP/PhEur	0.2%	0.2%	0.2%	0.2%	0.2%
EDTA, USP/PhEur	0.02%	0.02%	0.02%	0.02%	0.02%
Water for Injection, PhEur	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%
Container closure system (Primary	LDPE ampoules	LDPE ampoules	LDPE ampoules	LDPE ampoules	LDPE ampoules

packaging)					
Osmolality (mOsm/kg)	135	125	115	105	100

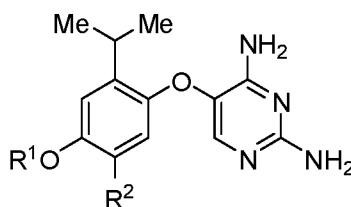
[0017] In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn sodium greater than about 200 ng*hr/mL and an average C_{max} of the cromolyn sodium greater than about 80 ng/mL. In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn sodium greater than about 330 ng*hr/mL and an average C_{max} of the cromolyn sodium greater than about 150 ng/mL. In some embodiments, the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn sodium greater than about 525 ng*hr/mL and an average C_{max} of the cromolyn sodium greater than about 230 ng/mL. In some embodiments, a nominal dose of about 40 mg cromolyn sodium is co-administered with the inhalation device. In some embodiments, a nominal dose of about 80 mg cromolyn sodium is co-administered with the inhalation device.

[0018] In some embodiments, co-administration is with a jet nebulizer, the pharmaceutically acceptable salt of cromolyn is cromolyn sodium, and co-administration with the jet nebulizer produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn sodium greater than about 40 ng*hr/mL and an average C_{max} of the cromolyn sodium greater than about 15 ng/mL. In some embodiments, a nominal dose of about 20 mg cromolyn sodium is co-administered with the jet nebulizer.

[0019] In some embodiments, the lung disease or condition is selected from the group consisting of idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction, hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangioliomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome,

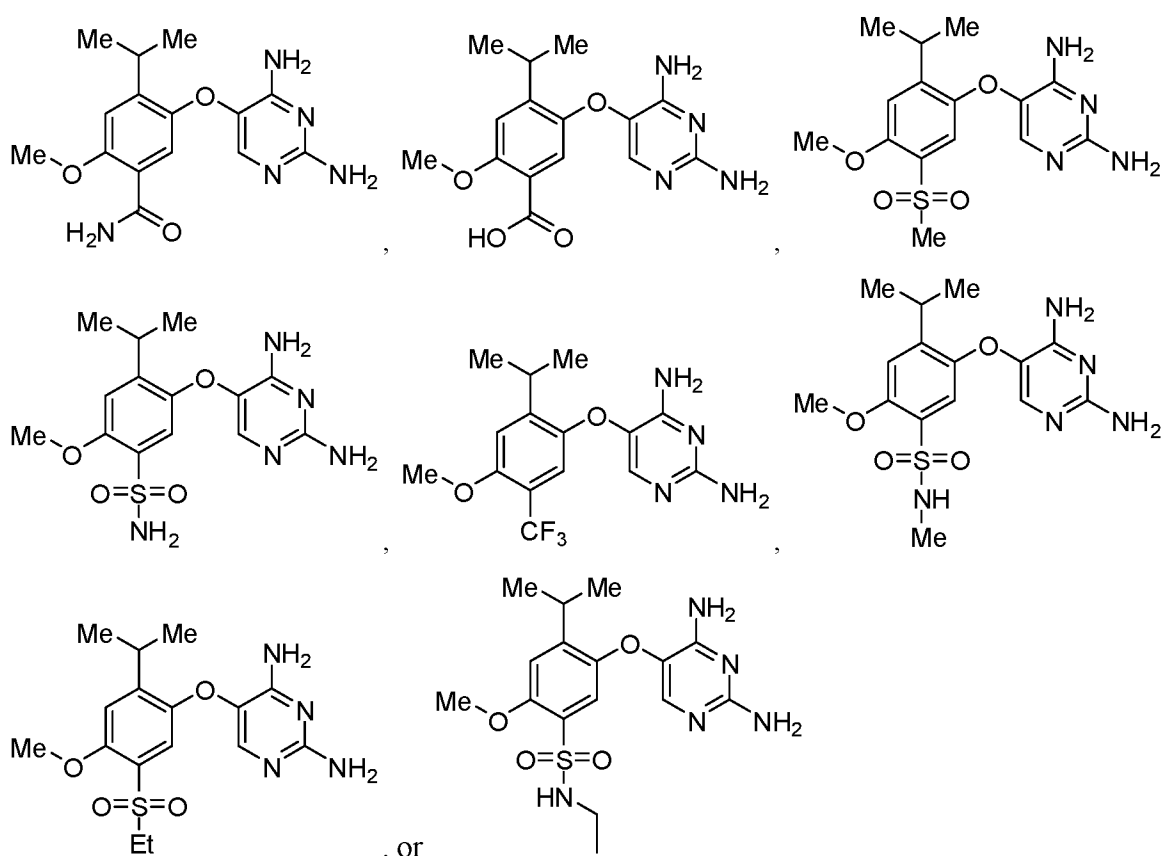
microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough. In some embodiments, the lung disease or condition is chronic cough. In some embodiments, the lung disease or condition is refractory chronic cough. In some embodiments, the lung disease or condition is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, wheezing, epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation. In some embodiments, the co-administration is with a dry powder inhaler, and wherein the composition comprises lactose. In some embodiments, the co-administration is with a dry powder inhaler, and wherein the composition does not comprise lactose.

[0020] In some embodiments, the P2X3 and/or the P2X2/3 receptor antagonist is a compound of Formula(I):



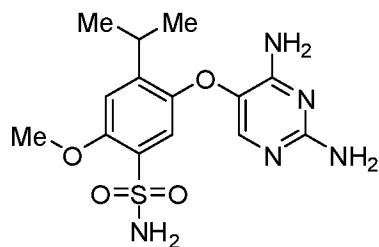
wherein R¹ is hydrogen or optionally substituted C₁-C₆ alkyl; and
 R² is alkyl, alkenyl, alkynyl, amino; aminosulfonyl, halo; amido, haloalkyl; alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alkynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano, or alkylcarbonyl;
 or a pharmaceutically acceptable salt thereof.

[0021] In some embodiments, the P2X3 and/or the P2X2/3 receptor antagonist is:



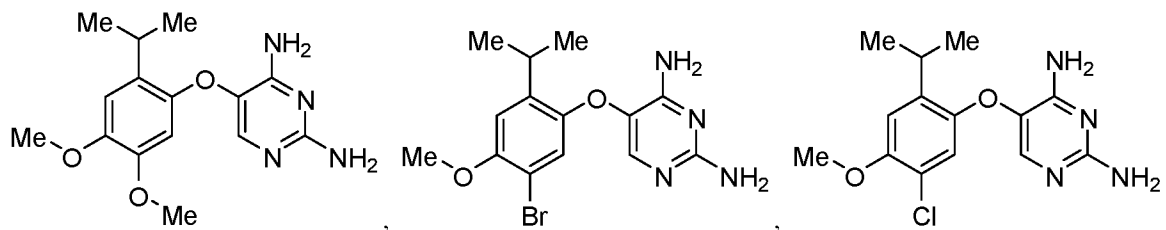
or a pharmaceutically acceptable salt thereof.

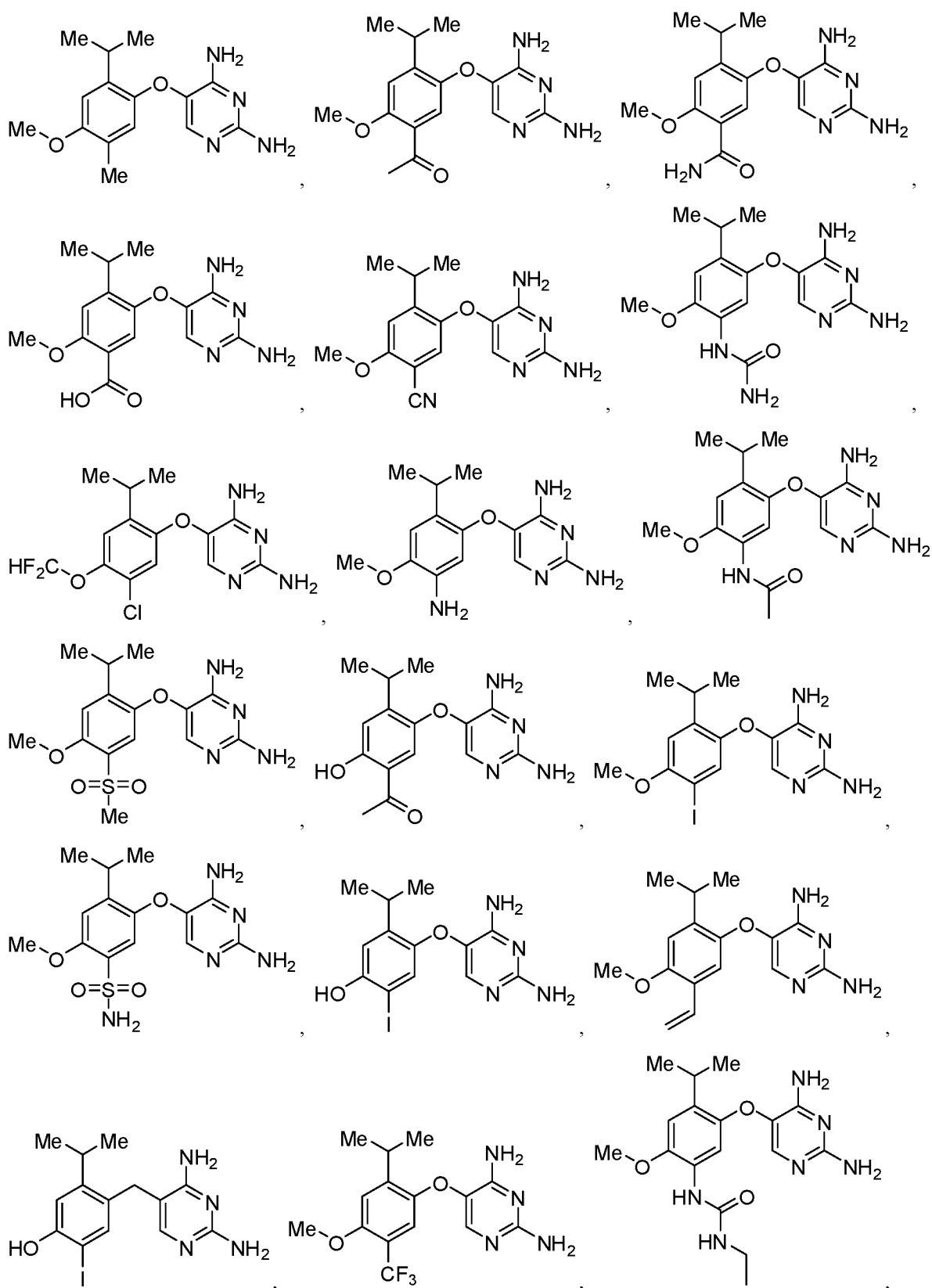
[0022] In some embodiments, the P2X3 and/or the P2X2/3 receptor antagonist is:

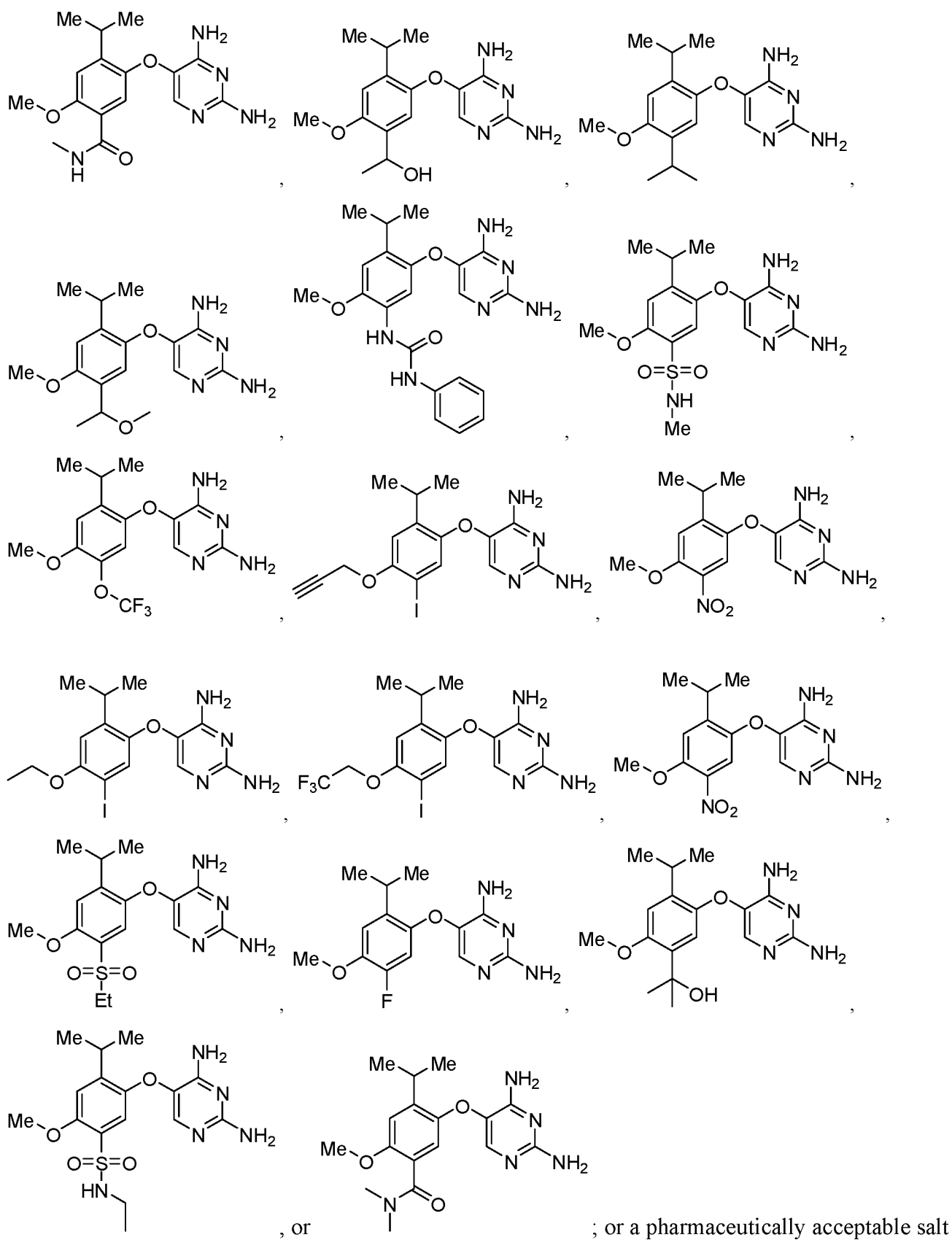


or a pharmaceutically acceptable salt thereof.

[0023] In some embodiments, the P2X3 and/or the P2X2/3 receptor antagonist is:







thereof.

[0024] Also disclosed herein are pharmaceutical compositions comprising cromolyn or a pharmaceutically acceptable salt thereof, a P2X3 and/or the P2X2/3 receptor antagonist, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable salt of cromolyn is selected from cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate. In some embodiments, the pharmaceutically acceptable salt of cromolyn is cromolyn sodium. In some embodiments, a pharmaceutical composition disclosed herein is administered with an inhalation device. In some embodiments, a pharmaceutical composition disclosed herein is for the treatment of a lung disease or condition. In some embodiments, the lung disease or condition is selected from the group consisting of idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction, hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangioleiomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough. In some embodiments, the lung disease or condition is chronic cough, refractory chronic cough, or chronic idiopathic cough. In some embodiments, the lung disease or condition is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, wheezing, epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia,

eosinophilic pneumonia, chemical pneumonia, atypic pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

DETAILED DESCRIPTION OF THE INVENTION

[0025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which the inventions described herein belong. All publications, patents, and patent applications mentioned in this specification are hereby incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

Definition of Terms

[0026] As used herein, the terms “co-administering” and “co-administration” refer to the administration of two or more active pharmaceutical ingredients (APIs). Co-administration can occur simultaneously or sequentially. In some embodiments, two or more active pharmaceutical ingredients (APIs) are co-administered in the same composition. In some embodiments, two or more active pharmaceutical ingredients (APIs) are co-administered in different compositions, either simultaneously or sequentially.

[0027] “Agonist” refers to a compound that binds to a receptor and activates the receptor to produce a biological response. The term “antagonist” refers to a compound that blocks or dampens agonist-mediated response rather than provoking a biological response upon binding to a receptor.

[0028] As used herein, the term “about” is used synonymously with the term “approximately.” Illustratively, the use of the term “about” with regard to a certain therapeutically effective pharmaceutical dose indicates that values slightly outside the cited values, e.g., plus or minus 0.1% to 10%, are also effective and safe.

[0029] As used herein, the terms “comprising,” “including,” “such as,” and “for example” (or “e.g.”) are used in their open, non-limiting sense.

[0030] As used herein, the phrase “consisting essentially of” is a transitional phrase used in a claim to indicate that the following list of ingredients, parts or process steps must be present in the claimed composition, machine or process, but that the claim is open to unlisted ingredients, parts or process steps that do not materially affect the basic and novel properties of the invention.

[0031] As used herein, “sub-therapeutic amount” of an agent or therapy is an amount less than the

effective amount for that agent or therapy, but when combined with an effective or sub-therapeutic amount of another agent or therapy can produce a desired therapeutic result, due to, for example, synergy in the resulting efficacious effects, or reduced side effects.

[0032] A “synergistically effective” therapeutic amount, or “synergistically effective” amount of an agent or therapy, is an amount which, when combined with an effective or sub-therapeutic amount of another agent or therapy, produces a greater effect than when either of the two agents is used alone.

[0033] The terms “synergistic” and “synergistically” as applied to the effect of two or more pharmaceutically active ingredients used in combination (whether simultaneously or sequentially) refer to a greater effect than when either of the two agents are used alone. In some embodiments, the effective or sub-therapeutic amount of an agent or therapy is combined with an effective or sub-therapeutic amount of another agent or therapy to produce a greater effect than when either of the two agents is used alone. In some embodiments, a synergistically effective therapeutic amount of an agent or therapy produces a greater effect when used in combination than the additive effects of each of the two agents or therapies when used alone. The term “greater effect” encompasses not only a reduction in symptoms of the disorder to be treated, but also an improved side effect profile, improved tolerability, improved patient compliance, improved efficacy, and/or any other improved clinical outcome.

[0034] “Nominal dose,” as used herein, refers to the loaded dose, which is the amount of cromolyn or the pharmaceutically acceptable salt thereof in an inhalation device prior to administration to the patient. The volume of solution containing the nominal dose is referred to as the “fill volume.”

[0035] “AUC_{last}” as used herein refers to the area under the curve from time zero to time of last measurable concentration of active pharmaceutical ingredient (API).

[0036] “AUC_{last}^{HEN}” as used herein refers to the area under a blood plasma concentration curve up to the last time point for the nominal dose of active pharmaceutical ingredient (API) administered with a high efficiency nebulizer.

[0037] “AUC_{last}^{Conv}” as used herein refers to the area under a blood plasma concentration curve up to the last time point for a nominal dose of active pharmaceutical ingredient (API) administered with a conventional inhalation device.

[0038] “AUC_(0-∞)” as used herein refers to the total area under a blood plasma concentration curve for an active pharmaceutical ingredient (API).

[0039] “AUC_(0-∞)^{HEN}” as used herein refers to the total area under a blood plasma concentration curve for a nominal dose of active pharmaceutical ingredient (API) administered with a high efficiency

nebulizer.

[0040] “ $AUC_{(0-\infty)}^{Conv}$ ” as used herein refers to the total area under a blood plasma concentration curve for a nominal dose of active pharmaceutical ingredient (API) administered with a conventional inhalation device.

[0041] $AUC_{(0-\infty)}$ can be determined by methods known to those of skill in the art. For example, the $AUC_{(0-\infty)}$ of an API can be determined by collecting blood samples from a subject at various time points after administration of an API to the subject, separating plasma from the blood samples, extracting the API from the separated plasma samples, e.g., by solid-phase extraction, quantifying the amount of the API extracted from each sample of separated plasma, e.g., by liquid chromatography-tandem mass spectrometry (LC-MS/MS), plotting the concentration of API in each sample versus the time of collection after administration, and calculating the area under the curve.

[0042] “Substantially the same nominal dose” as used herein means that a first nominal dose of an active pharmaceutical ingredient (API) contains approximately the same number of millimoles of cromolyn or the pharmaceutically acceptable salt thereof as a second nominal dose of cromolyn or the pharmaceutically acceptable salt thereof.

[0043] “Bioavailability” as used herein refers to the amount of unchanged API that reaches the systemic circulation, expressed as a percentage of the dosage of the API that is administered to a subject. By definition, the bioavailability of an intravenous solution containing the active pharmaceutical ingredient (API) is 100%. The bioavailability of an API can be determined by methods known to those of skill in the art. For example, the bioavailability of an API can be determined by collecting urine samples from a subject at various time points following administration of the API to the subject, extracting the API from the urine samples, e.g., by solid-phase extraction, quantifying the amount of the API in each urine sample, adjusting the amount of API collected from the urine by a factor based on the amount of API reaching systemic circulation that is excreted in the urine, and calculating the percentage of the API administered to the subject that reaches the systemic circulation of the subject. In a specific embodiment, the bioavailability of cromolyn sodium can be determined as described in Walker et al., 24 *J. Pharm. Pharmacol.* 525-31 (1972). In the case of cromolyn sodium, the amount of the compound isolated from the urine is multiplied by two to calculate the total amount reaching systemic circulation after administration because the compound is known to be excreted unmetabolized in equal parts in the urine and feces, i.e., approximately 50% of the amount of cromolyn sodium that reaches systemic circulation is excreted in the urine and approximately 50% of the amount of cromolyn sodium that

reaches systemic circulation is excreted in the feces.

[0044] “Enhanced lung deposition” as used herein refers to an increase in drug deposition (deposited lung dose) arising out of, for example, improved efficiency of drug delivery.

[0045] “Deposited dose” or “deposited lung dose” is the amount of cromolyn or the pharmaceutically acceptable salt thereof deposited in the lung. The deposited dose or deposited lung dose may be expressed in absolute terms, for example in mg or μg of API deposited in the lungs. The deposited lung dose may also be expressed in relative terms, for example calculating the amount of API deposited as a percentage of the nominal dose.

[0046] “ C_{max} ” as used herein refers to the maximum plasma concentration for an active pharmaceutical ingredient (API).

[0047] “ $C_{\text{max}}^{\text{HEN}}$ ” as used herein refers to the maximum blood plasma concentration for a nominal dose of the active pharmaceutical ingredient (API) administered with a high efficiency nebulizer.

[0048] “ $C_{\text{max}}^{\text{Conv}}$ ” as used herein refers to the maximum blood plasma concentration for a nominal dose of the active pharmaceutical ingredient (API) administered with a conventional inhalation device.

[0049] C_{max} can be determined by methods known to those of skill in the art. For example, the C_{max} of an API can be determined by collecting blood samples from a subject at various time points after administration of an API to the subject, separating plasma from the blood samples, extracting the API from the separated plasma samples, e.g., by solid-phase extraction, quantifying the amount of the API extracted from each sample of separated plasma, e.g., by LC-MS/MS, plotting the concentration of API in each sample versus the time of collection after administration, and identifying the peak concentration of the API on the curve.

[0050] “Enhanced pharmacokinetic profile” means an improvement in some pharmacokinetic parameter. Pharmacokinetic parameters that may be improved include AUC (0-4 or 0-6 or 0-8 h), AUC_{last} , $\text{AUC}_{(0-\infty)}$, T_{max} , $T_{1/2}$, and C_{max} . In some embodiments, the enhanced pharmacokinetic profile may be measured quantitatively by comparing a pharmacokinetic parameter obtained for a nominal dose of an active pharmaceutical ingredient (API) administered by one route of administration, such as an inhalation device (e.g., a high efficiency nebulizer) with the same pharmacokinetic parameter obtained with the same nominal dose of active pharmaceutical ingredient (API) administered by a different route of administration, such as a different type of inhalation device or an oral formulation (e.g., oral tablet, oral capsule, or oral solution).

[0051] “Blood plasma concentration” refers to the concentration of an active pharmaceutical ingredient

(API) in the plasma component of blood of a subject or patient population.

[0052] “Patient” or “subject” refers to the animal (especially mammal) or human being treated.

[0053] A “subject group” or “patient group” has a sufficient number of subjects or patients to provide a statistically significant average measurement of the relevant pharmacokinetic parameter. All members of the “subject group” or “patient group” have pharmacokinetic parameters for cromolyn or the pharmaceutically acceptable salt thereof that fall within statistically normal ranges (i.e., there are no outliers), and no member is included on the basis of non-standard or unusual measurements.

[0054] “Nebulizer,” as used herein, refers to a device that turns medications, compositions, formulations, suspensions, and mixtures, etc. into a fine aerosol mist for delivery to the lungs.

[0055] “Drug absorption” or simply “absorption” typically refers to the process of movement of drug from site of delivery of a drug across a barrier into a blood vessel or the site of action, e.g., a drug being absorbed via the pulmonary capillary beds of the alveoli into the systemic circulation.

[0056] “ $T_{\max}$ ” as used herein refers to the amount of time necessary for an active pharmaceutical ingredient (API) to attain maximum blood plasma concentration.

[0057] “ $T_{\max}^{\text{HEN}}$ ” as used herein refers to the amount of time necessary for a nominal dose of an active pharmaceutical ingredient (API) to attain maximum blood plasma concentration after administration with a high efficiency nebulizer.

[0058] “ $T_{\max}^{\text{Conv}}$ ” as used herein refers to the amount of time necessary for a nominal dose of an active pharmaceutical ingredient (API) to attain maximum blood plasma concentration after administration with a conventional inhalation device.

[0059] The term “treat” and its grammatical variants (e.g., “to treat,” “treating,” and “treatment”) refer to the amelioration or reduction of the incidence of one or more symptoms of a condition or disease state in a patient. Such symptoms may be chronic or acute, and such amelioration may be partial or complete. In the present context, treatment entails co-administration of cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist to a patient via any route of administration disclosed herein.

[0060] As used herein, the term “high concentration” refers to a concentration greater than 1% by weight. For example, in a specific embodiment, a “high concentration” formulation of cromolyn sodium comprises cromolyn sodium at a concentration of greater than 1% by weight.

[0061] As used herein, the term “hypotonic” refers to a formulation that has a tonicity less than 295 mOsm/kg.

[0062] The term “prophylaxis” refers to the reduction of the occurrence or recurrence of one or more acute symptoms associated with a disease state or a condition in a patient. Prophylaxis includes reduction in the occurrence or recurrence rate of a lung disease or condition. However, prophylaxis is not intended to include complete prevention of onset of a disease state or a condition in a patient who has not previously been identified as suffering from the disease or the condition. In the present context, prophylaxis entails the co-administration of cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist to a patient via any route of administration disclosed herein.

[0063] As used herein, a “systemically effective amount” is an amount of cromolyn or a pharmaceutically acceptable salt thereof in the body of a patient as a whole that is effective for the treatment or prophylaxis of a lung disease or condition. A “systemically effective amount” may be expressed, for example, as the mass of cromolyn or a pharmaceutically acceptable salt thereof, or concentration of or the pharmaceutically acceptable salt thereof, in a patient’s plasma. A “systemically effective amount” may differ depending on the specific pharmaceutically acceptable salt of cromolyn used and the specific lung disease or condition.

[0064] As used herein, a “locally effective amount” is an amount of cromolyn or a pharmaceutically acceptable salt thereof in a particular region of the body of a patient, namely the lungs of a patient, that is effective for the treatment or prophylaxis of a lung disease or condition. A “locally effective amount” may be expressed, for example, as the mass of cromolyn or a pharmaceutically acceptable salt thereof, or concentration of cromolyn or a pharmaceutically acceptable salt thereof, in a patient’s lung tissue. A “locally effective amount” may differ depending on the specific pharmaceutically acceptable salt of cromolyn and the specific lung disease or condition.

[0065] As used herein, a difference is “significant” if a person skilled in the art would recognize that the difference is probably real. In some embodiments, significance may be determined statistically, in which case two measured parameters may be referred to as statistically significant. In some embodiments, statistical significance may be quantified in terms of a stated confidence interval (CI), e.g., greater than 90%, greater than 95%, greater than 98%, etc. In some embodiments, statistical significance may be quantified in terms of a p value, e.g., less than 0.5, less than 0.1, less than 0.05, etc. The person skilled in the art will recognize these expressions of significance and will know how to apply them appropriately to the specific parameters that are being compared.

[0066] As used herein, “alkyl” is used to mean the monovalent linear or branched saturated hydrocarbon

moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. In some embodiments, the alkyl group is one to six carbon atoms, i.e. C₁-C₆ alkyl. Examples of alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

[0067] As used herein, “alkenyl” is used to mean the monovalent linear hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like.

[0068] As used herein, “alkynyl” is used to mean the monovalent linear hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, e.g., ethynyl, propynyl, and the like.

[0069] As used herein, “alkylene” is used to mean the divalent linear hydrocarbon radical of one to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms, , e.g., methylene, ethylene, propylene, butylene, pentylene and the like.

[0070] As used herein, “alkoxyl” is used to mean the moiety of the formula –OR, wherein R is an alkyl moiety as described herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

[0071] As used herein, “alkoxylalkyl” is used to mean the moiety of the formula R^a–O–R^b, wherein R^a is alkyl and R^b is alkylene as described herein. Examples of include, but are not limited to, 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

[0072] As used herein, “alkylcarbonyl” is used to mean the moiety of the formula –R'-R'', wherein R' is (C=O) and R'' is alkyl as defined herein.

[0073] As used herein, “alkylsulfonyl” is used to mean the moiety of the formula –R'-R'', wherein R' is –SO₂- and R'' is alkyl as defined herein.

[0074] As used herein, “amino” is used to mean the moiety of the formula –NHR, wherein R is hydrogen or alkyl.

[0075] As used herein, “amido” is used to mean the moiety of the formula –NR(CO)R', wherein R and R' are each independently hydrogen or alkyl.

[0076] As used herein, “hydroxy” is used to mean the moiety of –OH.

[0077] As used herein, “haloalkoxy” is used to mean the moiety of –OR, wherein R is a haloalkyl group as defined herein.

[0078] As used herein, “aminosulfonyl” is used to mean the moiety of the formula $-\text{SO}_2-\text{NRR}'$, wherein R and R' is each independently is hydrogen or alkyl as defined herein.

[0079] As used herein, “alkynylalkoxy” is used to mean the moiety of $-\text{O}-\text{R}-\text{R}'$, wherein R is alkylene and R' is alkynyl as defined herein.

[0080] As used herein, “aryl” is used to mean a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi-, tricyclic aromatic ring. In some embodiments, the aryl group is optionally substituted as defined herein.

[0081] As used herein, “arylsulfonyl” is used to mean a group of the formula $-\text{SO}_2-\text{R}$ wherein R is aryl as defined herein.

[0082] As used herein, “halo”, “halogen” and “halide” are used interchangeably and refer to fluoro, chloro, bromo, or iodo.

[0083] As used herein, “haloalkyl” is used to mean an alkyl as defined herein in which one or more hydrogen atoms have been replaced with the same of different halogens. Examples include $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CCl}_3$, $-\text{CF}_3$ and the like.

[0084] As used herein, “hydroxyalkoxy” is used to mean the moiety of $-\text{OR}$, wherein R is a hydroxyalkyl group as defined herein.

[0085] As used herein, “hydroxycarbonylalkyl” or “carboxyalkyl” is used to mean the moiety of $-\text{R}-(\text{CO})-\text{OH}$, wherein R is a alkylene as defined herein.

[0086] As used herein, “hydroxyalkyl” is used to mean the alkyl moiety as defined herein, substituted with one or more hydroxy groups, provided that the same carbon atom does not carry more than one hydroxy group. Examples of include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl.

[0087] As used herein, “nitro” means a group of the formula $-\text{NO}_2$.

[0088] As used herein, “optionally substituted” when used with the term alkyl, means that an alkyl group, is optionally substituted independently with one to three substituents, preferably one or two substituents selected from any one of the substituents as described herein, such as alkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, $-\text{COR}$ (wherein R is hydrogen, alkyl, phenyl or phenylalkyl), and $-(\text{CR}'\text{R}'')_n-\text{COOR}$ (where n is an integer from 0 to 5, R' and R'' are

independently hydrogen or alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

Methods of Treating Lung Diseases and Conditions

[0089] Disclosed herein are methods for the treatment or prophylaxis of a lung disease or condition comprising co-administering to a patient cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist are co-administered in the same composition. In some embodiments, a composition comprising cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist is administered with an inhalation device. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist are co-administered in different compositions. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist are co-administered separately with inhalation devices. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered with an inhalation device and a P2X₃ and/or a P2X_{2/3} receptor antagonist is co-administered by a route of administration selected from oral, rectal, nasal, topical, pulmonary, vaginal, and parenteral administration. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered with an inhalation device and a P2X₃ and/or a P2X_{2/3} receptor antagonist is co-administered by oral administration.

[0090] In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof to a patient with an inhalation device produces both a systemically effective amount of cromolyn or a pharmaceutically acceptable salt thereof and a locally effective amount of cromolyn or a pharmaceutically acceptable salt thereof to treat a lung disease or condition. In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof to a patient with an inhalation device produces a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a high deposited lung dose of cromolyn or the pharmaceutically acceptable salt thereof in the patient to treat a lung disease or condition. In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof to a patient with an inhalation device produces a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof, a locally effective amount of cromolyn or the pharmaceutically acceptable salt thereof, and a high deposited lung dose of cromolyn

or the pharmaceutically acceptable salt thereof in the patient to treat a lung disease or condition. Thus, in some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof with an inhalation device provides improved efficacy for the treatment of a lung disease or condition by producing both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a locally effective amount of cromolyn or the pharmaceutically acceptable salt thereof. In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof with an inhalation device provides improved efficacy for the treatment of a lung disease or condition by producing both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a high deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof. In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof with an inhalation device provides improved efficacy for the treatment of a lung disease or condition by producing a systemically effective amount of the cromolyn or the pharmaceutically acceptable salt thereof, a locally effective amount of cromolyn or the pharmaceutically acceptable salt thereof, and a high deposited lung dose of cromolyn or the pharmaceutically acceptable salt thereof.

[0091] In some embodiments, co-administration of cromolyn or a pharmaceutically acceptable salt thereof and a P2X₃ and/or a P2X_{2/3} receptor antagonist provides a synergistic effect. In some embodiments, the synergistic effect produces a greater efficacy than the additive effects of cromolyn or the pharmaceutically acceptable salt and the P2X₃ and/or a P2X_{2/3} receptor antagonist when used alone. In some embodiments, the synergistic effect provides for improved reduction of symptoms of the disorder to be treated, improved side effect profile, improved tolerability, improved patient compliance, improved efficacy, and/or any other improved clinical outcome. In some embodiments, the cromolyn or a pharmaceutically acceptable salt thereof is co-administered in a sub-therapeutic amount. In some embodiments, the P2X₃ and/or a P2X_{2/3} receptor antagonist is co-administered in a sub-therapeutic amount. In some embodiments, the co-administration of the cromolyn or the pharmaceutically acceptable salt thereof and/or P2X₃ and/or a P2X_{2/3} receptor antagonist in a sub-therapeutic amount provides a synergistic effect. In some embodiments, the cromolyn or a pharmaceutically acceptable salt thereof is co-administered in a therapeutically effective amount. In some embodiments, the P2X₃ and/or a P2X_{2/3} receptor antagonist is co-administered in a therapeutically effective amount. In some embodiments, co-administration of cromolyn or a pharmaceutically effective salt thereof and a P2X₃

and/or a P2X2/3 receptor antagonist provides an additive effect.

[0092] Lung diseases or conditions treatable by the methods disclosed herein include, but are not limited to, idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction, hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangiomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough

[0093] In some embodiments, a lung disease or condition treatable by the methods disclosed herein is chronic cough, chronic idiopathic cough, or refractory chronic cough.

[0094] In some embodiments, a lung disease or condition treatable by the methods disclosed herein is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, or wheezing. In some embodiments of the methods disclosed herein, the lung disease or condition is epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

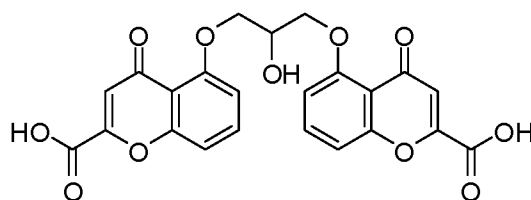
[0095] In some embodiments, a lung disease or condition treatable by the methods disclosed herein is

not chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, or wheezing. In some embodiments of the methods disclosed herein, the lung disease or condition is not epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

[0096] Co-administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to, delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. By way of example only, compounds described herein can be co-administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as creams or ointments, injection, catheter, or implant. The co-administration can also be by direct injection at the site of a diseased tissue.

Cromolyn, and Analogs, Derivatives, and Pharmaceutically Acceptable Salts Thereof

[0097] Cromolyn is a mast cell stabilizer that inhibits degranulation and/or the release of pro-inflammatory and vasoactive mediators from mast cells. As used herein, cromolyn refers to 5,5'-(2-hydroxypropane-1,3-diyl)bis(oxy)bis(4-oxo-4*H*-chromene-2-carboxylic acid) and has the following structure:



[0098] Cromolyn is also known as cromoglicic acid, cromoglycate, and cromoglicate. Pharmaceutically acceptable salts of cromolyn include but are not limited to cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate. Cromolyn sodium is also known as disodium 5,5'-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate].

[0099] In some embodiments, cromolyn and the pharmaceutically acceptable salts described herein may be prepared as prodrugs. A “prodrug” refers to an agent that is converted into the parent drug *in vivo*. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug, or to alter other characteristics or properties of a drug. In some embodiments, the prodrug has improved bioavailability relative to the parent drug. In some embodiments, the prodrug has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. In some embodiments, a prodrug of cromolyn is an ester of cromolyn, which is hydrolyzed to the carboxylic acid, the parent compound. In some embodiments, a prodrug comprises a short peptide (polyaminoacid) bonded to an acid group, wherein the peptide is metabolized *in vivo* to reveal the parent drug. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of cromolyn. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the parent compound. In certain embodiments, prodrug of cromolyn is used. In a specific embodiment, the prodrug of cromolyn is cromoglicate lisetil.

[00100] To produce a prodrug, a pharmaceutically active cromolyn is modified such that the active compound will be regenerated upon *in vivo* administration. In some embodiments, prodrugs of cromolyn are designed by virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*. See, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc., San Diego, pages 352-401, Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985; Rooseboom *et al.*, *Pharmacological Reviews*, 56:53–102, 2004; Miller *et al.*, *J. Med. Chem.* Vol.46, no. 24, 5097-5116, 2003; Aesop Cho, “Recent Advances in Oral Prodrug Discovery”, *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006.

[00101] In some embodiments, cromolyn and pharmaceutically acceptable salts thereof disclosed herein are isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from

the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F , ^{36}Cl , respectively. Certain isotopically labeled compounds described herein, for example those with isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. In certain embodiments, isotopically labeled cromolyn is co-administered. In some, the pharmaceutically acceptable salt of cromolyn, such as cromolyn sodium, is isotopically labeled. In some embodiments, the pharmaceutically acceptable salt of cromolyn is deuterium-labeled cromolyn sodium.

[00102] In some embodiments, cromolyn and the pharmaceutically acceptable salt thereof described herein are pegylated, wherein one or more polyethylene glycol (PEG) polymers are covalently attached to cromolyn or the pharmaceutically acceptable salt thereof. In some embodiments, pegylation increases the half-life of the pegylated compound in the body. In some embodiments, pegylation increases the hydrodynamic size of the pegylated compound and reduces renal clearance. In some embodiments, pegylation increases the solubility of the pegylated compound. In some embodiments, protects the pegylated compound from proteolytic degradation.

[00103] Cromolyn and pharmaceutically acceptable salts, prodrugs, and adducts thereof, may be prepared by methods known in the art.

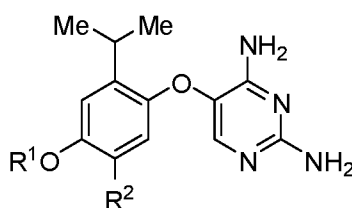
[00104] Cromolyn or a pharmaceutically acceptable salt thereof is co-administered in the methods disclosed herein in a suitable dose or nominal dose as determined by one of ordinary skill in the art. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered at a dosage or nominal dosage of less than about 1 mg/dose, about 1 mg/dose to about 100 mg/dose, about 1 mg/dose to about 120 mg/dose, about 5 mg/dose to about 80 mg/dose, about 20 mg/dose to about 60 mg/dose, about 30 mg/dose to about 50 mg/dose, or greater than about 100 mg/dose. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered in less than about 1 mg, about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg doses, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg,

about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg doses. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered in about 40 mg.

[00105] In some embodiments of the methods disclosed herein, cromolyn sodium is co-administered at a dosage or nominal dosage of less than about 1 mg/dose, about 1 mg/dose to about 100 mg/dose, about 1 mg/dose to about 120 mg/dose, about 5 mg/dose to about 80 mg/dose, about 20 mg/dose to about 60 mg/dose, or about 30 mg/dose to about 50 mg/dose, or greater than about 100 mg/dose. In other embodiments, cromolyn sodium is co-administered in less than about 1 mg, about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg doses, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg doses. In some embodiments, cromolyn sodium is co-administered in about 40 mg.

P2X3 and/or P2X2/3 Receptor Antagonists

[00106] Examples of P2X3 and/or P2X2/3 receptor antagonists that are used according to the instant disclosure include compounds of Formula (I):



wherein R^1 is hydrogen or optionally substituted C_1 - C_6 alkyl; and R^2 is alkyl, alkenyl, alkynyl, amino; aminosulfonyl, halo; amido, haloalkyl; alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alknynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano, or alkylcarbonyl; or a pharmaceutically acceptable salt thereof.

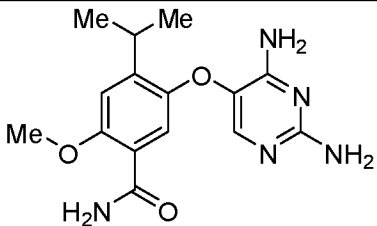
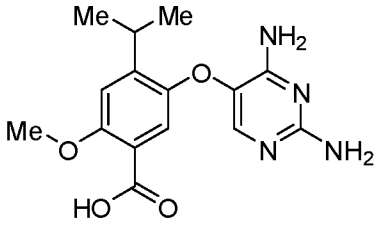
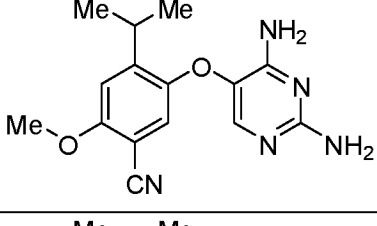
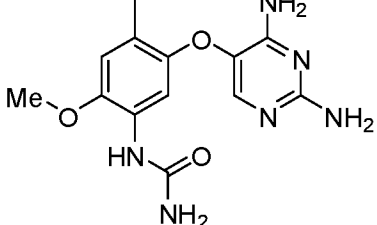
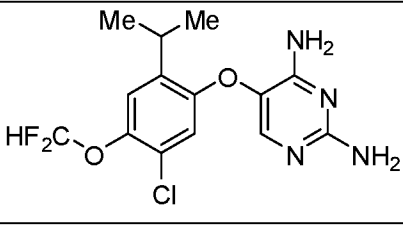
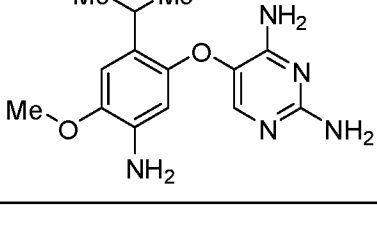
[00107] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1 - C_6 alkyl. In some embodiments, R^1 is methyl. In some embodiments, R^2 is haloalkyl, aminosulfonyl, alkylsulfonyl,

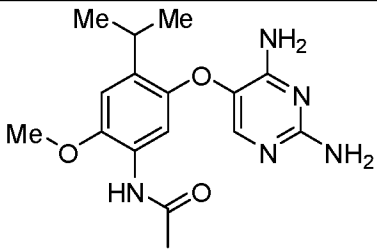
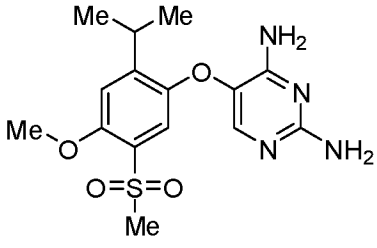
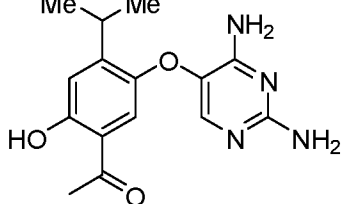
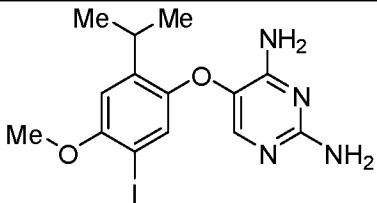
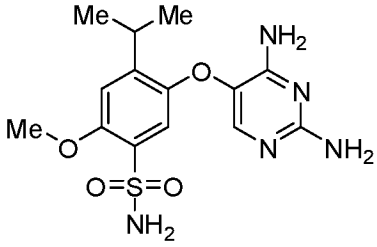
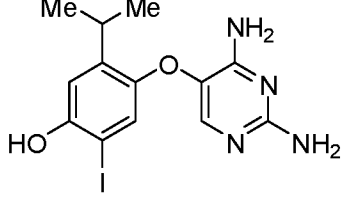
alkylcarbonyl, or carboxyalkyl. In some embodiments, R^2 is haloalkyl, wherein alkyl is methyl. In some embodiments, R^2 is aminosulfonyl. In some embodiments, R^2 is $-\text{SO}_2\text{NH}_2$. In some embodiments, R^2 is carboxyalkyl. In some embodiments, R^1 is methyl and R^2 is $-\text{SO}_2\text{NH}_2$.

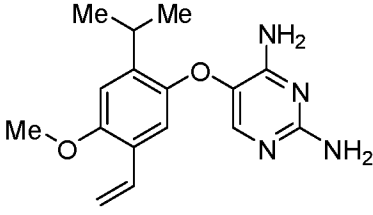
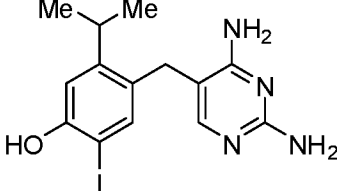
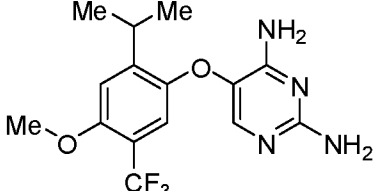
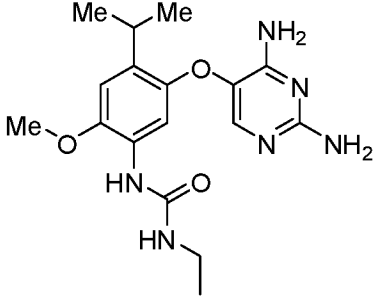
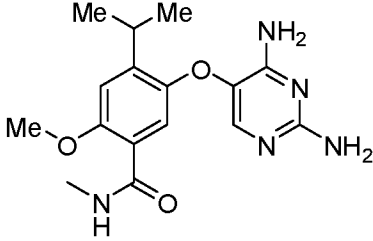
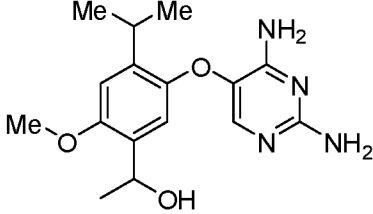
[00108] Further examples of P2X3 and/or P2X2/3 receptor antagonists include the compounds or pharmaceutically acceptable salts as shown in Table 2.

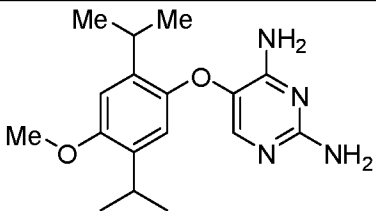
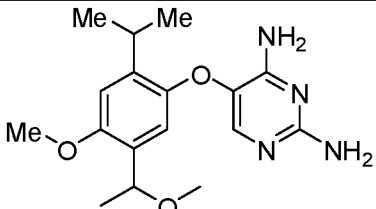
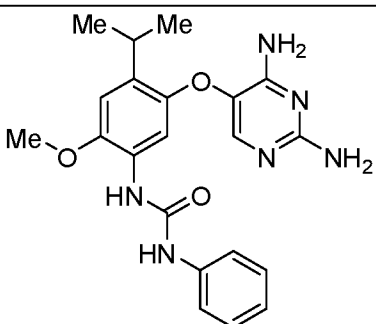
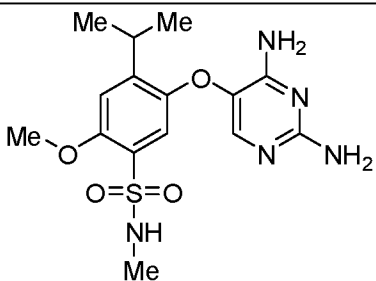
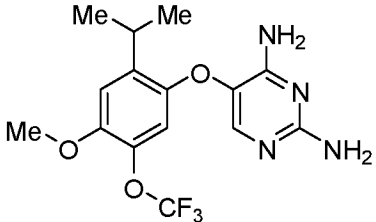
TABLE 2

Compound No.	Structure	Name
1		5-(2-Isopropyl-4,5-dimethoxyphenoxy)pyrimidine-2,4-diamine
2		5-(5-Bromo-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine
3		5-(5-Chloro-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine
4		5-(2-Isopropyl-4-methoxy-5-methylphenoxy)pyrimidine-2,4-diamine
5		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)ethanone

Compound No.	Structure	Name
6		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzamide
7		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzoic acid
8		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzonitrile
9		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)urea
10		5-(5-Chloro-4-(difluoromethoxy)-2-isopropylphenoxy)pyrimidine-2,4-diamine
11		5-(5-Amino-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine

Compound No.	Structure	Name
12		N-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)acetamide
13		5-(2-Isopropyl-4-methoxy-5-(methylsulfonyl)phenoxy)pyrimidine-2,4-diamine
14		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-2-hydroxy-4-isopropylphenyl)ethanone
15		5-(5-Iodo-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine
16		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide
17		4-(2,4-Diaminopyrimidin-5-yloxy)-2-iodo-5-isopropylphenol

Compound No.	Structure	Name
18		5-(2-Isopropyl-4-methoxy-5-vinylphenoxy)pyrimidine-2,4-diamine
19		4-((2,4-Diaminopyrimidin-5-yl)methyl)-2-iodo-5-isopropylphenol
20		5-(2-Isopropyl-4-methoxy-5-(trifluoromethyl)phenoxy)pyrimidine-2,4-diamine
21		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)-3-ethylurea
22		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methylbenzamide
23		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)ethanol

Compound No.	Structure	Name
24		5-(2,5-Diisopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine
25		5-(2-Isopropyl-4-methoxy-5-(1-methoxyethyl)phenoxy)pyrimidine-2,4-diamine
26		1-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)-3-phenylurea
27		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methylbenzenesulfonamide
28		5-(2-Isopropyl-4-methoxy-5-(trifluoromethoxy)phenoxy)pyrimidine-2,4-diamine

Compound No.	Structure	Name
29		5-(5-Iodo-2-isopropyl-4-(prop-2-ynyloxy)phenoxy)pyrimidine-2,4-diamine
30		5-(2-Isopropyl-4-methoxy-5-nitrophenoxy)pyrimidine-2,4-diamine
31		5-(4-Ethoxy-5-iodo-2-isopropylphenoxy)pyrimidine-2,4-diamine
32		5-(5-Iodo-2-isopropyl-4-(2,2,2-trifluoroethoxy)phenoxy)pyrimidine-2,4-diamine
33		5-(2-Isopropyl-4-methoxy-5-nitrophenoxy)pyrimidine-2,4-diamine
34		5-(5-(Ethylsulfonyl)-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine

Compound No.	Structure	Name
35		5-(5-Fluoro-2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine
36		2-(5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl)propan-2-ol
37		5-(2,4-Diaminopyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxybenzenesulfonamide
38		5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethylbenzamide

[00109] The compounds of Formula (I) and shown in Table 2 may be synthesized according to the procedures disclosed in US 2015/0057299, which is incorporated by reference in its entirety.

[00110] In some embodiments, P2X3 and/or P2X2/3 receptor antagonists described herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F , ^{36}Cl , respectively. Certain

isotopically labeled compounds described herein, for example those with isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. In certain embodiments, the P2X3 and/or P2X2/3 receptor antagonist is isotopically labeled P2X3 and/or P2X2/3 receptor antagonist. In some embodiments, the P2X3 and/or P2X2/3 receptor antagonist is deuterium-labeled P2X3 and/or P2X2/3 receptor antagonist.

[00111] The P2X3 and/or P2X2/3 receptor antagonist described herein may be co-administered according to the methods disclosed herein in a suitable dose as determined by one of ordinary skill in the art. Suitable dosages of the P2X3 and/or P2X2/3 receptor antagonists of the present application are described in US 2015/0057299, which is herein incorporated by reference in its entirety. In some embodiments, the dose of the P2X3 and/or P2X2/3 receptor antagonist is about 1-1000 mg daily or twice daily. In some embodiments, the dose of the P2X3 and/or P2X2/3 receptor antagonist is about 100-900 mg daily or twice daily. In some embodiments, the dose of the P2X3 and/or P2X2/3 receptor antagonist is about 500-700 mg daily or twice daily. Suitable dosage ranges include dosages comprising about 1-1000 mg multiple times (e.g, 3-4 times) per day

[00112] In some embodiments, the dose of the P2X3 and/or P2X2/3 receptor antagonist is co-administered is about 600 mg daily. In some embodiments, the dose of the P2X3 and/or P2X2/3 receptor antagonist co-administered is about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, or about 2400 mg daily.

[00113] In some embodiments, the dose of P2X3 and/or P2X2/3 receptor antagonist co-administered is about 600 mg twice daily. In some embodiments, the dose of P2X3 and/or P2X2/3 receptor antagonist co-administered is about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg twice daily.

Additional Active Agents for Combination Therapy

[00114] In some embodiments of the methods disclosed herein, additional active agents may be co-administered in addition to cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist for the treatment or prophylaxis of a lung disease or condition. In some embodiments, the further active agents are co-administered separately, or are incorporated into a composition comprising cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist. In some embodiments, the further active agent is incorporated into a composition comprising cromolyn or the pharmaceutically acceptable salt thereof. In some embodiments, the further active agent is incorporated into a composition comprising the P2X3 and/or the P2X2/3 receptor antagonist

[00115] Such further active agents include, but are not limited to, leukotriene antagonists, steroidal and non-steroidal anti-inflammatory drugs, anti-allergics, β -agonists, anticholinergics, corticosteroids, testosterone derivatives, phosphodiesterase inhibitors, endothelin antagonists, mucolytics, antibiotics, antifungals, antivirals, antioxidants, vitamins, heparinoids, α -antitrypsin, lung surfactants, anti-inflammatory compounds, glucocorticoids, anti-infective agents, antibiotics, antifungals, antivirals, antiseptics, vasoconstrictors, vasodilators, wound healing agents, local anesthetics, peptides, and proteins.

[00116] In some embodiments, anti-inflammatory compounds are co-administered with cromolyn or the pharmaceutically acceptable salt and the P2X3 and/or the P2X2/3 receptor antagonist in the methods disclosed herein. Such anti-inflammatory compounds include but are not limited to betamethasone, beclomethasone, budesonide, ciclesonide, dexamethasone, desoxymethasone, fluocinolone acetonide, flucinonide, flunisolide, fluticasone, icomethasone, rofleponide, triamcinolone acetonide, fluocortin butyl, hydrocortisone, hydroxycortisone-17-butyrate, prednicarbate, 6-methylprednisolone aceponate, mometasone furoate, elastane-, prostaglandin-, leukotriene, bradykinin-antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and indometacin.

[00117] In some embodiments, anti-allergic agents are co-administered with cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist in the methods disclosed herein. Anti-allergic agents include but are not limited to glucocorticoids, nedocromil, cetirizine, loratidine, montelukast, roflumilast, ziluton, omalizumab, heparins and heparinoids and other antihistamines, azelastine, cetirizine, desloratadine, ebastine, fexofenadine,

levocetirizine, loratadine.

[00118] In some embodiments, anti-infective agents are co-administered with cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist in the methods disclosed herein. Such anti-infective agents include but are not limited to benzylpenicillins (penicillin-G-sodium, clemizone penicillin, benzathine penicillin G), phenoxypenicillins (penicillin V, propicillin), aminobenzylpenicillins (ampicillin, amoxycillin, bacampicillin), acylaminopenicillins (azlocillin, mezlocillin, piperacillin, apalcillin), carboxypenicillins (carbenicillin, ticarcillin, temocillin), isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin, flucloxacillin), and amidine penicillins (mecillinam); cephalosporins, including cefazolins (cefazolin, cefazedone); cefuroximes (cefuroxime, cefamandole, cefotiam), cefoxitins (cefoxitin, cefotetan, latamoxef, flomoxef), cefotaximes (cefotaxime, ceftriaxone, ceftizoxime, cefinenoxime), ceftazidimes (ceftazidime, ceftiofime, cefepime), cefalexins (cefalexin, cefaclor, cefadroxil, cefradine, loracarbef, cefprozil), and cefiximes (cefixime, cefpodoxim proxetil, cefuroxime axetil, cefetamet pivoxil, cefotiam hexetil), loracarbef, cefepim, clavulanic acid/amoxicillin, ceftobiprole; synergists, including beta-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam; carbapenems, including imipenem, cilastin, meropenem, doripenem, tebipenem, ertapenem, ritipenem, and biapenem; monobactams, including aztreonam; aminoglycosides, such as apramycin, gentamicin, amikacin, isepamicin, arbekacin, tobramycin, netilmicin, spectinomycin, streptomycin, capreomycin, neomycin, paromycin, and kanamycin; macrolides, including erythromycin, clarythromycin, roxithromycin, azithromycin, dithromycin, josamycin, spiramycin and telithromycin; gyrase inhibitors or fluoroquinolones, including ciprofloxacin, gatifloxacin, norfloxacin, ofloxacin, levofloxacin, perfloxacin, lomefloxacin, fleroxacin, garenoxacin, clinafloxacin, sitafloxacin, prulifloxacin, olamufloxacin, caderofloxacin, gemifloxacin, balofloxacin, trovafloxacin, and moxifloxacin; tetracyclins, including tetracyclin, oxytetracyclin, rolitetracyclin, minocycline, doxycycline, tigecycline and aminocycline; glycopeptides, including vancomycin, teicoplanin, ristocetin, avoparcin, oritavancin, ramoplanin, and peptide 4; polypeptides, including plectasin, dalbavancin, daptomycin, oritavancin, ramoplanin, dalbavancin, telavancin, bacitracin, tyrothricin, neomycin, kanamycin, mupirocin, paromomycin, polymyxin B and colistin; sulfonamides, including sulfadiazine, sulfamethoxazole, sulfalene, co-trimoxazole, co-trimetrol, co-trimoxazine, and co-tetraxazine; azoles, including clotrimazole, oxiconazole, miconazole, ketoconazole, itraconazole, fluconazole, metronidazole, tinidazole, bifonazole, ravuconazole, posaconazole, voriconazole, and ornidazole and other antifungals including flucytosin, griseofluvin, tonofal, naftifine, terbinafine,

amorolfine, ciclopiroxolamin, echinocandins, such as micafungin, caspofungin, anidulafungin; nitrofurans, including nitrofurantoin and nitrofurazone; polyenes, including amphotericin B, natamycin, nystatin, flucytosine; other antibiotics, including tithromycin, lincomycin, clindamycin, oxazolidinones (linezolid), ranbezolid, streptogramin A+B, pristinamycin A+B, virginiamycin A+B, dalfopristin/quinupristin (Synercid), chloramphenicol, ethambutol, pyrazinamide, terizidone, dapson, prothionamide, fosfomicin, fucidinic acid, rifampicin, isoniazid, cycloserine, terizidone, ansamycin, lysostaphin, iclaprim, mirocin B17, clerocidin, filgrastim, and pentamidine; antivirals, including aciclovir, ganciclovir, birivudine, valaciclovir, zidovudine, didanosine, thiacytidine, stavudine, lamivudine, zalcitabine, ribavirin, nevirapine, delaviridine, trifluridine, ritonavir, saquinavir, indinavir, foscarnet, amantadine, podophyllotoxin, vidarabine, tromantadine, and proteinase inhibitors; plant extracts or ingredients, such as plant extracts from chamomile, hamamelis, echinacea, calendula, papain, pelargonium, essential oils, myrtol, pinen, limonen, cineole, thymol, mentol, tea tree oil, alpha-hederin, bisabolol, lycopodin, vitapherole; wound healing compounds including dexpanthenol, allantoin, vitamins, hyaluronic acid, alpha-antitrypsin, inorganic and organic zinc salts/compounds, interferones (alpha, beta, gamma), tumor necrosis factors, cytokines, interleukins.

[00119] In some embodiments, mucolytics are co-administered with cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist in the methods disclosed herein. Such mucolytics include but are not limited to DNase, P2Y2-agonists (denofosol), heparinoids, guaifenesin, acetylcysteine, carbocysteine, ambroxol, bromhexine, lecithins, myrtol, and recombinant surfactant proteins.

[00120] In some embodiments, local anesthetic agents are co-administered with cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist in the methods disclosed herein. Such local anesthetic agents include but are not limited to benzocaine, tetracaine, procaine, lidocaine and bupivacaine.

[00121] In some embodiments, peptides and proteins are co-administered with cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist in the methods disclosed herein. Such peptides and proteins include but are not limited to antibodies against toxins produced by microorganisms, antimicrobial peptides such as cecropins, defensins, thionins, and cathelicidins.

[00122] In some embodiments, immunomodulators are co-administered with cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist in the methods

disclosed herein. Such immunomodulators include but are not limited to methotrexate, azathioprine, cyclosporine A, tacrolimus, sirolimus, rapamycin, mycophenolate, mofetil, cytostatics and metastasis inhibitors, alkylants, such as nimustine, melphanlane, carmustine, lomustine, cyclophosphosphamide, ifosfamide, trofosfamide, chlorambucil, busulfane, treosulfane, prednimustine, thiotepea; antimetabolites, e.g. cytarabine, fluorouracil, methotrexate, mercaptopurine, tioguanine; alkaloids, such as vinblastine, vincristine, vindesine; antibiotics, such as alcarubicine, bleomycine, dactinomycine, daunorubicine, doxorubicine, epirubicine, idarubicine, mitomycine, plicamycine; complexes of secondary group elements (e.g., Ti, Zr, V, Nb, Ta, Mo, W, Pt) such as carboplatinum, cis-platinum and metallocene compounds such as titanocendichloride; amsacrine, dacarbazine, estramustine, etoposide, beraprost, hydroxycarbamide, mitoxanthrone, procarbazine, temiposide; paclitaxel, iressa, zactima, poly-ADP-ribose-polymerase (PRAP) enzyme inhibitors, banoxantrone, gemcitabine, pemetrexed, bevacizumab, ranibizumab.

[00123] In some embodiments, proteinase inhibitors are co-administered with cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist in the methods disclosed herein. Such proteinase inhibitors include but are not limited to alpha-anti-trypsin; antioxidants, such as tocopherols, glutathion; pituitary hormones, hypothalamic hormones, regulatory peptides and their inhibiting agents, corticotropine, tetracosactide, choriogonandotropine, urofolitropine, urogonadotropine, somatotropine, metergoline, desmopressine, oxytocine, argipressine, ornipressine, leuporeline, triptoreline, gonadoreline, busereline, nafareline, goselerine, somatostatine; parathyroid gland hormones, calcium metabolism regulators, dihydrotachysterole, calcitonine, clodronic acid, etidronic acid; thyroid gland therapeutics; sex hormones and their inhibiting agents, anabolics, androgens, estrogens, gestagenes, antiestrogenes; anti-migraine drugs, such as proxibarbal, lisuride, methysergide, dihydroergotamine, ergotamine, clonidine, pizotifene; hypnotics, sedatives, benzodiazepines, barbiturates, cyclopyrrolones, imidazopyridines, antiepileptics, zolpidem, barbiturates, phenyloin, primidone, mesuximide, ethosuximide, sultiam, carbamazepin, valproic acid, vigabatrine; antiparkinson drugs, such as levodopa, carbidopa, benserazide, selegiline, bromocriptine, amantadine, tiapride; antiemetics, such as thiethylperazine, bromopride, domperidone, granisetron, ondasetron, tropisetron, pyridoxine; analgesics, such as buprenorphine, fentanyl, morphine, codeine, hydromorphone, methadone; fentanyl, piritramide, pentazocine, buprenorphine, nalbuphine, tilidine; drugs for narcosis, such as N-methylated barbiturates, thiobarbiturates, ketamine, etomidate, propofol, benzodiazepines, droperidol, haloperidol, alfentanyl, sufentanyl; antirheumatism

drugs including tumor necrosis factor- α , nonsteroidal antiinflammatory drugs; antidiabetic drugs, such as insulin, sulfonylurea derivatives, biguanids, glitizols, glucagon, diazoxid; cytokines, such as interleukines, interferones, tumor necrosis factor (TNF), colony stimulating factors (GM-CSF, G-CSF, M-CSF); proteins, e.g. epoetine, and peptides, e.g. parathyrin, somatomedin C; heparine, heparinoids, urokinases, streptokinases, ATP-ase, prostacycline, sexual stimulants, and genetic material.

Pharmaceutical Compositions

[00124] Also provided herein are pharmaceutical compositions comprising cromolyn or a pharmaceutically acceptable salt thereof, a P2X3 and/or a P2X2/3 receptor antagonist, and a pharmaceutically acceptable excipient. In some embodiments, a pharmaceutically acceptable salt of cromolyn is selected from cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate. In some embodiments, a pharmaceutically acceptable salt of cromolyn is cromolyn sodium. In some embodiments, the composition is used for the treatment of a lung disease or condition.

[00125] In some embodiments, pharmaceutical compositions described herein are suitable for oral (including as buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Exemplary pharmaceutical formulations suitable for uses disclosed herein can be found in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[00126] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00127] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00128] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00129] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient;

and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00130] Pharmaceutical compositions may also be formulated as a depot preparation. Such long acting formulations may be co-administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00131] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[00132] Pharmaceutical compositions may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[00133] Pharmaceutical compositions may be formulated for topical administration. This includes the application of a composition externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration. Pharmaceutical compositions suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for co-administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation.

[00134] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Inhalation Therapy

[00135] An “inhalation device,” as used herein, refers to any device that is capable of administering a drug formulation to the respiratory airways of a patient. Inhalation devices include conventional inhalation devices such as metered dose inhalers (MDIs), dry powder inhalers (DPIs), jet nebulizers, ultrasonic wave nebulizers, heat vaporizers, and soft mist inhalers. Inhalation devices also include high efficiency nebulizers. Nebulizers, metered dose inhalers, and soft mist inhalers deliver pharmaceuticals by forming an aerosol which includes droplet sizes that can easily be inhaled. The aerosol can be used by a patient within the bounds of an inhalation therapy, whereby cromolyn or the pharmaceutically acceptable salt and/or the P2X3 and/or the P2X2/3 receptor antagonist reaches the patient’s respiratory tract upon inhalation. In some embodiments, the methods disclosed herein comprise administering to a patient a nominal dose of cromolyn or the pharmaceutically acceptable salt by an inhalation device. In some embodiments, cromolyn or the pharmaceutically acceptable salt and the P2X3 and/or the P2X2/3 receptor antagonist are co-administered in the same composition that is delivered with an inhalation device. In some embodiments, cromolyn or the pharmaceutically acceptable salt and the P2X3 and/or the P2X2/3 receptor antagonist are co-administered in different compositions, wherein each composition is delivered with an inhalation device. In some embodiments of the methods disclosed herein, an inhalation device is not a bronchoscope.

[00136] In some embodiments of the methods disclosed herein, the co-administration of cromolyn or the pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, with an inhalation device, e.g., a high efficiency nebulizer, a jet nebulizer, a dry powder inhaler, a metered dose inhaler, a thermal aerosol inhaler, or an electrohydrodynamic-based solution misting inhaler is effective for the treatment or prophylaxis of a lung disease or condition produces both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a high deposited lung dose of cromolyn or the pharmaceutically acceptable salt are achieved in the patient. Thus, in some embodiments of the methods disclosed herein, the co-administration of cromolyn or a pharmaceutically acceptable salt, e.g., cromolyn sodium to a patient with an inhalation device, e.g., a high efficiency nebulizer, a jet nebulizer, a dry powder inhaler, a metered dose inhaler, a thermal aerosol inhaler, or an electrohydrodynamic-based solution misting inhaler, is effective for the treatment or prophylaxis of a lung disease or condition that is not believed to be susceptible to treatment or prophylaxis with cromolyn or the pharmaceutically acceptable salt thereof because both a systemically effective amount of cromolyn or the

pharmaceutically acceptable salt thereof and a high deposited lung dose of cromolyn or the pharmaceutically acceptable salt thereof are achieved in the patient.

[00137] In some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, to a patient with an inhalation device, e.g., a high efficiency nebulizer, a jet nebulizer, a dry powder inhaler, a metered dose inhaler, a thermal aerosol inhaler, or an electrohydrodynamic-based solution misting inhaler, is effective for the treatment or prophylaxis of a lung disease or condition because both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a locally effective amount of cromolyn or the pharmaceutically acceptable salt thereof are achieved in the patient. Thus, in some embodiments of the methods disclosed herein, co-administration of cromolyn or a pharmaceutically acceptable salt, e.g., cromolyn sodium to a patient with an inhalation device, e.g., a high efficiency nebulizer, a jet nebulizer, a dry powder inhaler, a metered dose inhaler, a thermal aerosol inhaler, or an electrohydrodynamic-based solution misting inhaler, is effective for the treatment or prophylaxis of a lung disease or condition that is not believed to be susceptible to treatment or prophylaxis with cromolyn or the pharmaceutically acceptable salt because both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt and a locally effective amount of cromolyn or the pharmaceutically acceptable salt is achieved in the patient. Furthermore, in some embodiments wherein cromolyn or a pharmaceutically acceptable salt is co-administered with an inhalation device, e.g., a high efficiency nebulizer, the methods disclosed herein provide improved efficacy for the treatment or prophylaxis of a lung disease or condition relative to co-administration of a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof by a different route of administration, e.g., parenterally or orally, because administration of cromolyn or the pharmaceutically acceptable salt thereof with an inhalation device, e.g., a high efficiency nebulizer, a jet nebulizer, a dry powder inhaler, a metered dose inhaler, a thermal aerosol inhaler, or an electrohydrodynamic-based solution misting inhaler, provides both a systemically effective amount of cromolyn or the pharmaceutically acceptable salt thereof and a locally effective amount of cromolyn or the pharmaceutically acceptable salt thereof. In some embodiments, a systemically effective amount and a locally effective amount of cromolyn or a pharmaceutically acceptable salt thereof are achieved by delivering cromolyn or the pharmaceutically acceptable salt thereof in an aerosol generated by a vibrating mesh nebulizer that produces droplets with a MMD of 3.0-4.0 μm and a GSD of 1.5-1.8. In some embodiments of the methods disclosed herein, an aerosol is administered through a mouthpiece of a nebulizer using normal tidal breathing.

Characterization of Inhalation Devices

[00138] The efficiency of a particular inhalation device can be characterized in many different ways, including by pharmacokinetic properties, lung deposition (deposited lung dose), respirable dose (RD), delivered dose (DD), respirable fraction (RF), respirable drug delivery rate (RDDR), volumetric or mass median diameter (VMD or MMD), mass median aerodynamic diameter (MMAD) in combination with the geometric standard deviation (GSD), and total output rate (TOR), among others. The MMAD and GSD can be measured using a cascade impactor as described in United States Pharmacopeia (USP<1601>). The DD can be measured by using breath simulation apparatus as described in USP<1601>. The RF is derived from measuring the amount of drug deposited on the cascade impactor plates with a particular cut-off particle size, and expressing that as a fraction of the total amount deposited on the cascade impactor plates, the induction port and the filter. The RD is calculated by multiplying the DD by the RF. The TOR is measured by the difference in weight of the nebulizer before and after completion of nebulization divided by the duration of nebulization. VMD or MMD can be measured with a standard laser light scattering apparatus such as the Malvern Spraytec.

[00139] Pharmacokinetics is concerned with the uptake, distribution, metabolism and excretion of a drug substance. A pharmacokinetic profile comprises one or more biological measurements designed to measure the absorption, distribution, metabolism and excretion of a drug substance. One way of visualizing a pharmacokinetic profile is by means of a blood plasma concentration curve, which is a graph depicting mean active ingredient blood plasma concentration on the Y-axis and time (usually in hours) on the X-axis. Some pharmacokinetic parameters that may be visualized by means of a blood plasma concentration curve include AUC_{last} , $AUC_{(0-\infty)}$, C_{max} , $T_{1/2}$, and T_{max} . An enhanced pharmacokinetic profile in a patient can be indicated by increased AUC_{last} , $AUC_{(0-\infty)}$, C_{max} , or $T_{1/2}$, a decreased T_{max} , or an increased T_{max} . Enhanced levels of cromolyn or a pharmaceutically acceptable salt thereof in the blood plasma of a patient may result in better control of or improved symptoms of a lung disease or condition.

[00140] The deposited lung dose may be expressed as a percentage of the nominal dose that is deposited in the lung. For example, a lung deposition of 30% means 30% of the nominal dose is deposited in the lung. Likewise, a lung deposition of 60% means 60% of the nominal dose is deposited in the lung, and so forth. Lung deposition (deposited lung dose) can be determined using methods of scintigraphy or deconvolution.

[00141] RF, DD, RD, and RDDR are calculated parameters based on *in vitro* data that provide

technical dimensions for the efficiency of an inhalation device. RF represents the percentage of the delivered aerosol, or inhaled mass, that penetrates into the gas-exchange region of the lungs. RF may be measured with a cascade impactor or laser diffraction apparatus. RF is expressed herein as the percentage of an aerosol delivered with an inhalation device that has a particular particle diameter or range of particle diameters. For example, the term “RF ($\leq 3.3 \mu\text{m}$)” as used herein refers to the percentage of an aerosol delivered with an inhalation device that has a particle diameter less than or equal to $3.3 \mu\text{m}$. Similarly, the terms “RF (1-5 μm)” and “RF ($\leq 5 \mu\text{m}$)” as used herein refers to the percentage of an aerosol delivered with an inhalation device that has a particle diameter in the range of $1 \mu\text{m}$ to $5 \mu\text{m}$, or less than $5 \mu\text{m}$, respectively. DD is the portion of the nominal dose that is actually emitted from the mouthpiece of the device. The difference between the nominal dose and the DD is the amount of drug lost primarily as residues, i.e., the amount of drug remaining in the inhalation device after administration or lost in aerosol form. RD is an expression of the delivered mass of drug contained within droplets or particles having a certain diameter emitted from an inhalation device, such as a DPI, MDI, or nebulizer that, are small enough to penetrate into the lung of a patient. The RD is determined by multiplying the DD by the RF. RDDR is the speed at which a respirable dose of the drug is delivered to a patient’s lungs. RDDR, measured as a function of μg or mg/min , is determined by dividing the RD by the amount of time necessary for inhalation. The amount of time necessary for inhalation is measured as the amount of time from the first moment of administration of the emitted droplet or powder from the nebulizer, DPI, or MDI until the emitted or delivered droplet or powder of a respirable diameter is delivered to the lung.

[00142] Aerosol particle/droplet size is one factor determining the deposition of aerosol drugs in the airways. The distribution of aerosol particle/droplet size can be expressed in terms of one or more of VMD/MMAD and GSD. GSD is a dimensionless measure of a droplet size distribution curve relevant for characterizing terms such as VMD, MMD, and MMAD. In general, the smaller the GSD for a particular particle size distribution, the narrower the distribution curve.

Conventional Inhalation devices

[00143] Conventional inhalation devices may be mechanical or electrical, and include, for example, jet nebulizers and ultrasonic nebulizers. Jet nebulizers generally utilize compressors to generate compressed air, which breaks the liquid medication into small breathable droplets, which form an aerosolized (atomized) mist. In some embodiments, when the patient breathes in, a valve at the top

opens, which then allows air into the apparatus, thereby speeding up the mist generation; when the patient breathes out, the top valve closes, thereby slowing down the mist generation while simultaneously permitting the patient to breathe out through the opening of a mouthpiece flap. Some nebulizers may provide the aerosol in a continuous mode (e.g., the eFlow from PARI Pharma Starnberg), by a breath enhanced mode (e.g., the PARI LC Plus or Sprint from PARI Starnberg), by breath actuated mode dependent on the breathing pattern of the patient (e.g., the AeroEclipse from Trudell, Canada or the I-Neb from Philips Respironics), or according to given inhalation profile (e.g., the Akita from Activaero, Gmuenden, Germany).

[00144] Some conventional inhalation devices are disclosed in U.S. Patent Nos. 6,513,727, 6,513,519, 6,176,237, 6,085,741, 6,000,394, 5,957,389, 5,740,966, 5,549,102, 5,461,695, 5,458,136, 5,312,046, 5,309,900, 5,280,784, and 4,496,086, each of which is hereby incorporated by reference in its entirety. Commercial conventional inhalation devices are available from: PARI (Germany) under the trade names PARI LC Plus[®], LC Star[®], and PARI-Jet[®]; A & H Products, Inc. (Tulsa, OK) under the trade name AquaTower[®]; Hudson RCI (Temecula, CA) under the trade name AVA-NEB[®]; Intersurgical, Inc. (Liverpool, NY) under the trade name Cirrus[®]; Salter Labs (Arvin, CA) under the trade name Salter 8900[®]; Respironics (Murrysville, PA) under the trade name Sidestream[®]; Bunnell (Salt Lake City, UT) under the trade name Whisper Jet[®]; Smiths-Medical (Hyth Kent, UK) under the trade name Downdraft[®], and DeVilbiss (Somerset, PA) under the trade name DeVilbiss[®]; or Trudell, Canada under the trade name AeroEclipse[®].

[00145] In some embodiments, the compositions disclosed herein are co-administered with a jet nebulizer. In some embodiments, cromolyn or a pharmaceutically acceptable salt is co-administered with a jet nebulizer. In some embodiments, the P2X3 and/or the P2X2/3 receptor antagonist is co-administered with a jet nebulizer.

[00146] In some embodiments of the methods disclosed herein, compositions disclosed herein are administered with dry powder inhalers comprise one or more of nanoparticles, spray dried materials, engineered porous particles with low mass median diameter but a high geometric diameter, liposomes, and stealth (or PEGylated) liposomes. In some embodiments, compositions disclosed herein are administered by dry powder inhalers administered in the methods disclosed herein comprise nanoparticle clusters that aggregate into micrometer sized particles at neutral or basic pH but dissociate into nanoparticles at the pH encountered in the lung. In some embodiments the nanoparticle clusters comprise fumaryl diketopiperazine. In some embodiments, the compositions are co-administered with

dry powder inhalers comprise lactose. In some embodiments, the compositions are co-administered with dry powder inhalers do not comprise lactose. In some embodiments, compositions are co-administered with a dry powder inhaler have a MMAD between 2 and 4 μm , a GSD between 1.5 and 2.5 μm , and an RF($\leq 5 \mu\text{m}$) between 30% and 80%. In some embodiments, a dry powder inhaler used to administer an inhalation formulation in the methods disclosed herein comprises a pre-metered dose, such as Plastiapre Monodose inhaler, which comprises a capsule pre-filled with a powder. In some embodiments, a dry powder inhaler used to administer an inhalation formulation in the methods disclosed herein has a device-metered system such as Twisthaler, sold by Schering Plough, which comprises a reservoir to store a powder and a twisting top to dispense each dose. In some embodiments, the inhalation formulations for administration with a dry powder inhaler are prepared by blending cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, with lactose, or spray drying cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, or by pelletizing cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, to form free-flowing spherical agglomerates.

[00147] In some embodiments of the methods disclosed herein, a composition is co-administered with a metered dose inhaler. In some embodiments, the composition co-administered with a metered dose inhaler in the methods disclosed herein comprises one or more of nanoparticles, spray dried materials, engineered porous particles with low mass median diameter but a high geometric diameter, liposomes, and stealth (or PEGylated) liposomes.

[00148] In some embodiments of the methods disclosed herein, a composition is co-administered with a thermal aerosol inhaler. In some embodiments, the aerosol in a thermal aerosol inhaler is generated by directly heating and vaporizing a thin solid film of cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, or by heating and vaporizing a solution of cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, in solvents such as propylene glycol and/or glycerol and water.

[00149] In some embodiments of the methods disclosed herein, a composition is co-administered with an electrohydrodynamic-based solution misting inhaler. In some embodiments, the aerosol in the electrohydrodynamic-based solution-misting inhaler is generated by subjecting a solution of cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, or a liposome or pegylated liposome comprising cromolyn or a pharmaceutically acceptable salt thereof, e.g., cromolyn sodium, to electrohydrodynamic forces through electrostatic energy.

High Efficiency Nebulizers

[00150] High efficiency nebulizers are inhalation devices that comprise a micro-perforated membrane through which a liquid solution is converted through electrical or mechanical means into aerosol droplets suitable for inhalation. High efficiency nebulizers can deliver a large fraction of a loaded dose to a patient. In some embodiments, the high efficiency nebulizer also utilizes one or more actively or passively vibrating microperforated membranes. In some embodiments, the high efficiency nebulizer contains one or more oscillating membranes. In some embodiments, the high efficiency nebulizer contains a vibrating mesh or plate with multiple apertures and optionally a vibration generator with an aerosol mixing chamber. In some such embodiments, the mixing chamber functions to collect (or stage) the aerosol from the aerosol generator. In some embodiments, an inhalation valve is also used to allow an inflow of ambient air into the mixing chamber during an inhalation phase and is closed to prevent escape of the aerosol from the mixing chamber during an exhalation phase. In some such embodiments, the exhalation valve is arranged at a mouthpiece which is removably mounted at the mixing chamber and through which the patient inhales the aerosol from the mixing chamber. Still yet, in some embodiments, the high efficiency nebulizer contains a pulsating membrane. In some embodiments, the high efficiency nebulizer is continuously operating.

[00151] In some embodiments, the high efficiency nebulizer contains a vibrating micro-perforated membrane of tapered nozzles that generates a plume of droplets without the need for compressed gas. In these embodiments, a solution in the micro-perforated membrane nebulizer is in contact with a membrane, the opposite side of which is open to the air. The membrane is perforated by a large number of nozzle orifices of an atomizing head. An aerosol is created when alternating acoustic pressure in the solution is built up in the vicinity of the membrane causing the fluid on the liquid side of the membrane to be emitted through the nozzles as uniformly sized droplets.

[00152] Some embodiments of high efficiency nebulizers use passive nozzle membranes and a separate piezoelectric transducer that stimulates the membrane. In contrast, some high efficiency nebulizers employ an active nozzle membrane, which use the acoustic pressure in the nebulizer to generate very fine droplets of solution via the high frequency vibration of the nozzle membrane.

[00153] Some high efficiency nebulizers contain a resonant system. In some such high efficiency nebulizers, the membrane is driven by a frequency for which the amplitude of the vibrational movement at the center of the membrane is particularly large, resulting in a focused acoustic pressure in the vicinity of the nozzle; the resonant frequency may be about 100 kHz. A flexible mounting is used to keep

unwanted loss of vibrational energy to the mechanical surroundings of the atomizing head to a minimum. In some embodiments, the vibrating membrane of the high efficiency nebulizer may be made stainless steel, or of a nickel-palladium alloy by electroforming.

[00154] In some embodiments, a high efficiency nebulizer may be adapted or adaptable to operate in conjunction with a unit dosage form, such as an ampule or vial, which contains a single dose of cromolyn or a pharmaceutically acceptable salt thereof for the treatment of a lung disease or condition. The unit dosage form comprises a container that contains an inhalation formulation comprising cromolyn or a pharmaceutically acceptable salt thereof, such as cromolyn sodium. The container is adapted to cooperate with the high efficiency nebulizer device in such a way as to permit administration of the nominal dose of the inhalation formulation to a patient. In some embodiments, the high efficiency nebulizer and the unit dosage form are configured so that they are useable together, but not with other devices or dosage forms. In some particular embodiments, the unit dosage form is configured such that it fits into a keyhole-like structure in the high efficiency nebulizer, but will not operate with other nebulizer devices. In such embodiments, the high efficiency nebulizer is configured such that it will accept and properly operate with the unit dosage form containing cromolyn or a pharmaceutically acceptable salt thereof but not with other dosage forms.

[00155] In some embodiments, co-administration is with a high efficiency nebulizer. In some embodiments, cromolyn or a pharmaceutically acceptable salt thereof is co-administered with a high efficiency nebulizer. In some embodiments, cromolyn sodium is co-administered with a high efficiency nebulizer. In some embodiments, a P2X3 and/or a P2X2/3 receptor antagonist, is co-administered with a high efficiency nebulizer.

[00156] Commercial high efficiency nebulizers are available from: PARI (Germany) under the trade name eFlow[®]; Aerogen, Ltd.(Ireland) under the trade names AeroNeb[®] Go and AeroNeb[®] Pro, AeroNeb[®] Solo, and other nebulizers utilizing the OnQ[®] nebulizer technology; Respironics (Murrysville, CA) under the trade names I-Neb[®]; Omron (Bannockburn, IL) under the trade name Micro-Air[®]; Activaero (Germany) under the trade name Akita[®], and AerovectRx (Atlanta, GA) under the trade name AerovectRx[®].

[00157] In some embodiments, the DD expressed as the percentage of the nominal dose of cromolyn or the pharmaceutically acceptable salt thereof administered with a high efficiency nebulizer in the methods disclosed herein is at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, about 65%,

about 70%, about 30% to about 90%, about 40% to about 80%, about 45% to about 75%, about 50% to about 70%, about 30% to about 75%, about 40% to about 70%, about 45% to about 60%, or about 60% to about 70%.

[00158] TOR is the speed at which the liquid containing cromolyn or the pharmaceutically acceptable salt thereof is administered from the inhalation device. In some embodiments, administration of cromolyn or the pharmaceutically acceptable salt thereof with the high efficiency nebulizer provides a TOR of at least about 2 times, 3 times or 4 times the TOR achievable with a conventional inhalation device, such as a nebulizer. For example, in some embodiments the TOR is at least about at least about 150 mg/min, at least about 200 mg/min, at least about 250 mg/min, at least 300 mg/min, at least 350 mg/min, at least 400 mg/min, at least 500 mg/min, or from 200 to about 700 mg /min.

[00159] In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF ($\leq 3.3 \mu\text{m}$) of cromolyn or a pharmaceutically acceptable salt thereof of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, or about 55% to about 90%. In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF ($\leq 3.3 \mu\text{m}$) of cromolyn or a pharmaceutically acceptable salt thereof of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, about 55% to about 90%, about 40% to about 50%, about 35% to about 45%, about 35% to about 50%, about 30% to about 50%, about 44%, or about 36%.

[00160] In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF (1-5 μm) of cromolyn or a pharmaceutically acceptable salt thereof of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at

least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, or about 55% to about 90%. In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF (1-5 μ m) of cromolyn sodium of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, or about 55% to about 90%.

[00161] In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF ($\leq 5 \mu$ m) of cromolyn or a pharmaceutically acceptable salt thereof of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, or about 55% to about 90%. In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RF ($\leq 5 \mu$ m) of cromolyn or a pharmaceutically acceptable salt thereof of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 20% to about 95%, about 35% to about 90%, or about 40% to about 80%, about 40% to about 90%, about 40% to about 95%, about 45% to about 90%, about 45% to about 95%, about 50 % to about 90%, about 65% to about 90%, about 60% to about 95%, about 65% to about 95%, about 70% to about 90%, about 55% to about 90%, about 70% to about 80%, about 65% to about 75%, about 65% to about 80%, about 60% to about 80%, about 66%, or about 75%.

[00162] In some embodiments, use of a high efficiency nebulizer in the methods disclosed herein provides a RDDR of at least about 2 times, at least about 3 times or at least about 4 times the RDDR achievable with a conventional inhalation device. For example, wherein the pharmaceutically acceptable salt of cromolyn is cromolyn sodium, in some embodiments the RDDR is at least about 5 mg/min, at least about 10 mg/min, at least about 15 mg/min, at least about 20 mg/min, at least about 25 mg/min, at least about 30 mg/min, at least about 35 mg/min, at least about 40 mg/min, at least about 45 mg/min, at least about 50 mg/min, at least about 55 mg/min, or at least about 60 mg/min.

[00163] In some embodiments, administration of cromolyn or a pharmaceutically acceptable salt thereof with a high efficiency nebulizer in the methods disclosed herein provides a GSD of emitted droplet size distribution of about 1.1 to about 2.1, about 1.2 to about 2.0, about 1.3 to about 1.9, less than about 2, at least about 1.4 to about 1.8, at least about 1.5 to about 1.7, about 1.4, about 1.5, about 1.6, or about 1.7. In some embodiments, administration of cromolyn or a pharmaceutically acceptable salt thereof with a high efficiency nebulizer in the methods disclosed herein provides a MMAD of droplet size of about 1 μm to about 5 μm , about 2 to about 4 μm , about 3 to about 4 μm , about 3.5 to about 4.5 μm , or about 3.5 μm . In some particular embodiments, administration of cromolyn or a pharmaceutically acceptable salt thereof in the methods disclosed herein provides droplets having a particular combination of MMAD and GSD, for example: an MMAD of less than about 5 μm and a GSD of about 1.1 to about 2.1; an MMAD of less than about 4.5 μm and a GSD of about 1.1 to about 2.1; an MMAD of about 1 μm to about 5 μm and a GSD of about 1.1 to about 2.1; an MMAD of about 1.5 to about 4.5 μm and a GSD of about 1.1 to about 2.1; an MMAD of less than about 5 μm and a GSD of about 1.1 to about 2.0; an MMAD of less than about 4.5 μm and a GSD of about 1.1 to about 2.0; an MMAD of about 1 μm to about 5 μm and a GSD of about 1.1 to about 2.0; an MMAD of about 1.5 to about 4.5 μm and a GSD of about 1.1 to about 2.0; an MMAD of less than about 5 μm and a GSD of about 1.1 to about 1.9; an MMAD of less than about 4.5 μm and a GSD of about 1.1 to about 1.9; an MMAD of about 1 μm to about 5 μm and a GSD of about 1.1 to about 1.9; an MMAD of about 1.5 to about 4.5 μm and a GSD of about 1.1 to about 1.9; an MMAD of less than about 5 μm and a GSD of about 1.1 to about 1.8; an MMAD of less than about 4.5 μm and a GSD of about 1.1 to about 1.8; an MMAD of about 1 μm to about 5 μm and a GSD of about 1.1 to about 1.8; an MMAD of about 1.5 to about 4.5 μm and a GSD of about 1.1 to about 1.8; an MMAD of about 3.5 μm or less and a GSD of about 1.7; an MMAD of about 4.1 μm or less and a GSD of about 1.7; an MMAD of about 3.5 μm and a GSD of about 1.7; or an MMAD of about 4.1 μm and a GSD of about 1.7.

[00164] In some embodiments, the median particle size of cromolyn or a pharmaceutically acceptable salt thereof aerosol administered with a high efficiency nebulizer is between about 1 μm and about 6 μm , between about 2 μm and about 5 μm , between about 3 μm and about 5 μm , between about 3 μm and about 4 μm , about 1 μm , about 2 μm , about 3 μm , about 4 μm , about 5 μm , or about 6 μm . In some embodiments, the median particle size of cromolyn sodium aerosol administered with a high efficiency nebulizer is between about 1 μm and about 6 μm , between about 2 μm and about 5 μm , between about 3 μm and about 5 μm , between about 3 μm and about 4 μm , about 1 μm , about 2 μm , about 3 μm , about 4 μm , about 5 μm , or about 6 μm .

Inhalation Formulations

[00165] In some embodiments of the methods disclosed herein, inhalation formulations are administered with an inhalation device to provide a systemically effective amount of cromolyn or a pharmaceutically acceptable salt thereof and a locally effective amount of cromolyn or a pharmaceutically acceptable salt thereof for the treatment of a lung disease or condition. In some embodiments of the methods disclosed herein, inhalation formulations are administered with an inhalation device to provide a systemically effective amount of cromolyn or a pharmaceutically acceptable salt thereof and a high deposited lung dose of cromolyn or a pharmaceutically acceptable salt thereof for the treatment of a lung disease or condition. In some embodiments of the methods disclosed herein, inhalation formulations are administered with an inhalation device to provide a systemically effective amount of cromolyn or a pharmaceutically acceptable salt thereof, a locally effective amount of cromolyn or a pharmaceutically acceptable salt thereof, and a high deposited lung dose of cromolyn or a pharmaceutically acceptable salt thereof for the treatment of a lung disease or condition. In some embodiments, the methods disclosed herein comprise administering a nominal dose of one or more cromolyn or a pharmaceutically acceptable salt thereof in an aqueous inhalation solution to the patient with an inhalation device, e.g., a high efficiency nebulizer.

[00166] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 100 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 110 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 120 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 130 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 140 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 150 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 160 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 170 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about 180 $\text{ng}\cdot\text{hr}/\text{mL}$, greater than about

190 ng*hr/mL, greater than about 200 ng*hr/mL, greater than about 225 ng*hr/mL, greater than about 250 ng*hr/mL, greater than about 275 ng*hr/mL, greater than about 300 ng*hr/mL, greater than about 325 ng*hr/mL, greater than about 350 ng*hr/mL, greater than about 375 ng*hr/mL, greater than about 400 ng*hr/mL, greater than about 425 ng*hr/mL, greater than about 450 ng*hr/mL, greater than about 475 ng*hr/mL, greater than about 500 ng*hr/mL, greater than about 525 ng*hr/mL, greater than about 550 ng*hr/mL, greater than about 575 ng*hr/mL, greater than about 600 ng*hr/mL, greater than about 625 ng*hr/mL, greater than about 650 ng*hr/mL, greater than about 675 ng*hr/mL, greater than about 700 ng*hr/mL, greater than about 725 ng*hr/mL, greater than about 750 ng*hr/mL, greater than about 775 ng*hr/mL, greater than about 800 ng*hr/mL, greater than about 825 ng*hr/mL, greater than about 850 ng*hr/mL, greater than about 875 ng*hr/mL, greater than about 900 ng*hr/mL, greater than about 925 ng*hr/mL, greater than about 950 ng*hr/mL, greater than about 975 ng*hr/mL, or greater than about 1000 ng*hr/mL after administration of the formulation to the patient. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof of about 100 ng*hr/mL, about 110 ng*hr/mL, about 120 ng*hr/mL, about 130 ng*hr/mL, about 140 ng*hr/mL, about 150 ng*hr/mL, about 160 ng*hr/mL, about 170 ng*hr/mL, about 180 ng*hr/mL, about 190 ng*hr/mL, about 200 ng*hr/mL, about 225 ng*hr/mL, about 250 ng*hr/mL, about 275 ng*hr/mL, about 300 ng*hr/mL, about 325 ng*hr/mL, about 350 ng*hr/mL, about 375 ng*hr/mL, about 400 ng*hr/mL, about 425 ng*hr/mL, about 450 ng*hr/mL, about 475 ng*hr/mL, about 500 ng*hr/mL, about 525 ng*hr/mL, about 550 ng*hr/mL, about 575 ng*hr/mL, about 600 ng*hr/mL, about 625 ng*hr/mL, about 650 ng*hr/mL, about 675 ng*hr/mL, about 700 ng*hr/mL, about 725 ng*hr/mL, about 750 ng*hr/mL, about 775 ng*hr/mL, about 800 ng*hr/mL, about 825 ng*hr/mL, about 850 ng*hr/mL, about 875 ng*hr/mL, about 900 ng*hr/mL, about 925 ng*hr/mL, about 950 ng*hr/mL, about 975 ng*hr/mL, or about 1000 ng*hr/mL after administration of the formulation to the patient.

[00167] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 5 ng*hr/mL, greater than about 10 ng*hr/mL, greater than about 15 ng*hr/mL, greater than about 20 ng*hr/mL, greater than about 25 ng*hr/mL, greater than about 30 ng*hr/mL, greater than about 35 ng*hr/mL, greater than about 40 ng*hr/mL, greater than about 45 ng*hr/mL, greater than about 50

ng*hr/mL, greater than about 55 ng*hr/mL, greater than about 60 ng*hr/mL, greater than about 65 ng*hr/mL, greater than about 70 ng*hr/mL, greater than about 75 ng*hr/mL, greater than about 80 ng*hr/mL, greater than about 85 ng*hr/mL, greater than about 90 ng*hr/mL, greater than about 95 ng*hr/mL, greater than about 100 ng*hr/mL, greater than about 105 ng*hr/mL, greater than about 110 ng*hr/mL, greater than about 115 ng*hr/mL, or greater than about 120 ng*hr/mL after administration of the formulation to the patient. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof about 5 ng*hr/mL, about 10 ng*hr/mL, about 15 ng*hr/mL, about 20 ng*hr/mL, about 25 ng*hr/mL, about 30 ng*hr/mL, about 35 ng*hr/mL, about 40 ng*hr/mL, about 45 ng*hr/mL, about 50 ng*hr/mL, about 55 ng*hr/mL, about 60 ng*hr/mL, about 65 ng*hr/mL, about 70 ng*hr/mL, about 75 ng*hr/mL, about 80 ng*hr/mL, about 85 ng*hr/mL, about 90 ng*hr/mL, about 95 ng*hr/mL, about 100 ng*hr/mL, about 105 ng*hr/mL, about 110 ng*hr/mL, about 115 ng*hr/mL, or about 120 ng*hr/mL after administration of the formulation to the patient.

[00168] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof greater than about 40 ng/mL, greater than about 50 ng/mL, greater than about 60 ng/mL, greater than about 70 ng/mL, greater than about 80 ng/mL, greater than about 90 ng/mL, greater than about 100 ng/mL, greater than about 110 ng/mL, greater than about 120 ng/mL, greater than about 130 ng/mL, greater than about 140 ng/mL, greater than about 150 ng/mL, greater than about 160 ng/mL, greater than about 170 ng/mL, greater than about 180 ng/mL, greater than about 190 ng/mL, greater than about 200 ng/mL, greater than about 210 ng/mL, greater than about 220 ng/mL, greater than about 230 ng/mL, greater than about 240 ng/mL, greater than about 250 ng/mL, greater than about 260 ng/mL, greater than about 270 ng/mL, greater than about 280 ng/mL, greater than about 290 ng/mL, greater than about 300 ng/mL, greater than about 310 ng/mL, greater than about 320 ng/mL, greater than about 330 ng/mL, greater than about 340 ng/mL, greater than about 350 ng/mL, greater than about 360 ng/mL, greater than about 370 ng/mL, greater than about 380 ng/mL, greater than about 390 ng/mL, or greater than about 400 ng/mL after administration of the formulation to the patient. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof about 50

mg/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, 90 ng/mL, about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL, about 150 ng/mL, about 160 ng/mL, about 170 ng/mL, about 180 ng/mL, about 190 ng/mL, about 200 ng/mL, about 210 ng/mL, about 220 ng/mL, about 230 ng/mL, about 240 ng/mL, about 250 ng/mL, 260 ng/mL, about 270 ng/mL, about 280 ng/mL, about 290 ng/mL, about 300 ng/mL, about 310 ng/mL, about 320 ng/mL, about 330 ng/mL, about 340 ng/mL, about 350 ng/mL, about 360 ng/mL, about 370 ng/mL, about 380 ng/mL, about 390 ng/mL, or about 400 ng/mL after administration of the formulation to the patient.

[00169] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof greater than about 55 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof greater than about 55 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 200 ng*hr/mL and an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof greater than about 80 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 330 ng*hr/mL and an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof greater than about 150 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 525 ng*hr/mL and an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof greater than about 230 ng/mL.

[00170] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 200 ng*hr/mL and an average C_{max} of

cromolyn sodium of about 80 ng/mL when a nominal dose of 40 mg of cromolyn sodium is administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 330 ng*hr/mL and an average C_{max} of cromolyn sodium of about 150 ng/mL when a nominal dose of 40 mg of cromolyn sodium is administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 525 ng*hr/mL and an average C_{max} of cromolyn sodium of about 230 ng/mL when a nominal dose of 80 mg of cromolyn sodium is administered with the inhalation device.

[00171] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 180 ng*hr/mL to about 220 ng*hr/mL and an average C_{max} of cromolyn sodium of about 70 ng/mL to about 90 ng/mL when a nominal dose of 40 mg of cromolyn sodium is administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 300 ng*hr/mL to about 360 ng*hr/mL and an average C_{max} of cromolyn sodium of about 135 ng/mL to about 165 ng/mL when a nominal dose of 40 mg of cromolyn sodium is administered with the inhalation device. In some embodiments, of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 475 ng*hr/mL to about 575 ng*hr/mL and an average C_{max} of cromolyn sodium of about 200 ng/mL to about 260 ng/mL when a nominal dose of 80 mg of cromolyn sodium is administered with the inhalation device.

[00172] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 120 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 200 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%. In some

embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 330 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%. In some embodiments, of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 525 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%.

[00173] In some embodiments of the methods disclosed herein, an inhalation formulation comprising 40 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 200 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%. In some embodiments of the methods disclosed herein, an inhalation formulation comprising 40 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 330 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%. In some embodiments, of the methods disclosed herein, an inhalation formulation comprising 80 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 525 ng*hr/mL and a deposited lung dose of cromolyn sodium greater than about 30%.

[00174] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 30% and produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 30% and produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 200 ng*hr/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 330 ng*hr/mL. In some embodiments, of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high

efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 525 $\text{ng}\cdot\text{hr}/\text{mL}$.

[00175] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 30% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 120 $\text{ng}\cdot\text{hr}/\text{mL}$. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 30% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 200 $\text{ng}\cdot\text{hr}/\text{mL}$. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 330 $\text{ng}\cdot\text{hr}/\text{mL}$. In some embodiments, of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 525 $\text{ng}\cdot\text{hr}/\text{mL}$.

[00176] In some embodiments of the methods disclosed herein, an inhalation formulation comprising 40 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 30% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 200 $\text{ng}\cdot\text{hr}/\text{mL}$. In some embodiments of the methods disclosed herein, an inhalation formulation comprising 40 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 330 $\text{ng}\cdot\text{hr}/\text{mL}$. In some embodiments of the methods disclosed herein, an inhalation formulation comprising 80 mg cromolyn sodium administered with an inhalation device, e.g., a high efficiency nebulizer, has an RF ($\leq 3.3 \mu\text{m}$) of at least about 40% and produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium greater than about 525 $\text{ng}\cdot\text{hr}/\text{mL}$.

[00177] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of cromolyn sodium of about 8.5 $\text{ng}\cdot\text{hr}/\text{mL}$ and an average C_{max} of cromolyn

sodium of about 3.9 ng/mL per mg of cromolyn sodium administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 6.6 ng*hr/mL and an average C_{max} of cromolyn sodium of about 3.0 ng/mL per mg of cromolyn sodium administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 5.3 ng*hr/mL and an average C_{max} of cromolyn sodium of about 2.2 ng/mL per mg of cromolyn sodium administered with the inhalation device. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of from about 5.3 ng*hr/mL to about 8.5 ng*hr/mL and an average C_{max} of cromolyn sodium of about 2.2 ng/mL to about 3.9 ng/mL per mg of cromolyn sodium administered with the inhalation device when the nominal dose of cromolyn sodium administered is in the range of about 40 mg to about 80 mg.

[00178] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof greater than about 1 ng/mL, greater than about 2 ng/mL, greater than about 3 ng/mL, greater than about 4 ng/mL, greater than about 5 ng/mL, greater than about 6 ng/mL, greater than about 7 ng/mL, greater than about 8 ng/mL, greater than about 9 ng/mL, greater than about 10 ng/mL, greater than about 11 ng/mL, greater than about 12 ng/mL, greater than about 13 ng/mL, greater than about 14 ng/mL, greater than about 15 ng/mL, greater than about 16 ng/mL, greater than about 17 ng/mL, greater than about 18 ng/mL, greater than about 19 ng/mL, greater than about 20 ng/mL, greater than about 21 ng/mL, greater than about 22 ng/mL, greater than about 23 ng/mL, greater than about 24 ng/mL, greater than about 25 ng/mL, greater than about 26 ng/mL, greater than about 27 ng/mL, greater than about 28 ng/mL, greater than about 29 ng/mL, greater than about 30 ng/mL, greater than about 35 ng/mL, greater than about 40 ng/mL, greater than about 45 ng/mL, greater than about 50 ng/mL, greater than about 55 ng/mL, greater than about 60 ng/mL, or greater than about 65 ng/mL after administration of the formulation to the patient. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average C_{max} of cromolyn or a pharmaceutically acceptable salt thereof about 1 ng/mL, about 2 ng/mL, about 3 ng/mL, about 4 ng/mL,

about 5 ng/mL, about 6 ng/mL, about 7 ng/mL, about 8 ng/mL, about 9 ng/mL, about 10 ng/mL, about 11 ng/mL, about 12 ng/mL, about 13 ng/mL, about 14 ng/mL, about 15 ng/mL, about 16 ng/mL, about 17 ng/mL, about 18 ng/mL, about 19 ng/mL, about 20 ng/mL, about 21 ng/mL, about 22 ng/mL, about 23 ng/mL, about 24 ng/mL, about 25 ng/mL, about 26 ng/mL, about 27 ng/mL, about 28 ng/mL, about 29 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 45 ng/mL, about 50 ng/mL, about 55 ng/mL, about 60 ng/mL, or about 65 ng/mL after administration of the formulation to the patient.

[00179] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $C_{\max}$ of cromolyn sodium greater than about 1 ng/mL, greater than about 2 ng/mL, greater than about 3 ng/mL, greater than about 4 ng/mL, greater than about 5 ng/mL, greater than about 6 ng/mL, greater than about 7 ng/mL, greater than about 8 ng/mL, greater than about 9 ng/mL, greater than about 10 ng/mL, greater than about 11 ng/mL, greater than about 12 ng/mL, greater than about 13 ng/mL, greater than about 14 ng/mL, greater than about 15 ng/mL, greater than about 16 ng/mL, greater than about 17 ng/mL, greater than about 18 ng/mL, greater than about 19 ng/mL, greater than about 20 ng/mL, greater than about 21 ng/mL, greater than about 22 ng/mL, greater than about 23 ng/mL, greater than about 24 ng/mL, greater than about 25 ng/mL, greater than about 26 ng/mL, greater than about 27 ng/mL, greater than about 28 ng/mL, greater than about 29 ng/mL, greater than about 30 ng/mL, greater than about 35 ng/mL, greater than about 40 ng/mL, greater than about 45 ng/mL, greater than about 50 ng/mL, greater than about 55 ng/mL, greater than about 60 ng/mL, or greater than about 65 ng/mL after administration of the formulation to the patient. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $C_{\max}$ of cromolyn sodium about 1 ng/mL, about 2 ng/mL, about 3 ng/mL, about 4 ng/mL, about 5 ng/mL, about 6 ng/mL, about 7 ng/mL, about 8 ng/mL, about 9 ng/mL, about 10 ng/mL, about 11 ng/mL, about 12 ng/mL, about 13 ng/mL, about 14 ng/mL, about 15 ng/mL, about 16 ng/mL, about 17 ng/mL, about 18 ng/mL, about 19 ng/mL, about 20 ng/mL, about 21 ng/mL, about 22 ng/mL, about 23 ng/mL, about 24 ng/mL, about 25 ng/mL, about 26 ng/mL, about 27 ng/mL, about 28 ng/mL, about 29 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 45 ng/mL, about 50 ng/mL, about 55 ng/mL, about 60 ng/mL, or about 65 ng/mL after administration of the formulation to the patient.

[00180] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an

average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof greater than about 15 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof greater than about 15 ng/mL.

[00181] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium thereof greater than about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof greater than about 15 ng/mL. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 40 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof greater than about 15 ng/mL.

[00182] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium thereof greater than about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof greater than about 15 ng/mL when a nominal dose of 20 mg of sodium cromolyn is administered with the inhalation device, e.g., a jet nebulizer. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium greater than about 40 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof greater than about 15 ng/mL when a nominal dose of 20 mg of cromolyn sodium is administered with the inhalation device, e.g., a jet nebulizer.

[00183] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium thereof of about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof of about 15 ng/mL when a nominal dose of 20 mg of sodium cromolyn is administered with the inhalation device, e.g., a jet nebulizer. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation

device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 40 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof of about 15 ng/mL when a nominal dose of 20 mg of cromolyn sodium is administered with the inhalation device, e.g., a jet nebulizer.

[00184] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium thereof of about 20 ng*hr/mL to about 60 ng*hr/mL and/or an average C_{max} of the cromolyn or a pharmaceutically acceptable salt thereof of about 5 ng/mL to about 25 ng/mL when a nominal dose of 20 mg of sodium cromolyn is administered with the inhalation device, e.g., a jet nebulizer. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn sodium of about 20 ng*hr/mL to about 60 ng*hr/mL and an average C_{max} of cromolyn or the pharmaceutically acceptable salt thereof of about 5 ng/mL to about 25 ng/mL when a nominal dose of 20 mg of cromolyn sodium is administered with the inhalation device, e.g., a jet nebulizer.

[00185] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, produces in a human subject group an average $AUC_{(0-\infty)}$ of cromolyn or a pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL and a deposited lung dose of cromolyn or a pharmaceutically acceptable salt thereof greater than about 5%.

[00186] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn or a pharmaceutically acceptable salt thereof lung deposition (deposited lung dose) of at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, about 20% to about 40%, about 25% to about 35%, about 25 to about 30%, about 25% to about 75%, about 30% to about 50%, about 35% to about 90%, about 40% to about 80%, about 40% to about 60%, about 50% to about 60%, about 50% to about 70%, or about 60% to about 75% based on the nominal dose of cromolyn or a pharmaceutically acceptable salt thereof. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn sodium deposition (deposited lung dose) of at least about 15%, at least about 20%, at least

about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, about 20% to about 40%, about 25% to about 35%, about 25 to about 30%, about 25% to about 75%, about 30% to about 50%, about 35% to about 90%, about 40% to about 80%, about 40% to about 60%, about 50% to about 60%, about 50% to about 70%, or about 60% to about 75% based on the nominal dose of the cromolyn sodium.

[00187] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn or a pharmaceutically acceptable salt thereof lung deposition (deposited lung dose) of about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% about 80%, about 85%, about 90%, about 95%, or about 100% based on the nominal dose of the cromolyn or pharmaceutically acceptable salt thereof. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn sodium lung deposition (deposited lung dose) of about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% about 80%, about 85%, about 90%, about 95%, or about 100% based on the nominal dose of the cromolyn sodium.

[00188] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, provides cromolyn or a pharmaceutically acceptable salt thereof lung deposition (deposited lung dose) of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% about 80%, about 85%, about 90%, about 95%, or about 100% based on the nominal dose of the cromolyn or pharmaceutically acceptable salt thereof. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a jet nebulizer, provides cromolyn sodium lung deposition (deposited lung dose) of about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% about 80%, about 85%, about 90%, about 95%, or about 100% based on the nominal dose of the cromolyn sodium.

[00189] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn or a pharmaceutically acceptable salt thereof lung deposition (deposited lung dose) of greater than about 0.5 mg, greater than about 1 mg, greater than about 1.5 mg, greater than about 2 mg, greater than about 2.5

mg, greater than about 3 mg, greater than about 3.5 mg, greater than about 4 mg, greater than about 5 mg, greater than about 6 mg, greater than about 7 mg, greater than about 8 mg, greater than about 9 mg, greater than about 10 mg, greater than about 11 mg, greater than about 12 mg, greater than about 13 mg, greater than about 14 mg, or greater than about 15 mg. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn or a pharmaceutically acceptable salt thereof lung deposition (deposited lung dose) of about 0.5 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 5.0 mg, about 6.0 mg, about 7.0 mg, about 8.0 mg, about 9.0 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, or about 15 mg.

[00190] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn sodium lung deposition (deposited lung dose) of greater than about 0.5 mg, greater than about 1 mg, greater than about 1.5 mg, greater than about 2 mg, greater than about 2.5 mg, greater than about 3 mg, greater than about 3.5 mg, greater than about 4 mg, greater than about 5 mg, greater than about 6 mg, greater than about 7 mg, greater than about 8 mg, greater than about 9 mg, greater than about 10 mg, greater than about 11 mg, greater than about 12 mg, greater than about 13 mg, greater than about 14 mg, or greater than about 15 mg. In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, provides cromolyn sodium lung deposition (deposited lung dose) of about 0.5 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 5.0 mg, about 6.0 mg, about 7.0 mg, about 8.0 mg, about 9.0 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, or about 15 mg.

[00191] In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device, e.g., a high efficiency nebulizer, at an administration of less than about 1 mg/dose, about 1 mg/dose to about 100 mg/dose, about 5 mg/dose to about 80 mg/dose, about 20 mg/dose to about 60 mg/dose, about 30 mg/dose to about 50 mg/dose, or greater than 100 mg/dose. In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn sodium is administered with an inhalation device, e.g., a high efficiency nebulizer, at an administration of less than about 1 mg/dose, about 1 mg/dose to about 100 mg/dose, about 5 mg/dose to about 80 mg/dose, about 20 mg/dose to about 60 mg/dose, about 30 mg/dose to about 50 mg/dose, or greater than 100 mg/dose. In some embodiments of the methods disclosed herein, cromolyn or the pharmaceutically acceptable salt

thereof is administered in an inhalation formulation with an inhalation device, e.g., a high efficiency nebulizer, in about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg doses, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg doses. In some embodiments of the methods disclosed herein, cromolyn sodium is administered in an inhalation formulation with an inhalation device, e.g., a high efficiency nebulizer, in about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg doses, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg doses.

[00192] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer provides a bioavailability of cromolyn or a pharmaceutically acceptable salt thereof of greater than about 5%, greater than about 6%, greater than about 7%, greater than about 8%, greater than about 9%, greater than about 10%, greater than about 11%, greater than about 12%, greater than about 13%, greater than about 14%, greater than about 15%, greater than about 16%, greater than about 17%, greater than about 18%, greater than about 19%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 55%, or greater than about 60% of the nominal dose. In some embodiments, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, in the methods disclosed herein provides a bioavailability of cromolyn or a pharmaceutically acceptable salt thereof of about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60% of the nominal dose.

[00193] In some embodiments of the methods disclosed herein, an inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer provides a bioavailability of cromolyn sodium of greater than about 5%, greater than about 6%, greater than about 7%, greater than about 8%, greater than about 9%, greater than about 10%, greater than about 11%, greater than about 12%, greater than about 13%, greater than about 14%, greater than about 15%, greater than about 16%, greater than about 17%, greater than about 18%, greater than about 19%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, or greater than about 50% of the nominal dose. In some embodiments, an aqueous inhalation formulation administered with an inhalation device, e.g., a high efficiency nebulizer, in the methods disclosed herein provides a bioavailability of cromolyn sodium of about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, or about 50% of the nominal dose.

[00194] In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn or a pharmaceutically acceptable salt thereof, such as cromolyn sodium, is administered with an inhalation device, e.g., a high efficiency nebulizer, at a fill volume of less than about 0.25 mL, less than about 0.5 mL, at least about 0.5 mL to about 1.5 mL, at least about 0.5 mL to about 1.8 mL, at least about 1.5 mL, or at least about 2.0 mL. In some embodiments, an inhalation formulation is administered with an inhalation device, e.g., a high efficiency nebulizer, at a fill volume about 0.1 mL to about 5.0 mL, about 0.25 mL to about 2.0 mL, about 0.5 mL to about 1.8 mL, about 0.5 mL to about 2 mL, about 0.5 mL to about 1.5 mL, about 0.5 mL to about 1.0 mL, about 0.5 mL or less, about 1 mL or less, about 1.5 mL or less, about 2.0 mL or less, about 2.5 mL or less, about 3.0 mL or less, about 3.5 mL or less, about 4.0 mL or less, about 4.5 mL or less, or about 5.0 mL or less. In some embodiments, an inhalation formulation is administered with an inhalation device, e.g., a high efficiency nebulizer, at a fill volume of about 0.5 mL, about 1.0 mL, about 1.5 mL, about 1.8 mL, about 2.0 mL, about 2.5 mL, about 3.0 mL, about 3.5 mL, about 4.0 mL, about 4.5 mL, or about 5.0 mL. In some embodiments, an inhalation formulation is administered with an inhalation device, e.g., a high efficiency nebulizer, which provides for a residual volume of cromolyn or a pharmaceutically acceptable salt thereof after administration of cromolyn or a pharmaceutically acceptable salt thereof of less than about 10%, less than about 5%, or less than about 3% of the nominal dose.

[00195] In some embodiments of the methods disclosed herein, an inhalation formulation

containing cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of the cromolyn or a pharmaceutically acceptable salt is greater than about 1% by weight, greater than about 2% by weight, greater than about 3% by weight, greater than about 4% by weight, greater than about 5% by weight, greater than about 6% by weight, greater than about 7% by weight, greater than about 8% by weight, greater than about 9% by weight, or greater than about 10% by weight. In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of cromolyn is from about 1% by weight to about 10% by weight, from about 2% by weight to about 8% by weight, from about 2% by weight to about 6% by weight, or from about 3% by weight to about 5% by weight. In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of cromolyn or a pharmaceutically acceptable salt thereof is about 1% by weight, about 2% by weight, about 3% by weight, about 4% by weight, about 5% by weight, about 6% by weight, about 7% by weight, about 8% by weight, about 9% by weight, or about 10% by weight.

[00196] In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn sodium is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of the cromolyn sodium is greater than about 1% by weight, greater than about 2% by weight, greater than about 3% by weight, greater than about 4% by weight, greater than about 5% by weight, greater than about 6% by weight, greater than about 7% by weight, greater than about 8% by weight, greater than about 9% by weight, or greater than about 10% by weight. In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn sodium is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of the cromolyn sodium is from about 1% by weight to about 10% by weight, from about 2% by weight to about 8% by weight, from about 2% by weight to about 6% by weight, or from about 3% by weight to about 5% by weight. In some embodiments of the methods disclosed herein, an inhalation formulation containing cromolyn sodium is administered with an inhalation device, e.g., a high efficiency nebulizer, wherein the concentration of the cromolyn sodium is about 1% by weight, about 2% by weight, about 3% by weight, about 4% by weight, about 5% by weight, about 6% by weight, about 7% by weight, about 8% by weight, about 9% by weight, or about 10% by weight.

[00197] In some embodiments, an inhalation formulation containing cromolyn or a pharmaceutically acceptable salt thereof is administered with an inhalation device, e.g., a high efficiency nebulizer, in about 0.25 to about 10 minutes, about 0.50 to about 8 minutes, less than about 8 minutes, less than about 7 minutes, less than about 6 minutes, less than about 5 minutes, less than about 4 minutes, less than about 3 minutes, less than about 2 minutes, less than about 1.8 minutes, less than about 1.5 minutes, or less than 1 minute. In some embodiments, the inhalation formulation is administered in about 3 minutes or less. In some embodiments, the inhalation formulation is administered in about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes, or about 10 minutes.

[00198] In some embodiments of the methods disclosed herein, administration of cromolyn or a pharmaceutically acceptable salt thereof with a high efficiency nebulizer provides at least about a 1.5-fold, at least about a 1.8-fold, at least about a two-fold, at least about a three-fold, at least about a four-fold, or at least about a five-fold increase in one or more of AUC_{last} , $AUC_{(0-\infty)}$, or C_{max} as compared to the same or lower nominal dose of the cromolyn or the pharmaceutically acceptable salt thereof administered with a conventional inhalation device.

[00199] In some embodiments of the methods disclosed herein, inhalation formulations administered with a high efficiency nebulizer are substantially free of a preservative, such as benzyl alcohol. In some embodiments of the methods disclosed herein, inhalation formulations administered with a high efficiency nebulizer further comprise at least one excipient. In some embodiments, the excipient is selected from the group consisting of stabilizers and antioxidants (such as citric acid, ascorbic acid, ethylenediamine tetra acetic acid (EDTA), sodium metabisulfite, or a salt of any thereof), an osmolarity adjusting agent (such as sodium chloride, mannitol, or sorbitol), a surfactant (such as polysorbate 80, vitamin E, tocopherol polyethylene glycol, and Tyloxapol), or a pH buffer.

[00200] In some embodiments of the methods disclosed herein, inhalation formulations administered with an inhalation device, e.g., a high efficiency nebulizer, are hypotonic. In some embodiments of the methods disclosed herein, inhalation formulations administered with an inhalation device, e.g., a high efficiency nebulizer, are sub-isotonic. In some embodiments of the methods disclosed herein, inhalation formulations administered with an inhalation device, e.g., a high efficiency nebulizer, have an osmolality greater than about 70 mOsm/kg. In some embodiments of the methods disclosed herein, inhalation formulations administered with an inhalation device, e.g., high efficiency nebulizer, have an osmolality of at least about 100 mOsm/kg. In some embodiments of the methods

disclosed herein, inhalation formulations administered with an inhalation device, e.g., high efficiency nebulizer, have an osmolality of at least about 150 mOsm/kg. [NTD – please add a paragraph that includes ranges for the osmolality of the solution that is used with the nebulizer and brackets values ranging from about 70 to about 295, which is the value used in the definition of “hypotonic.” Please see the document entitled “051616 Patara cromolyn formulations w Osmolality” for details regarding the osmolality of the solutions that have been tested by Patara.]

EXAMPLES

[00201] The examples below describe some embodiments of the methods described herein. Methods and materials that are not specifically described in the following examples are within the scope of the invention and will be apparent to those skilled in the art with reference to the disclosure herein.

Example 1: Formulations

[00202] The formulations described in Table 3 are prepared as follows: The composition ingredients are added sequentially to a glass beaker with a magnet stirrer and about 90 g of purified water in the order listed in Table 3, ensuring that each ingredient is dissolved before the next is added. The weight is then adjusted to 100.0 g by adding additional purified water. The resulting solutions are then sterilized by filtration through 0.2 - 0.22 μ m sterile filters, and 0.5 to 5 mL aliquots are added to pre-sterilized glass or sterile polyethylene or polypropylene blow fill and seal vials by a standard blow fill and seal procedure. Alternative sterilization methods may be applied using heat sterilization in an autoclave.

Table 3

Formulation No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Cromolyn sodium (DSCG) (wt%)	2.0	3.0	4.0	4.0	4.0	4.0	4.0	5.0	6.0	3.0	3.0	3.0	3.0
NaCl (wt%)	0.7	0.5	0.3	0.25	0.2	0.2	0.2	0.15	0.1	0.2	0.3	0.4	0.5
Mannitol (wt%)	0.4	0.8	1.0	1.1	1.2	1.25	1.25	1.4	1.5				
EDTA-Na (wt%)	0.01	0.02	0.03	0.01	0.02	0.03	0.02	0.03	0.04	0.01	0.02	0.03	0.04
Hyaluronic acid (wt%)			0.25	0.5	1.0						0.25	0.5	1.0
Propylene glycol (wt%)										1.0	2.0	3.0	4.0
Purified Water (wt%)	96.9	95.7	94.4	94.1	93.6	94.5	94.5	93.4	92.4	95.8	94.4	93.1	91.5

Example 2: Characterization of an Aerosol Produced with a High Efficiency Nebulizer

[00203] The MMAD, GSD, DD, and RF of a representative inhaled cromolyn sodium formulation (PA-101) delivered via a high efficiency nebulizer (eFlow[®], PARI, 30L) were determined as described in USP<1601>. The values determined were: MMAD = 3.5 μm; GSD = 1.7; DD = 68%; RF (≤ 5 μm) = 75%; and RF (≤ 3.3 μm) = 44%.

[00204] The MMAD, GSD, and RF of a representative inhaled cromolyn sodium formulation (PA-101) delivered via a high efficiency nebulizer (eFlow[®], PARI, 40L) were determined as described in USP<1601>. The values determined were: MMAD = 4.1 μm; GSD = 1.7; RF (≤ 5 μm) = 66%; and RF (≤ 3.3 μm) = 36%.

Example 3: Single-Dose, Dose Escalation Study

Objectives:

[00205] The objectives of the study are as follows:

Primary:

[00206] To determine the systemic availability and pharmacokinetic (PK) profile of single doses of a representative inhaled cromolyn sodium formulation (PA-101) delivered via a high efficiency nebulizer (eFlow[®], PARI) using two different aerosol membranes (30L and 40L) in comparison with marketed formulations of cromolyn sodium (oral solution and inhalation aerosol) in healthy subjects.

Secondary:

[00207] To assess the safety and tolerability of PA-101 in comparison with marketed formulations of cromolyn sodium (oral solution and inhalation aerosol).

Methodology:

[00208] This was a Phase 1, randomized, open-label, single-centre, dose-ranging, cross-over study conducted in a total of 12 healthy adult subjects of 18-45 years of age.

Study Treatments, Dose and Mode of Administration:

1. 40 mg PA-101 (4% DSCG, 40 mg/1 mL), oral inhalation via eFlow 30L.
2. 80 mg PA-101 (4% DSCG, 80 mg/2 mL), oral inhalation via eFlow 30L.
3. 40 mg PA-101 (4% DSCG, 40 mg/1 mL), oral inhalation via eFlow 40L.
4. 20 mg cromolyn sodium inhalation aerosol (1% DSCG, 20 mg/2 mL) (commercially available product), oral inhalation via LC Plus.
5. 200 mg oral sodium cromoglycate solution (commercially available product), oral administration.

[00209] All study subjects received each study treatment in the morning (at 8:00 am, +/- 30 minutes) as a single dose treatment. Prior to each dosing day, subjects were admitted to the clinic in the morning for baseline (pre-dose) assessments. Subjects were required to remain in the clinic for 12h after study drug administration on each dosing day. Treatment Visits were separated by a washout period of 2 to 5 days.

[00210] The main delivery device for administering PA-101 was the open system eFlow nebulizer using the 30L aerosol head, which generates aerosol particles with a median size of about 3.0 μm . The 40L aerosol head (generating aerosol particles with a median size of about 4.0 μm) was tested as a comparator arm.

Duration of Study:

[00211] The duration of the study was one day.

Criteria for Evaluation:

[00212] Pharmacokinetic measurements: The PK parameters evaluated for plasma cromolyn sodium (DSCG) are maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination half-life ($T_{1/2}$), area under the plasma concentration-time curve from time = 0 to time of last measurable drug concentration (AUC_{0-t}), and area under the plasma concentration-time curve from time = 0 to infinity ($\text{AUC}_{0-\infty}$). Urine DSCG levels are measured for total DSCG excretion in the urine, and the bioavailability of the DSCG was calculated from the measured levels.

[00213] Safety measurements: Adverse events including gastrointestinal disturbance (e.g., abdominal pain, nausea, vomiting), changes in vital signs, 12-lead ECG and clinical laboratory tests (hematology, chemistry and urinalysis).

Statistical Measurements:

[00214] Pharmacokinetic parameters and plasma concentrations are listed and summarized. The summary statistics are presented as the geometric mean, arithmetic mean, arithmetic standard deviation (SD), min, median, max and n. The geometric statistics are not presented for T_{max} . Analysis of variance (ANOVA) including terms for subject and treatment are used to calculate point estimates, and confidence intervals (CI) for treatment differences with respect to PK parameters (90% CI) are calculated.

[00215] The incidence of AEs was compared between treatment groups. Summary tables and individual subject listings are provided for all safety measurements and the results are presented by treatment group. Descriptive statistics are used to summarise data where appropriate.

Results:

[00216] The pharmacokinetic parameters measured in the single dose study are shown in the following table:

Table 2

PK parameter	Oral solution, 200mg	Inhalation aerosol, 20mg	PA-101 (40L), 40mg	PA-101 (30L), 40mg	PA-101 (30L), 80mg	Ratio (PA-101 (30L; 40 mg)) / (oral solution (200 mg))	Ratio (PA-101 (30L; 40 mg) / (inhalation aerosol (20 mg))
C_{max} (ng/mL)	5.2 ($\pm$ 3.1)	17.8 ($\pm$ 10.4)	88.6 ($\pm$ 45.5)	156 ($\pm$ 104)	236 ($\pm$ 124)	x30	x8.8
T_{max} (h)	3.2 ($\pm$ 2.1)	0.6 ($\pm$ 0.1)	0.6 ($\pm$ 0.1)	0.7 ($\pm$ 0.1)	0.7 ($\pm$ 0.1)		
AUC_{0-t} (h*ng/mL)	29.4 ($\pm$ 10.4)	39.1 ($\pm$ 15.1)	206 ($\pm$ 94.3)	329 ($\pm$ 144)	514 ($\pm$ 186)	x11	x8.4
$AUC_{(0-\infty)}$ (h*ng/mL)	33.3 ($\pm$ 11.7)	40.6 ($\pm$ 15.6)	212 ($\pm$ 96.0)	338 ($\pm$ 146)	526 ($\pm$ 198)		
$T_{1/2}$ (h)	4.3 ($\pm$ 1.3)	2.5 ($\pm$ 0.8)	2.5 ($\pm$ 0.7)	2.2 ($\pm$ 0.6)	2.1 ($\pm$ 0.5)		
Bioavailability (%)	0.6	6.5	16.3	25.0	22.7	X42	X3.8

Values shown in parentheses are ($\pm$ SD).

[00217] Modeling of lung deposition with an aerosol from the 30L and 40L devices using the Finaly model (Finlay, WH, and AR Martin, "Recent advances in predictive understanding respiratory tract deposition", Journal of Aerosol Medicine, Vol 21:189-205 (2008)) indicated that the lung deposition with the two devices should be very similar. However, the AUC value obtained with 40 mg dose using the 30L device (338ng*hr/mL) was surprisingly high compared to the value (212ng*hr/mL) from the 40L device. Cromolyn sodium is not metabolized in the body and is excreted intact via bile and urine. Cromolyn sodium deposited in the lung during inhalation will appear in the plasma and the AUC would therefore be a surrogate for cromolyn sodium deposited in the lung. Any cromolyn sodium

swallowed during inhalation will contribute negligibly to the AUC since the oral bioavailability of cromolyn is only about 1% (Richards et al., J Pharmacol Exp Ther, Vol. 241, No. 3: 1028-1032 (1987)). The AUC data therefore indicate that at the same dose (40mg), the lung deposition with the 30L device was surprisingly higher than that with the 40L device.

[00218] The numbers of adverse events observed in the single dose study are shown in the following table:

Table 3

Adverse Event	Placebo	PA-101 (40L), 40mg	PA-101 (30L), 40mg	PA-101 (30L), 80mg	Inhalation aerosol, 20mg	Oral solution, 200mg
Cough	1	1	-	1	1	-
Oropharyngeal pain	-	-	-	-	1	1
Rhinorrhoea	1	-	-	-	-	-
Dizziness	-	-	2	-	-	-
Headache	-	-	-	1	-	1
Dysgeusia	-	-	-	-	-	1
Somnolence	-	-	-	1	-	-
Catheter-site Reaction	-	-	1	-	-	1
Nasopharyngitis	-	-	-	-	1	-
Sinusitis	-	-	-	1	-	-

Abdominal Discomfort	-	-	-	-	-	1
Increased Appetite	-	1	-	-	-	-

Example 4: Efficacy Study with Inhalation Therapy

Objective

[00219] The objectives of the study are: to determine the efficacy profile of the co-administration of cromolyn sodium and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide in a composition with a high efficiency nebulizer to patients with chronic cough; and to assess the safety and tolerability of the co-administration of cromolyn sodium and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide when administered to patients with chronic cough using a high efficiency nebulizer.

Methodology

[00220] This is a Phase 2, randomized, double-blind, placebo-controlled, 2-period crossover, 2-cohort, multi-center efficacy study in 48 patients with chronic cough: 24 patients with idiopathic pulmonary fibrosis (IPF, Cohort 1) and 24 patients with chronic idiopathic cough (CIC, Cohort 2).

[00221] The study consists of two treatment periods of 14 days each separated by a Washout Period of 14 days (± 2 days) between Period 1 and Period 2. A Screening Visit is conducted within 14 days before the Baseline Visit of Period 1. The two periods are identical except that in Period 2, patients crossover to the alternate treatment from that received in Period 1, according to a 1:1 randomization scheme. At the Screening Visit patients with a daytime cough severity score >40 mm using a linear 100 mm visual analogue scale are placed on 24-hour objective cough count monitoring using the LCM cough monitor. Patients with an average daytime cough count of at least 15 coughs per hour using LCM at the Screening Visit are eligible for randomization.

[00222] During each period, patients self-administer a composition comprising cromolyn sodium and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide, or placebo. The test composition comprises 40 mg cromolyn sodium and 50mg-600 mg 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide, and is administered three times daily (i.e., 8:00 am ± 1 hour, 2:00 pm ± 1 hour, and 8:00 pm ± 1 hour) for 14 consecutive days of each period (e.g., Days 1-14).

[00223] Patients attend a Pre-study Visit (Visit 1, Day -1) at the clinic in the morning prior to the

Baseline/Treatment Visit (Visit 2, Day 1) and a cough count device (LCM) is dispensed for measurement of baseline 24-hour cough count. Patients return to the clinic next day in the morning (Visit 2, Day 1) to return the devices, assessment of quality of life measures, and to receive the first dose of the study treatment. Additional treatment visits during the Treatment Period occur on Day 7 $\pm$ 1 day (Visit 3) and Day 15 $\pm$ 1 day (Visit 5). Patients visit the clinic on Day 7 $\pm$ 1 day (Visit 3) and Day 14 $\pm$ 1 day (Visit 4) in the morning and the LCM device is dispensed for measurement of 24-hour cough count. Study assessments includes assessment of quality of life (LCQ and K-BILD), cough severity (VAS), pulmonary function tests (forced expiratory volume in one second [FEV1], forced vital capacity [FVC], and FEV1/FVC ratio), fraction of exhaled nitric oxide (FeNO), and safety assessments (AEs, vital signs, and ECG) on Days 1, 7 and 15 of each treatment period. Pulmonary function tests and K-BILD assessment are only performed in the IPF cohort. A safety follow-up call is placed within 7 $\pm$ 2 days following the last study treatment.

[00224] Clinical safety laboratory samples are collected at the start and end of the treatment of each treatment period (Screening Visit and Visit 5 during the Treatment Period 1, and at Visit 2 and Visit 5 during the Treatment Period 2). All post-dose study procedures are conducted from time 0. Time 0 will be defined as the start of the first study drug administration (i.e., when the nebulizer has been turned on) of each period.

[00225] In the IPF cohort, patients are allowed to use antifibrotic therapy, i.e., pirfenidone, nintedanib, and N-acetylcysteine, during the course of the study provided that the dose is stabilized at least 3 months prior to the Screening Visit and throughout the study period.

[00226] Patients are not allowed to use prednisone, narcotic antitussives, baclofen, gabapentin, inhaled corticosteroids, benzonatate, dextromethorphan, carbetapentane, and H1 antihistamines, leukotriene modifiers, or cromolyn sodium for at least 2 weeks prior to the Screening Visit and throughout the study. Drugs containing bronchodilators (including beta-2 agonists and anticholinergics) are not allowed for at least 1 week prior to the Baseline Visit and during the study.

Duration of Study

[00227] The total duration of study is approximately 8 weeks, consisting of a Screening Period within 14 days before the first Treatment Visit (Visit 2, Day 1), two Treatment Periods of 14 days each ($\pm$ 1 day), a wash-out period of 14 days ($\pm$ 2 days) between the treatments, and a safety follow-up phone call within 7 days ($\pm$ 2 days) following the last study treatment.

Criteria for Evaluation:

[00228] The primary criteria for efficacy evaluation are: change from baseline in daytime average cough count measured by LCM; change from baseline in 24-hour average cough count measured by LCM; change from baseline in the LCQ score; change from baseline in quality of life as measured by K-BILD score (IPF cohort only); change from baseline in cough severity as measured by VAS score; change from baseline in pulmonary function tests (PFTs) (IPF cohort only); and change from baseline in FeNO as measured by Niox Vero.

[00229] The safety parameters include adverse events (AEs); change in vital signs (i.e., blood pressure and heart rate); change in 12-lead ECG; and clinical laboratory tests (i.e., hematology, biochemistry, urinalysis).

Results:

[00230] At the end of the treatment period, patients exhibit a significant decrease from baseline in daytime average cough count measured by LCM, a significant decrease from baseline in 24-hour average cough count measured by LCM, a significant decrease from baseline in the LCQ score, a significant increase from baseline in quality of life as measured by K-BILD score, a significant decrease from baseline in cough severity as measured by VAS score, a significant increase from baseline in PFTs and a significant increase from baseline in FeNo as measured by Niox Vero. Minimal AEs are observed.

Example 5: Efficacy Study with Combination Inhalation and Oral Therapy

Objective

[00231] The objectives of the study are: to determine the efficacy profile of the co-administration of cromolyn sodium and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide by different modes of administration in patients with chronic cough; and to assess the safety and tolerability of the co-administration of cromolyn sodium and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide when administered to patients with chronic cough by different routes of administration. The cromolyn sodium is co-administered with a high efficiency nebulizer and the 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide is co-administered orally.

Methodology

[00232] This is a Phase 2, randomized, double-blind, placebo-controlled, 2-period crossover, 2-cohort, multi-center efficacy study in 48 patients with chronic cough: 24 patients with idiopathic

pulmonary fibrosis (IPF, Cohort 1) and 24 patients with chronic idiopathic cough (CIC, Cohort 2).

[00233] The study consists of two treatment periods of 14 days each separated by a Washout Period of 14 days (± 2 days) between Period 1 and Period 2. A Screening Visit is conducted within 14 days before the Baseline Visit of Period 1. The two periods are identical except that in Period 2, patients crossover to the alternate treatment from that received in Period 1, according to a 1:1 randomization scheme. At the Screening Visit patients with a daytime cough severity score >40 mm using a linear 100 mm visual analogue scale are placed on 24-hour objective cough count monitoring using the LCM cough monitor. Patients with an average daytime cough count of at least 15 coughs per hour using LCM at the Screening Visit are eligible for randomization.

[00234] During each period, patients self-co-administer the sodium cromolyn and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide, or placebo. Patients co-administer sodium cromolyn (40 mg PA101 or Placebo PA101 via eFlow) three times daily (i.e., 8:00 am ± 1 hour, 2:00 pm ± 1 hour, and 8:00 pm ± 1 hour), and 5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzenesulfonamide (600 mg in tablet) two times daily (i.e., 8:00 am ± 1 hour and 8:00 pm ± 1 hour) for 14 consecutive days of each period (e.g., Days 1-14)

[00235] Patients attend a Pre-study Visit (Visit 1, Day -1) at the clinic in the morning prior to the Baseline/Treatment Visit (Visit 2, Day 1) and a cough count device (LCM) is dispensed for measurement of baseline 24-hour cough count. Patients return to the clinic next day in the morning (Visit 2, Day 1) to return the devices, assessment of quality of life measures, and to receive the first dose of the study treatment. Additional treatment visits during the Treatment Period occur on Day 7 ± 1 day (Visit 3) and Day 15 ± 1 day (Visit 5). Patients visit the clinic on Day 7 ± 1 day (Visit 3) and Day 14 ± 1 day (Visit 4) in the morning and the LCM device is dispensed for measurement of 24-hour cough count. Study assessments includes assessment of quality of life (LCQ and K-BILD), cough severity (VAS), pulmonary function tests (forced expiratory volume in one second [FEV1], forced vital capacity [FVC], and FEV1/FVC ratio), fraction of exhaled nitric oxide (FeNO), and safety assessments (AEs, vital signs, and ECG) on Days 1, 7 and 15 of each treatment period. Pulmonary function tests and K-BILD assessment are only performed in the IPF cohort. A safety follow-up call is placed within 7 ± 2 days following the last study treatment.

[00236] Clinical safety laboratory samples are collected at the start and end of the treatment of each treatment period (Screening Visit and Visit 5 during the Treatment Period 1, and at Visit 2 and Visit 5 during the Treatment Period 2). All post-dose study procedures are conducted from time 0.

Time 0 will be defined as the start of the first study drug administration (i.e., when the nebulizer has been turned on) of each period.

[00237] In the IPF cohort, patients are allowed to use antifibrotic therapy, i.e., pirfenidone, nintedanib, and N-acetylcysteine, during the course of the study provided that the dose is stabilized at least 3 months prior to the Screening Visit and throughout the study period.

[00238] Patients are not allowed to use prednisone, narcotic antitussives, baclofen, gabapentin, inhaled corticosteroids, benzonatate, dextromethorphan, carbetapentane, and H1 antihistamines, leukotriene modifiers, or cromolyn sodium for at least 2 weeks prior to the Screening Visit and throughout the study. Drugs containing bronchodilators (including beta-2 agonists and anticholinergics) are not allowed for at least 1 week prior to the Baseline Visit and during the study.

Duration of Study

[00239] The total duration of study is approximately 8 weeks, consisting of a Screening Period within 14 days before the first Treatment Visit (Visit 2, Day 1), two Treatment Periods of 14 days each (± 1 day), a wash-out period of 14 days (± 2 days) between the treatments, and a safety follow-up phone call within 7 days (± 2 days) following the last study treatment.

Criteria for Evaluation:

[00240] The primary criteria for efficacy evaluation are: change from baseline in daytime average cough count measured by LCM; change from baseline in 24-hour average cough count measured by LCM; change from baseline in the LCQ score; change from baseline in quality of life as measured by K-BILD score (IPF cohort only); change from baseline in cough severity as measured by VAS score; change from baseline in pulmonary function tests (PFTs) (IPF cohort only); and change from baseline in FeNO as measured by Niox Vero.

[00241] The safety parameters include adverse events (AEs); change in vital signs (i.e., blood pressure and heart rate); change in 12-lead ECG; and clinical laboratory tests (i.e., hematology, biochemistry, urinalysis).

Results:

[00242] At the end of the treatment period, patients exhibit a significant decrease from baseline in daytime average cough count measured by LCM, a significant decrease from baseline in 24-hour average cough count measured by LCM, a significant decrease from baseline in the LCQ score, a significant increase from baseline in quality of life as measured by K-BILD score, a significant decrease from baseline in cough severity as measured by VAS score, a significant increase from baseline in PFTs

and a significant increase from baseline in FeNo as measured by Niox Vero. Minimal AEs are observed.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a patient having a lung disease or condition comprising co-administering to a patient cromolyn or a pharmaceutically acceptable salt thereof and a P2X3 and/or a P2X2/3 receptor antagonist.
2. The method of claim 1, wherein the cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist are co-administered in the same composition.
3. The method of claim 1, wherein the cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist are co-administered in different compositions.
4. The method of claim 3, wherein the cromolyn or the pharmaceutically acceptable salt thereof and the P2X3 and/or the P2X2/3 receptor antagonist are each co-administered with an inhalation device.
5. The method of claim 3, wherein the cromolyn or the pharmaceutically acceptable salt thereof is co-administered with an inhalation device and the P2X3 and/or the P2X2/3 receptor antagonist is co-administered from a route of administration selected from oral, rectal, nasal, topical, pulmonary, vaginal, and parenteral administration.
6. The method of claim 5, wherein the cromolyn or the pharmaceutically acceptable salt thereof is co-administered with an inhalation device and the P2X3 and/or the P2X2/3 receptor antagonist is co-administered by oral administration.
7. The method of claim 2, wherein the composition is administered with an inhalation device.
8. The method of any one of claims claim 4-7, wherein the inhalation device produces a systemically effective amount of the cromolyn or the pharmaceutically acceptable salt thereof and/or a locally effective amount of the cromolyn or the pharmaceutically acceptable salt thereof to treat the lung disease or condition.
9. The method of claims any one of claims 1-8, wherein the pharmaceutically acceptable salt of cromolyn is selected from cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate.
10. The method of claims any one of claims 1-8, wherein the pharmaceutically acceptable salt of cromolyn is cromolyn sodium.

11. The method of any one of claims 4-10, wherein the inhalation device is a dry powder inhaler, metered dose inhaler, nebulizer, jet nebulizer, or soft mist inhaler.

12. The method of any one of claims 4-10, wherein the inhalation device is a high efficiency nebulizer.

13. The method of any one of claims 8-12, wherein co-administration with the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%.

14. The method of any one of claims 8-12, wherein co-administration with the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 120 ng*hr/mL and/or an average C_{max} of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 55 ng/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%.

15. The method of any one of claims 8-12, wherein the co-administration with the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 200 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%.

16. The method of any one of claims 8-12, wherein the co-administration with the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 330 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%.

17. The method of any one of claims 8-12, wherein the co-administration with the inhalation device produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 525 ng*hr/mL and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 30%.

18. The method of claim 15 or 16, wherein a nominal dose of about 40 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the inhalation device.

19. The method of claim 17, wherein a nominal dose of about 80 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the inhalation device.

20. The method of claim 11, wherein co-administration is with a jet nebulizer and co-administration with the jet nebulizer produces in a human subject group an average $AUC_{(0-\infty)}$ of the

cromolyn or the pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 5%.

21. The method of claim 11, wherein co-administration is with a jet nebulizer and co-administration with the jet nebulizer produces in a human subject group an average $AUC_{(0-\infty)}$ of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 40 ng*hr/mL and/or an average C_{max} of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 15 ng/mL, and a deposited lung dose of the cromolyn or the pharmaceutically acceptable salt thereof greater than about 5%.

22. The method of claim 20 or 21, wherein a nominal dose of about 20 mg cromolyn or the pharmaceutically acceptable salt thereof is co-administered with the jet nebulizer.

23. The method of claim 12, wherein the composition co-administered with a high efficiency nebulizer comprises greater than about 2% of cromolyn or the pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the composition co-administered with a high efficiency nebulizer comprises about 4% of cromolyn or the pharmaceutically acceptable salt thereof.

25. The method of claim 12, wherein the composition co-administered with a high efficiency nebulizer comprises one or more purified water, sodium chloride, mannitol, and sodium EDTA.

26. The method of claim 10, wherein about 1 mg to about 120 mg of cromolyn sodium is co-administered.

27. The method of claim 10, wherein about 5 mg to about 80 mg of cromolyn sodium is co-administered.

28. The method of claim 10, wherein about 20 mg to about 60 mg of cromolyn sodium is co-administered.

29. The method of claim 10, wherein about 30 mg to about 50 mg of cromolyn sodium is co-administered.

30. The method of claim 10, wherein about 40 mg of cromolyn sodium is co-administered.

31. The method of claim 12, wherein the composition co-administered with a high efficiency nebulizer has an osmolality greater than about 70 mOsm/kg.

32. The method of any one of claims 4-31, wherein the median particle size of the cromolyn or the pharmaceutically acceptable salt thereof aerosol is between about 3 μm and about 4 μm .

33. The method of claim 12, wherein the high efficiency nebulizer emits droplets having an

MMAD of about 4.1 μm or less and a GSD of about 1.7.

34. The method of claim 12, wherein the high efficiency nebulizer emits droplets having an MMAD of about 3.5 μm or less and a GSD of about 1.7.

35. The method of any one of the claims 8-19 and 23-34, wherein the RF ($\leq 3.3 \mu\text{m}$) is at least about 30% and/or the RF ($\leq 5 \mu\text{m}$) is at least about 65%.

36. The method of any one of the claims 8-19 and 23-34, wherein the RF ($\leq 3.3 \mu\text{m}$) is at least about 40%.

37. The method of any one of the claims 8-19 and 23-34, wherein the RF ($\leq 3.3 \mu\text{m}$) is at least about 45% and/or the RF ($\leq 5 \mu\text{m}$) is at least about 75%.

38. The method of claim 10, wherein the co-administration with the inhalation device produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of the cromolyn sodium greater than about 200 $\text{ng}\cdot\text{hr}/\text{mL}$ and an average C_{max} of the cromolyn sodium greater than about 80 ng/mL .

39. The method of claim 10, wherein the co-administration with the inhalation device produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of the cromolyn sodium greater than about 330 $\text{ng}\cdot\text{hr}/\text{mL}$ and an average C_{max} of the cromolyn sodium greater than about 150 ng/mL .

40. The method of claim 10, wherein the co-administration with the inhalation device produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of the cromolyn sodium greater than about 525 $\text{ng}\cdot\text{hr}/\text{mL}$ and an average C_{max} of the cromolyn sodium greater than about 230 ng/mL .

41. The method of claim 38 or 39, wherein a nominal dose of about 40 mg cromolyn sodium is co-administered with the inhalation device.

42. The method of claim 40, wherein a nominal dose of about 80 mg cromolyn sodium is co-administered with the inhalation device.

43. The method of claim 11, wherein the co-administration is with a jet nebulizer, the pharmaceutically acceptable salt of cromolyn is cromolyn sodium, and co-administration with the jet nebulizer produces in a human subject group an average $\text{AUC}_{(0-\infty)}$ of the cromolyn sodium greater than about 40 $\text{ng}\cdot\text{hr}/\text{mL}$ and an average C_{max} of the cromolyn sodium greater than about 15 ng/mL .

44. The method of claim 43, wherein a nominal dose of about 20 mg cromolyn sodium is co-administered with the jet nebulizer.

45. The method of any one of claims 1-44, wherein the lung disease or condition is selected from the group consisting of idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction,

hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangi leiomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough.

46. The method of any one of claims 1-44, wherein the lung disease or condition is chronic cough.

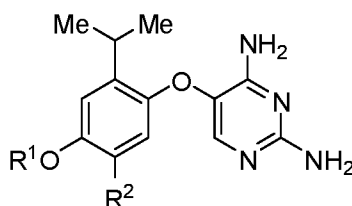
47. The method of claim 46, wherein the chronic cough is refractory chronic cough.

48. The method of any one of claims 1-44, wherein the lung disease or condition is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, wheezing, epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

49. The method of claim 11, wherein the inhalation device is a dry powder inhaler, and wherein the composition comprises lactose.

50. The method of claim 11, wherein the inhalation device is a dry powder inhaler, and wherein the composition does not comprise lactose.

51. The method of any one of the claims 1-50, wherein the P2X3 and/or the P2X2/3 receptor antagonist is a compound of Formula(I):

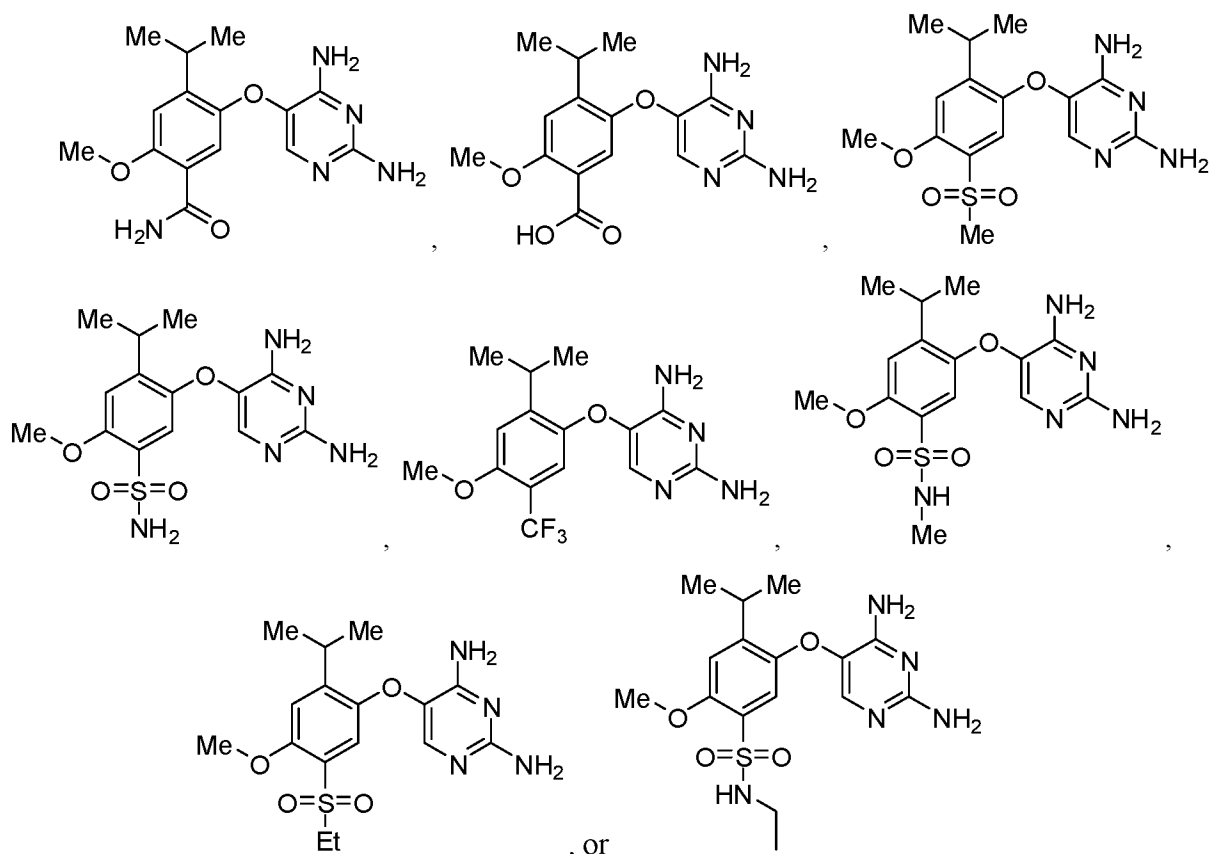


wherein R¹ is hydrogen or optionally substituted C₁-C₆ alkyl; and

R² is alkyl, alkenyl, alkynyl, amino; aminosulfonyl, halo; amido, haloalkyl; alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alknynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano, or alkylcarbonyl;

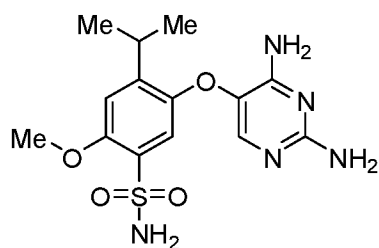
or a pharmaceutically acceptable salt thereof.

52. The method of claim 51, wherein the P2X3 and/or the P2X2/3 receptor antagonist is:



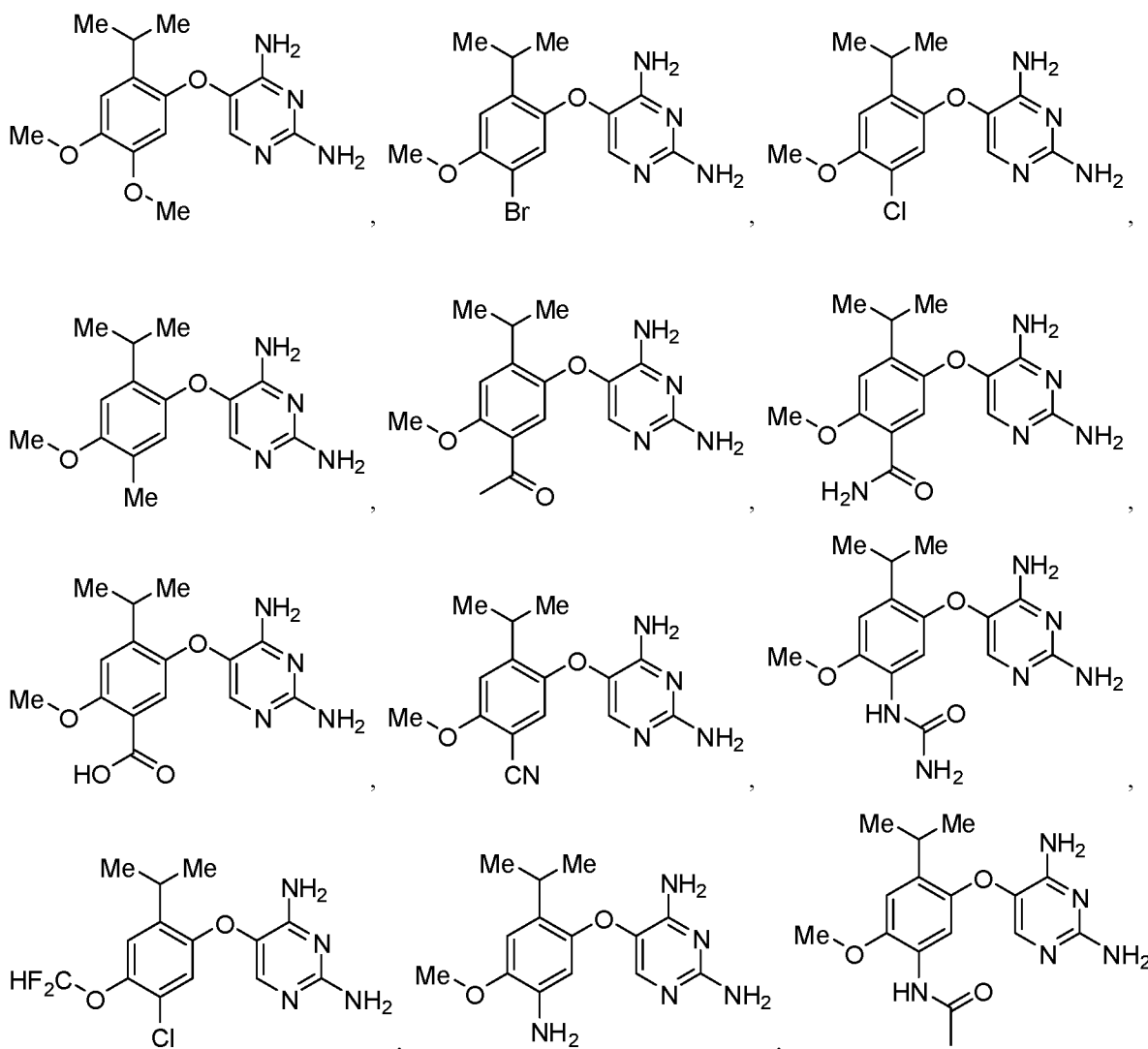
or a pharmaceutically acceptable salt thereof.

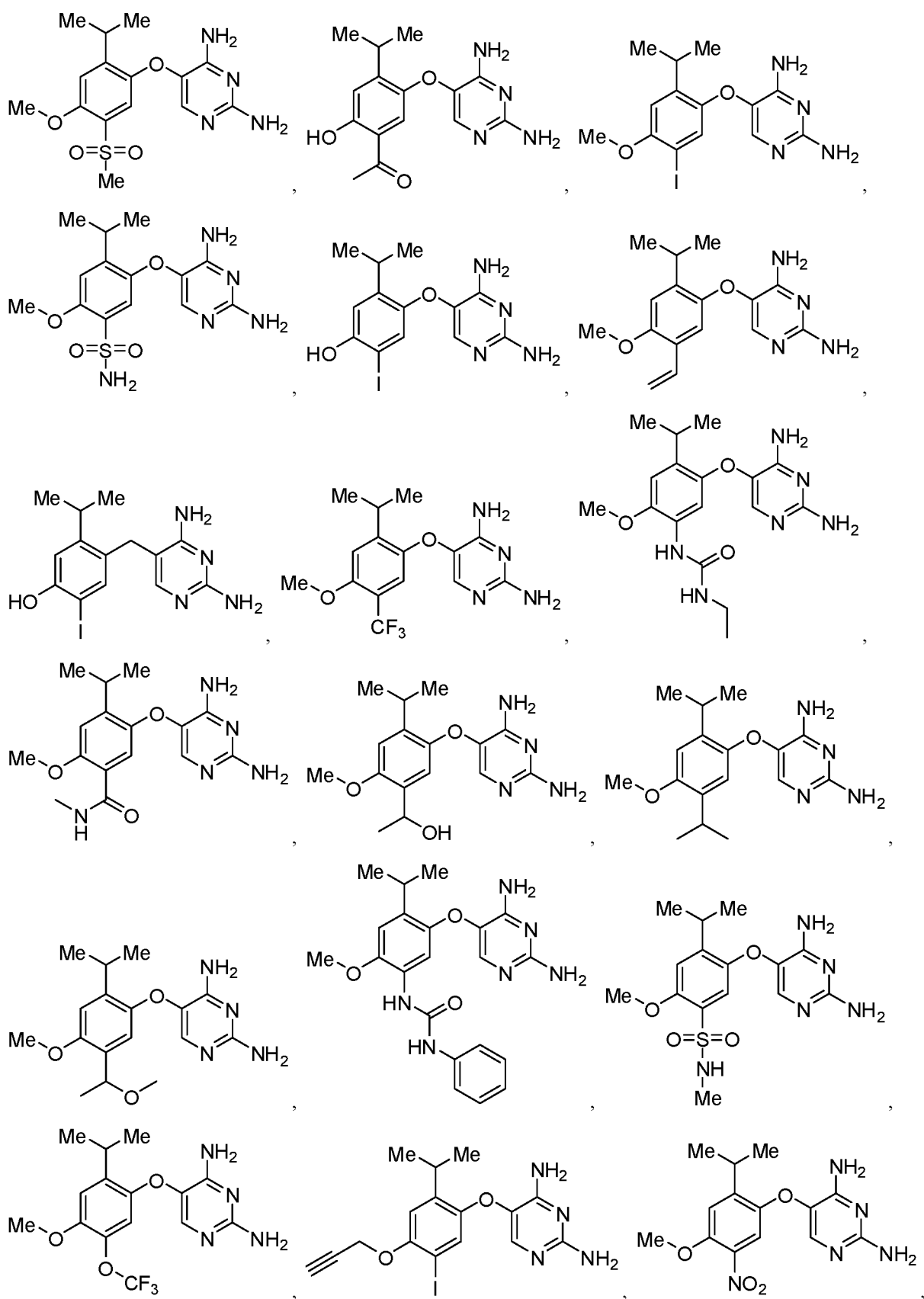
53. The method of claim 52, wherein the P2X3 and/or the P2X2/3 receptor antagonist is

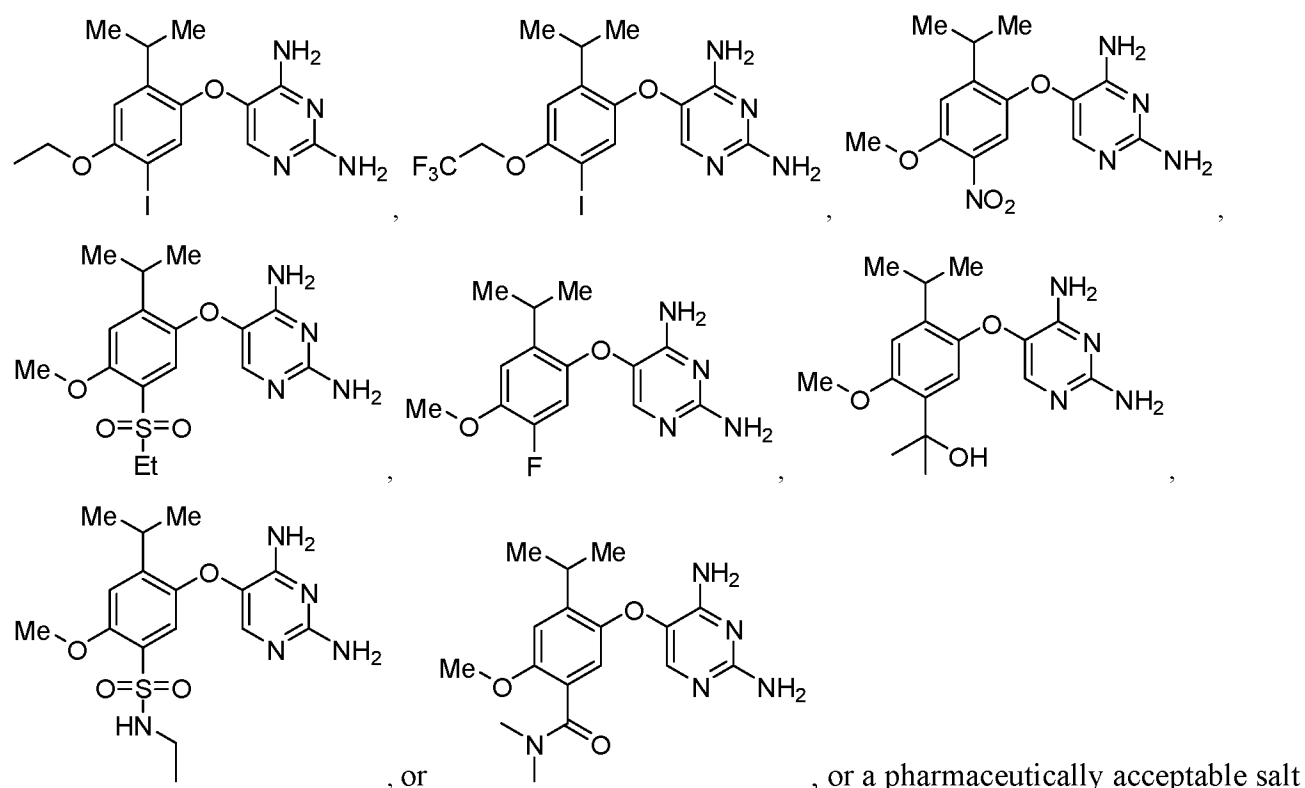


or a pharmaceutically acceptable salt thereof.

54. The method of any one of the claims 1-50, wherein the P2X3 and/or the P2X2/3 receptor antagonist is:





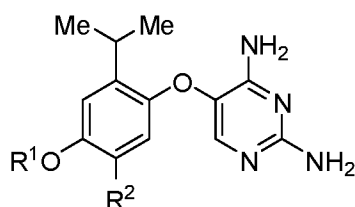


55. A pharmaceutical composition comprising cromolyn or a pharmaceutically acceptable salt thereof, a P2X3 and/or a P2X2/3 receptor antagonist, and a pharmaceutically acceptable excipient.

56. The pharmaceutical composition of claim 55, wherein the pharmaceutically acceptable salt of cromolyn is selected from cromolyn sodium, cromolyn lysinate, ammonium cromoglycate, and magnesium cromoglycate.

57. The pharmaceutical composition of claim 55, wherein the pharmaceutically acceptable salt of cromolyn is cromolyn sodium.

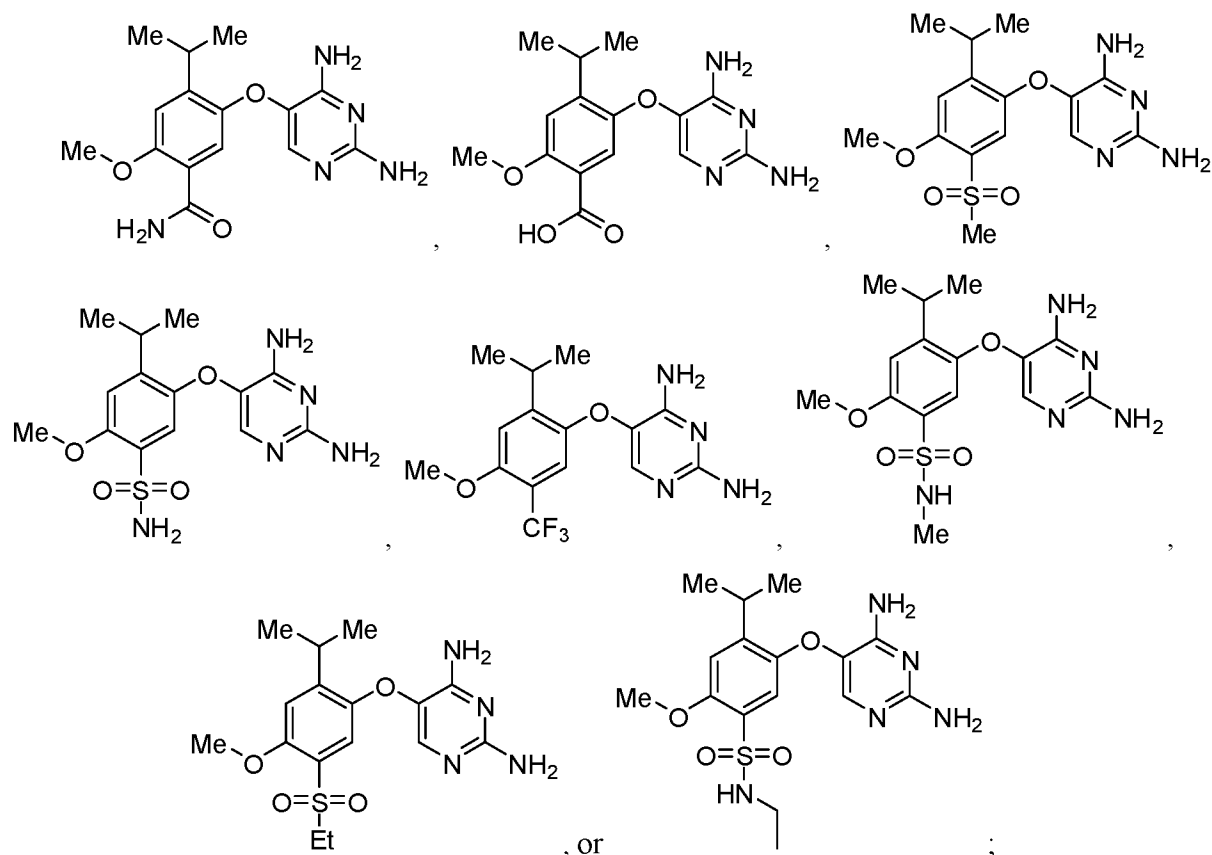
58. The pharmaceutical composition of any one of claims 55-57, wherein the P2X3 and/or the P2X2/3 receptor antagonist is a compound of Formula(I):



wherein R¹ is hydrogen or optionally substituted C₁-C₆ alkyl; and

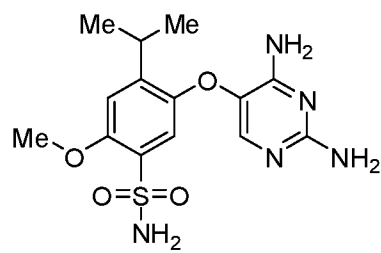
R^2 is alkyl, alkenyl, alkynyl, amino; aminosulfonyl, halo; amido, haloalkyl; alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alknynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano, or alkylcarbonyl;
or a pharmaceutically acceptable salt thereof.

59. The pharmaceutical composition of claim 58, wherein the P2X3 and/or the P2X2/3 receptor antagonist is:



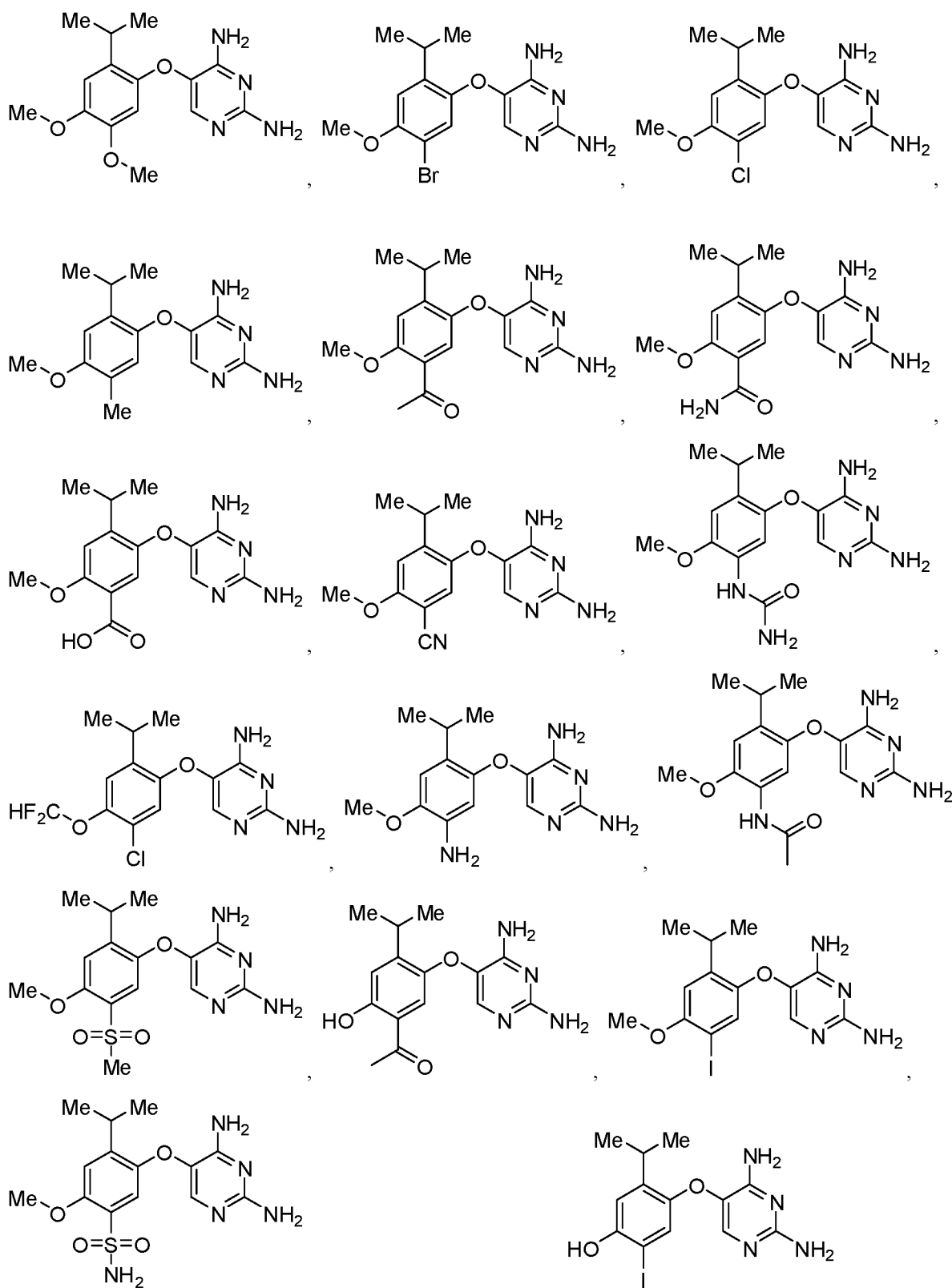
or a pharmaceutically acceptable salt thereof.

60. The pharmaceutical composition of any one of claims 55-57, wherein the P2X3 and/or the P2X2/3 receptor antagonist is

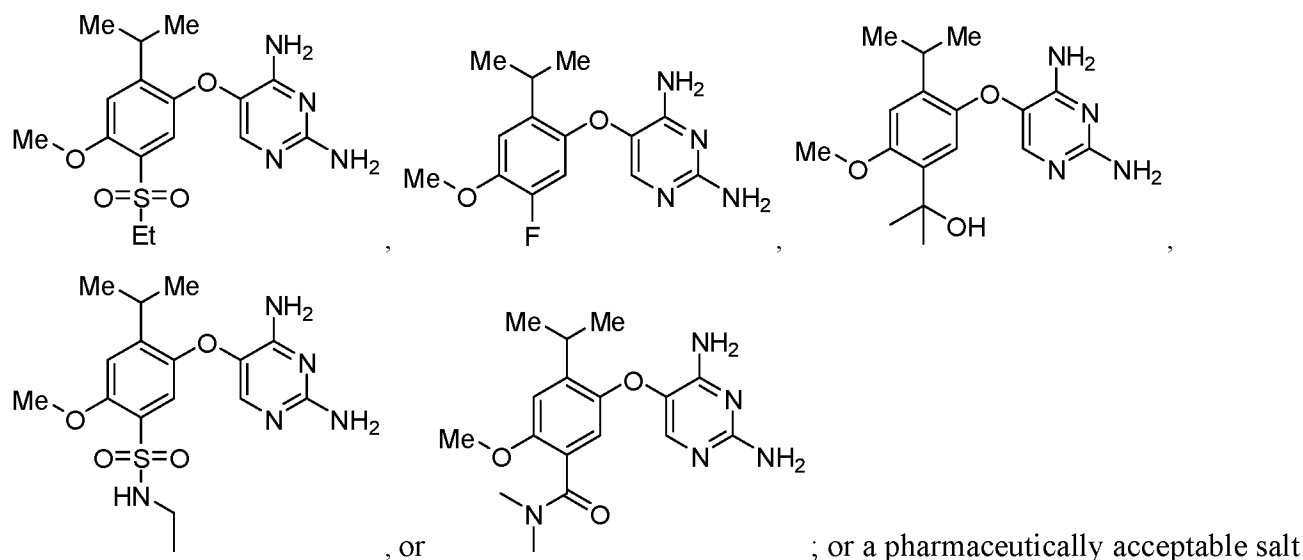


or a pharmaceutically acceptable salt thereof.

61. The pharmaceutical composition of any one of the claims 55-57, wherein the P2X3 and/or the P2X2/3 receptor antagonist is:







62. The pharmaceutical composition of any one of claims 55-61, wherein the composition is for administration with an inhalation device.

63. The pharmaceutical composition of any one of claims 55-62 for use in the treatment of a lung disease or condition.

64. The pharmaceutical composition of claim 63, wherein the lung disease or condition is selected from the group consisting of idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction, hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangioleiomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis,

Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough.

65. The pharmaceutical composition of claim 64, wherein the lung disease or condition is chronic cough.

66. The pharmaceutical composition of claim 65, wherein the chronic cough is refractory chronic cough.

67. The pharmaceutical composition of claim 66, wherein the lung disease or condition is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, wheezing, epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

68. A method of treating a lung disease or condition in a patient in need thereof comprising administering to the patient cromolyn or a pharmaceutically acceptable salt thereof and an antitussive composition.

69. The method of claim 68, wherein the antitussive composition comprises an H₁-Receptor antagonist, dextromethorphan, an opiate, a local anesthetic, caramiphen, carbetapentane, chlophedianol, levodropropizine, menthol, a TRPM8 (Transient Receptor Potential Cation Channel Subfamily M Member 8) agonist, erdosteine, an antibiotic, a glucocorticosteroid, a β_2 -agonist, a muscarinic receptor antagonist, a mucolytic, an expectorant, an antacid, a proton pump inhibitor, a gastrointestinal motility drug, xanthine, levocloperastine, amitriptyline, an N-Methyl-D-aspartate (NMDA) receptor antagonist, glaucine, moguisteine, a phosphodiesterase inhibitor, a potassium (K⁺) channel opener, a chloride (Cl⁻) pump inhibitor, an ouabain-sensitive sodium-potassium (Na⁺-K⁺) ATPase inhibitor, a leukotriene receptor antagonist, interferon-alpha (interferon- α), a tropan derivative, nociceptin, a selective cannabinoid 2 receptor agonist, a neurokinin receptor antagonist, a transient receptor potential vanilloid 1 (TRPV1) receptor antagonist, a transient receptor potential A₁ (TRPA1) receptor antagonist, VRP700, a gamma-aminobutyric acid (GABA) receptor agonist, an enaminone, E121, gabapentin, thalidomide, Botulinum A Toxin, a voltage-gated sodium (Na_v) channel blocker, a P2X2/3 antagonist, or any

combination thereof.

70. The method of claim 68, wherein the antitussive composition consists essentially of an H₁-Receptor antagonist, dextromethorphan, an opiate, a local anesthetic, caramiphen, carbetapentane, chlophedianol, levodropropizine, menthol, a TRPM8 (Transient Receptor Potential Cation Channel Subfamily M Member 8) agonist, erdosteine, an antibiotic, a glucocorticosteroid, a β_2 -agonist, a muscarinic receptor antagonist, a mucolytic, an expectorant, an antacid, a proton pump inhibitor, a gastrointestinal motility drug, xanthine, levocloperastine, amitriptyline, an N-Methyl-D-aspartate (NMDA) receptor antagonist, glaucine, moguisteine, a phosphodiesterase inhibitor, a potassium (K⁺) channel opener, a chloride (Cl⁻) pump inhibitor, an ouabain-sensitive sodium-potassium (Na⁺-K⁺) ATPase inhibitor, a leukotriene receptor antagonist, interferon-alpha (interferon- α), a tropan derivative, nociceptin, a selective cannabinoid 2 receptor agonist, a neurokinin receptor antagonist, a transient receptor potential vanilloid 1 (TRPV1) receptor antagonist, a transient receptor potential A₁ (TRPA1) receptor antagonist, VRP700, a gamma-aminobutyric acid (GABA) receptor agonist, an enaminone, E121, gabapentin, thalidomide, Botulinum A Toxin, a voltage-gated sodium (Na_v) channel blocker, a P2X2/3 antagonist, or any combination thereof.

71. The method of claim 68, wherein the antitussive composition consists of an H₁-Receptor antagonist, dextromethorphan, an opiate, a local anesthetic, caramiphen, carbetapentane, chlophedianol, levodropropizine, menthol, a TRPM8 (Transient Receptor Potential Cation Channel Subfamily M Member 8) agonist, erdosteine, an antibiotic, a glucocorticosteroid, a β_2 -agonist, a muscarinic receptor antagonist, a mucolytic, an expectorant, an antacid, a proton pump inhibitor, a gastrointestinal motility drug, xanthine, levocloperastine, amitriptyline, an N-Methyl-D-aspartate (NMDA) receptor antagonist, glaucine, moguisteine, a phosphodiesterase inhibitor, a potassium (K⁺) channel opener, a chloride (Cl⁻) pump inhibitor, an ouabain-sensitive sodium-potassium (Na⁺-K⁺) ATPase inhibitor, a leukotriene receptor antagonist, interferon-alpha (interferon- α), a tropan derivative, nociceptin, a selective cannabinoid 2 receptor agonist, a neurokinin receptor antagonist, a transient receptor potential vanilloid 1 (TRPV1) receptor antagonist, a transient receptor potential A₁ (TRPA1) receptor antagonist, VRP700, a gamma-aminobutyric acid (GABA) receptor agonist, an enaminone, E121, gabapentin, thalidomide, Botulinum A Toxin, a voltage-gated sodium (Na_v) channel blocker, a P2X2/3 antagonist, or any combination thereof.

72. The method of any one of claims 68-71, wherein the lung disease or condition is selected from the group consisting of idiopathic pulmonary fibrosis, chronic idiopathic cough, pulmonary

fibrosis, bronchopulmonary fibrosis, pulmonary artery hypertension, exercise-induced bronchoconstriction, hyperactive airway disorder, respiratory infections, respiratory syncytial virus infection, bronchiolitis obliterans, sarcoidosis, lung fibrosis, cystic fibrosis, chronic cough, steroid resistant pediatric asthma, bronchiectasis, radiation fibrosis, radiation pneumonitis, fibrosing mediastinitis, Birt-Hogg-Dubé syndrome, lymphangioliomyomatosis, neurofibromatosis type I, alpha-1 antitrypsin deficiency, elastin mutations, salla disease, familial pulmonary arterial hypertension, pulmonary alveolar proteinosis, pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, Kartagener syndrome, primary ciliary dyskinesia, central alveolar hypoventilation, narcolepsy, Marfan syndrome, Ehler-Danlos syndrome, ABCA3-related lung disease, SP-A-related lung disease, SP-B-related lung disease, SP-C-related lung disease, Hermansky-Pudlak syndrome, Gaucher disease, Neiman Pick C, Wegener's granulomatosis, Goodpasture syndrome, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome, cystic adenomatoid malformation, pulmonary sequestration, neuroendocrine cell hyperplasia, amyotrophic lateral sclerosis, myasthenia gravis, dermatomyositis, polymyositis, sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary hemosiderosis, sickle cell anemia, lymphangiomatosis, and refractory chronic cough.

73. The method of any one of claims 68-71, wherein the lung disease or condition is chronic cough.

74. The method of claim 73, wherein the chronic cough is refractory chronic cough.

75. The method of any one of claims 68-71, wherein the lung disease or condition is chronic obstructive pulmonary disease, allergic asthma, non-allergic asthma, wheezing, epistaxis, laryngotracheobronchitis, bronchitis, diffuse bronchiolitis, bronchiolitis obliterans, bronchiectasis, alveolitis, community acquired pneumonia, hospital acquired pneumonia, ventilator associated pneumonia, healthcare associated pneumonia, aspiration pneumonia, lipid pneumonia, eosinophilic pneumonia, chemical pneumonia, atypical pneumonia, severe acute respiratory system disease, pulmonary infection, emphysema, sarcoidosis, tuberculosis, nontuberculous mycobacterial pulmonary diseases, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, interstitial lung disease, pertussis, or graft rejection after lung transplantation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/042437

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K45/06 A61K9/00 A61K31/352 A61K31/505 A61P11/14
A61P11/00

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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, CHEM ABS Data, 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.
Y	US 2015/057299 A1 (FORD ANTHONY P [US] ET AL) 26 February 2015 (2015-02-26) cited in the application paragraph 123; Table 1; Examples 28, 30; claims 1, 12 ----- -/--	1-75



Further documents are listed in the continuation of Box C.



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

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"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

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Date of the actual completion of the international search

6 September 2016

Date of mailing of the international search report

25/11/2016

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

Scheithe, Rupert

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/042437

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	A G Leitch ET AL: "Disodium cromoglycate relieves symptoms in symptomatic young smokers. A double blind placebo controlled trial", Allergy, 1 April 1984 (1984-04-01), pages 211-215, XP055299961, DENMARK DOI: 10.1111/j.1398-9995.1984.tb02626.x Retrieved from the Internet: URL:http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.1984.tb02626.x/epdf abstract -----	1-75
Y	CARLA A. LUQUE ET AL: "Treatment of ACE Inhibitor-Induced Cough", PHARMACOTHERAPY : THE JOURNAL OF HUMAN PHARMACOLOGY AND DRUG THERAPY, vol. 19, no. 7, 1 July 1999 (1999-07-01), pages 804-810, XP055299975, US ISSN: 0277-0008, DOI: 10.1592/phco.19.10.804.31563 page 807 -----	1-75
Y	A.A. HEMMATI ET AL: "THE ROLE OF SODIUM CROMOLYN IN TREATMENT OF PARAQUAT-INDUCED PULMONARY FIBROSIS IN RAT", PHARMACOLOGICAL RESEARCH., vol. 46, no. 3, 1 September 2002 (2002-09-01), pages 229-234, XP055299944, GB ISSN: 1043-6618, DOI: 10.1016/S1043-6618(02)00122-6 the whole document -----	1-75
Y,P	WO 2015/120392 A1 (PATARA PHARMA LLC [US]) 13 August 2015 (2015-08-13) the whole document -----	1-75
A	KÜPPER T ET AL: "Cromoglycate, reproterol, or both-what's best for exercise-induced", SLEEP AND BREATHING ; INTERNATIONAL JOURNAL OF THE SCIENCE AND PRACTICE OF SLEEP MEDICINE, SPRINGER, BERLIN, DE, vol. 16, no. 4, 27 December 2011 (2011-12-27), pages 1229-1235, XP035139412, ISSN: 1522-1709, DOI: 10.1007/S11325-011-0638-2 abstract, Fig. 1 -----	1-75

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/042437

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.:
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:
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.:

1-67(completely); 68-75(partially)

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: 1-67(completely); 68-75(partially)

A method of treating according to claim 1, a pharmaceutical composition according to claim 55, for use according to claim 63.

A method according to claim 68, as far as relating to a P2X2/3 antagonist representing the antitussive.

2. claims: 68-75(partially)

A method according to claim 68, as far as not encompassed by the first invention.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/042437

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015057299 A1	26-02-2015	AU 2014308606 A1	10-03-2016
		CA 2921395 A1	26-02-2015
		CN 105682659 A	15-06-2016
		EP 3035932 A1	29-06-2016
		JP 2016528301 A	15-09-2016
		KR 20160052581 A	12-05-2016
		SG 11201601145R A	30-03-2016
		US 2015057299 A1	26-02-2015
		US 2016263112 A1	15-09-2016
		WO 2015027212 A1	26-02-2015

WO 2015120392 A1	13-08-2015	AU 2015213681 A1	25-08-2016
		CA 2938996 A1	13-08-2015
		US 2015224078 A1	13-08-2015
		WO 2015120392 A1	13-08-2015
