ANTIARRHYTHMIC FORMULATION

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/881,689, filed August 1, 2019, U.S. Non-Provisional Application No. 16/901,909, filed June 15, 2020, and U.S. Non-Provisional Application No. 16/901,941, filed June 15, 2020, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Cardiac arrhythmia (also dysrhythmia) is a term for any of a large and heterogeneous group of conditions in which there is abnormal electrical activity in the heart. The heart beat may be too fast or too slow and may be regular or irregular.

[0003] Atrial arrhythmia therapy is a field with a high level of unmet clinical need. Many drugs used today have been on the market since the early 1980s and 1990s and are mostly inadequate due to either lack of efficacy or a side-effect profile that is often cardiac related, that necessitates extensive monitoring of the patient.

[0004] What is needed for fast and safe cardioversion (resolution of arrhythmia) is therapy that:

(a) causes little to no risk of acceleration of ventricular rate before cardioversion;

(b) slows atrio-ventricular (AV) conduction so that there is ventricular rate control and cardioversion at the same time;

(c) causes minimal to no effect in prolonging the QRS interval above the upper range of normal value (about 120 milliseconds) and should have a low risk of torsade de pointes; and

(d) causes minimal to no negative inotropic effect; it should have only mild negative chronotropic effect, without the risk of severe bradycardia when the patient reverts to sinus rhythm.

(e) causes minimal to no hypotension.

(f) causes no adverse event other than one that is mild, is transient (*i.e.* lasting no more than several minutes), does not require treatment, and has no sequelae.

[0005] None of the current approved drug products exhibit these characteristics. High oral and intravenous (IV) doses required to compensate for absorption, metabolism, and dilution result in blood high blood concentrations for an extended period of time that can cause the dangerous adverse cardiac events like pro-arrhythmias, QT prolongation, and torsade de pointes. FELDMAN et al., "Analysis of Coronary Response to Various Doses of Intracoronary

Nitroglycerin," Circulation, 66:321-327 (1982); and BARBATO et al., "Adrenergic Receptors in Human Atherosclerotic Coronary Arteries," Circulation, 111:288-294 (2005). Comorbid conditions also limit use of ideal drugs in some patients, for example the case with intravenous adenosine. GAGLIONE et al., "Is There Coronary Vasoconstriction after Intracoronary Beta-adrenergic Blockade in Patients with Coronary Artery Disease," J Am Coll Cardiol, 10:299-310 (1987). Drugs like verapamil and diltiazem injections are second line of therapy requiring close monitoring of patients. NOGUCHI et al., "Effects of Intracoronary Propranolol on Coronary Blood Flow and Regional Myocardial Function in Dogs," Eur J Pharmacol., 144(2):201-10 (1987); and ZALEWSKI et al., "Myocardial Protection during Transient Coronary Artery Occlusion in Man: Beneficial Effects of Regional Beta-adrenergic Blockade," Circulation, 73:734-73 (1986).

[0006] Paroxysmal atrial fibrillation (PAF) is a subset of the overall atrial fibrillation (AF) population and is estimated to be 25-30% of the overall AF population. About 2.5 million patients are affected by AF in the United States. The population of PAF patients is estimated to be 900,000 to 1.5 million worldwide.

[0007] Paroxysmal supraventricular tachycardia (PSVT) is a type of arrhythmia that affects about 500,000 to 600,000 patients in the United States.

[0008] Ablation techniques, e.g., RF ablation, are often used to treat arrhythmias. But ablation is expensive with the cost typically ranging from about $25,000 to $36,000 per procedure. Despite the high expense, ablation may not completely correct the arrhythmia. Often, multiple ablation procedures are required to achieve a satisfactory therapeutic result.

[0009] Oral medications, e.g., pills, tend to require high doses and long time for onset of action. The oral dose for heart medications generally tends to be well over 1 mg. High doses increase the likelihood of side effects and drug-drug interactions as these patients typically take multiple medications. The time for onset for oral cardiovascular medications tends to be around 60 minutes. Oral antiarrhythmic medications have been predominantly developed for prevention whereas treatment being given intravenously.

[0010] Intravenous injection usually requires a hospital setting for administering a medicine and typically involves a visit to the emergency room (ER). These overheads result in this therapy being expensive compared to therapies where the patients can self-administer their medicines. Intravenous injection requires a dose that is higher than what is actually needed in the heart to compensate for dilution and metabolism. Drug injected by IV passes through the right side of the heart and then the lungs before reaching the left side of the heart. The drug remains in the blood stream at a high concentration bathing all the organs and tissues with this drug in a high

concentration, until the drug gets excreted through the kidneys or through other metabolic routes (e.g., hepatic). As a result, IV drugs may cause unwanted side effects. Drugs administered via the IV route are significantly diluted in the venous blood volume and lungs before reaching the cardiac circulation.

[0011] Injecting a drug to the heart directly is usually a last-resort taken by a cardiologist as a life saving measure in an emergency. The doses of the drugs injected directly into the heart in this manner are usually less than their IV and/or oral doses.

[0012] In some cases, an unplanned surgery is necessary to save the patient's life. Of course, unplanned surgeries are expensive and risky to the patient.

[0013] Cardiac arrhythmias are associated with disabling symptoms like tightness around the chest, palpitations, feeling tired, shortness of breath, and sometimes chest pain.

[0014] In view of the above, arrhythmias frequently result in emergency room (ER) visits, where intravenous drugs are administered, sometimes necessitating an extended stay in the hospital and in some cases also leading to unplanned invasive procedures. Pipeline Insights: Antiarrhythmics, Datamonitor (06/2006); and TWISS et al., "Efficacy of Calcium Channel Blockers as Maintenance Therapy for Asthma," British J of Clinical Pharmacology (November 2001).

[0015] There remains, however, a need for improved compositions and methods for treating heart conditions. Accordingly, there also remains a need for methods of making these compositions.

SUMMARY

[0016] Described herein, in some aspects, is a pharmaceutical composition, comprising: a therapeutically effective amount of a salt of flecainide, wherein the pharmaceutical composition is in the form of a liquid solution that has the salt of flecainide at a concentration above 60 mg/mL.

[0017] In some cases, the pharmaceutical composition further comprises a cyclodextrin. In some cases, a pH of the solution is above 5.5 when the pH is measured at room temperature. In some cases, a pH of the solution is from about 5.5 to about 6.5 when the pH is measured at room temperature. In some cases, the pharmaceutical composition further comprises a cyclodextrin, and wherein a pH of the solution is above 5.5 when the pH is measured at room temperature. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin,

hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins. In some cases, the cyclodextrin comprises hydroxypropyl-β-cyclodextrin. In some cases, a concentration of the cyclodextrin in the pharmaceutical composition is about 1% (w/v) to about 80% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is from about 15% (w/v) to about 25% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is from about 10% (w/v) to about 30% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at least about 5% (w/v) of the solution. In some cases, in the concentration of the cyclodextrin is at least about 10% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is about 20% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at most about 20% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is about 25% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at most about 25% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is from about 10% (w/v) to about 30% (w/v) of the solution. In some cases, the concentration of the salt of flecainide is at most about 200 mg/mL. In some cases, the concentration of the salt of flecainide is from about 65 mg/mL to about 130 mg/mL. In some cases, the concentration of the salt of flecainide is about 65 mg/mL to about 95 mg/mL. In some cases, the concentration of the salt of flecainide is from about 70 mg/mL to about 115 mg/mL. In some cases, the concentration of the salt of flecainide is about 100 mg/mL. In some cases, the concentration of the salt of flecainide is about 75 mg/mL. In some cases, the salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate. In some cases, the salt of flecainide comprises flecainide acetate. In some cases, the salt of flecainide comprises flecainide hydrochloride.

[0018] In some cases, the pharmaceutical composition further comprises an acid. In some cases, the acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid. In some cases, a concentration of the acid in the pharmaceutical composition is from about 2 mM to about 200 mM. In some cases, a

concentration of the acid in the pharmaceutical composition is about 2 mM to about 50 mM. In some cases, a concentration of the acid in the pharmaceutical composition is about 2 mM to about 10 mM. In some cases, the concentration of the acid is at most about 50 mM. In some cases, the concentration of the acid is about 20 mM. In some cases, the concentration of the acid is about 5 mM. In some cases, the acid comprises acetic acid. In some cases, the concentration of acetic acid is about 5 mM. In some cases, the acid comprises citric acid. In some cases, the concentration of citric acid is about 5 mM. In some cases, the acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuricsulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid. In some cases, the acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid. , and sulfuric acid. In some cases, the acid comprises hydrochloric acid.

[0019] In some cases, the salt of flecainide comprises flecainide acetate, and wherein the acid comprises acetic acid. In some cases, the pH of the solution is at most about 6.5. In some cases, the pH of the solution is about 5.9. In some cases, the pH of the solution is from about 5.5 to about 6.5.

[0020] In some cases, the pharmaceutical composition further comprises an artificial sweetener configured to improve organoleptic properties of the pharmaceutical composition. In some cases, the artificial sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof. In some cases, the artificial sweetener comprises saccharin. In some cases, the artificial sweetener comprises a salt of saccharin. In some cases, the artificial sweetener comprises saccharin sodium. In some cases, wherein a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

[0021] In some cases, the pharmaceutical composition is formulated for administration via inhalation. In some cases, the pharmaceutical composition is a nebulized solution that comprises nebulized droplets having a mass median aerodynamic diameter of less than 10 μm.

[0022] Described herein, in some aspects, is a unit dose of any pharmaceutical composition provided herein, comprising from about 50 mg to about 350 mg of the salt of flecainide.

[0023] In some cases, the unit dose comprises about 60 mg to about 150 mg of the salt of flecainide. In some cases, the unit dose comprises about 75 mg to about 125 mg of the salt of flecainide. In some cases, the unit dose comprises from about 250 mg to about 350 mg of the salt of flecainide. In some cases, the unit dose comprises from about 100 mg to about 250 mg of the salt of flecainide. In some cases, the unit dose comprises about 315 mg of the salt of flecainide. In some cases, the unit dose comprises about 260 mg of the salt of flecainide. In some cases, the unit dose comprises about 230 mg of the salt of flecainide. In some cases, the unit dose comprises about 200 mg of the salt of flecainide.

[0024] Described herein, in some aspects, is a kit, comprising: any pharmaceutical composition or any unit dose described herein and instructions for use of the pharmaceutical composition for treatment of a heart condition. In some cases, the heart condition comprises atrial fibrillation. In some cases, the atrial fibrillation comprises tachycardia. In some cases, the atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation. In some cases, the kit further comprises a container containing the pharmaceutical composition. In some cases, the container is selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.

[0025] Described herein, in some aspects, is a system, comprising: any pharmaceutical composition provided herein and a nebulizer. In some cases, the system further comprises instructions for use of the nebulizer and the pharmaceutical composition for treatment of a heart condition. In some cases, the pharmaceutical composition is formulated for administration via the nebulizer, wherein the nebulizer is selected from the group consisting of a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer. In some cases, the nebulizer selected from the group consisting of: a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer. In some cases, the system further comprises instructions for use of the nebulizer and the pharmaceutical composition for treatment of atrial arrhythmia. In some cases, the system further comprises instructions for use of a nebulizer to inhalationally administer a dose of the pharmaceutical composition in aerosol to a subject. In some cases, the atrial arrhythmia comprises tachycardia. In some cases, the atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial

fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation. In some cases, the nebulizer is configured to deliver the dose of the pharmaceutical composition in aerosol, wherein the aerosol of the pharmaceutical composition has droplets that have a mass median aerodynamic diameter of less than 10 μm. In some cases, the nebulizer is a breath-actuated nebulizer. In some cases, the nebulizer is a jet nebulizer. In some cases, the instructions contain instructions for use of the nebulizer to inhalationally administer the dose of the pharmaceutical composition in aerosol to a subject, wherein the dose contains from about 50 mg to about 150 mg of the salt of flecainide. In some cases, the pharmaceutical composition is in the form of a liquid solution that has: (i) the salt of flecainide at a concentration of from about 65 mg/mL to about 95 mg/mL; (ii) the cyclodextrin at a concentration of from about 10% (w/v) to about 30% (w/v) of the solution; and (iii) a pH of from about 5.5 to about 6.5 when the pH is measured at room temperature. In some cases, the concentration of the salt of flecainide is from about 65 mg/mL to about 95 mg/mL. In some cases, the concentration of the salt of flecainide is from about 70 mg/mL to about 80 mg/mL. In some cases, the instructions contain instructions for use of the nebulizer to deliver the pharmaceutical composition in an aerosolized dose that contains about 90 mg of the salt of flecainide. In some cases, the instructions contain instructions for use of the nebulizer to deliver the pharmaceutical composition in an aerosolized dose that contains about 120 mg of the salt of flecainide.

[0026] Described herein, in some aspects, is a system, comprising: a pharmaceutical composition that comprises a salt of flecainide, a cyclodextrin, and an acid; a nebulizer configured to deliver the pharmaceutical composition as droplets having a mass median aerodynamic diameter of less than 10 μm; and instructions for use of the nebulizer to deliver the pharmaceutical composition in an aerosolized dose that contains from about 50 mg to about 250 mg of the salt of flecainide, wherein the pharmaceutical composition is in the form of a liquid solution that has (i) the salt of flecainide at a concentration of between 65 mg/mL and 100 mg/mL, (ii) the cyclodextrin at a concentration of from about 10% (w/v) to about 30% (w/v) of the solution; and (iii) a pH of from about 5.5 to about 6.5 when the pH is measured at room temperature. In some embodiments, the system further comprises a nose clip. A nose clip can be used to hinder passage of air through a nose of a subject during inhalation and increase the proportion of a total inhaled volume that is the aerosol issued by the nebulizer. In some embodiments, the dose contains from about 150 mg to about 250 mg of the salt of flecainide. In some embodiments, the dose contains about 200 mg of the salt of flecainide.

[0027] Described herein, in some aspects, is a method of treating a subject suffering from a heart condition, comprising: administering to the subject via inhalation a pharmaceutical composition

in the form of a liquid solution, wherein the pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein a concentration of the salt of flecainide in the pharmaceutical composition is above 60 mg/mL. In some cases, the pharmaceutical composition further comprises a cyclodextrin. In some cases, a pH of the solution is above 5.5 when the pH is measured at room temperature.

[0028] Described herein, in some aspects, is a method of treating a human subject suffering from a heart condition, comprising administering to the subject via inhalation within about 10 min a pharmaceutical composition in the form of a liquid solution, wherein the pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein the administration results in a peak plasma concentration (C_{max}) of the salt of flecainide in the subject that is at least 200 ng/mL. In some cases, a concentration of the salt of flecainide in the pharmaceutical composition is above 60 mg/mL of the solution. In some cases, the pharmaceutical composition further comprises a cyclodextrin. In some cases, the administration of the pharmaceutical composition results in a peak plasma concentration (C_{max}) of the salt of flecainide in the subject that is at least 200 ng/mL. In some cases, the administration of the pharmaceutical composition results in a peak plasma concentration (C_{max}) of the salt of flecainide in the subject that is at least 250 ng/mL. In some cases, the C_{max} is from about 250 ng/mL and about 1000 ng/mL. In some cases, the C_{max} is from about 300 ng/mL and about 700 ng/mL. In some cases, the C_{max} is from about 400 ng/mL and about 600 ng/mL. In some cases, the administration of the pharmaceutical composition is performed within about 10 min. In some cases, the administration of the pharmaceutical composition is performed within about 5 min. In some cases, the administration of the pharmaceutical composition is performed via one or two inhalations. In some cases, the administration of the pharmaceutical composition is performed via two inhalations that are separated by a break for from about 10 seconds to about 1 minute. In some cases, the administration is performed via a nebulizer. In some cases, the nebulizer is a breath-actuated nebulizer. In some cases, the nebulizer is a jet nebulizer. In some cases, the nebulizer is a vibrating mesh nebulizer. In some cases, the nebulizer is an ultrasonic nebulizer.

[0029] In some cases, from about 50 mg to about 150 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, from about 75 mg to about 125 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, from about 250 mg to about 350 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, from about 150 mg to about 250 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, about 90 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, about 120 mg of the salt of flecainide is administered to the subject via

inhalation. In some cases, about 150 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, about 200 mg of the salt of flecainide is administered to the subject via inhalation. In some cases, the heart condition comprises atrial arrhythmia. In some cases, the atrial arrhythmia comprises tachycardia. In some cases, the atrial arrhythmia the atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation. In some cases, the method comprises aerosolizing the pharmaceutical composition by forming droplets having a mass median aerodynamic diameter of less than 10 μm. In some cases, the method comprises acute treatment after detection of the atrial arrhythmia. In some cases, the subject has normal sinus rhythm within 10 minutes after the administering. In some cases, the subject has normal sinus rhythm within 8 minutes after the administering. In some cases, the subject has normal sinus rhythm within 5 minutes after the administering. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins. In some cases, the cyclodextrin comprises hydroxypropyl-β-cyclodextrin. In some cases, a concentration of the cyclodextrin in the pharmaceutical composition is about 1% (w/v) to about 80% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is from about 15% (w/v) to about 25% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is from about 10% (w/v) to about 30% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at least about 5% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at least about 10% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is about 20% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is about 22.5% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at most about 20% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at most about 25% (w/v) of the solution. In some cases, the

concentration of the cyclodextrin is at most about 23% (w/v) of the solution. In some cases, the concentration of the cyclodextrin is at most about 22.5% (w/v) of the solution. In some cases, the concentration of the salt of flecainide is at most about 200 mg/mL. In some cases, the concentration of the salt of flecainide is from about 65 mg/mL to about 130 mg/mL. In some cases, the concentration of the salt of flecainide is about 65 mg/mL to about 95 mg/mL. In some cases, the concentration of the salt of flecainide is from about 70 mg/mL to about 115 mg/mL. In some cases, the concentration of the salt of flecainide is about 100 mg/mL. In some cases, the concentration of the salt of flecainide is about 75 mg/mL. In some cases, the salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate. In some cases, the salt of flecainide comprises flecainide acetate. In some cases, the salt of flecainide comprises flecainide hydrochloride. In some cases, the pharmaceutical composition further comprises an acid. In some cases, the acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid. In some cases, the acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid. In some cases, a concentration of the acid in the pharmaceutical composition is from about 2 mM to about 200 mM. In some cases, a concentration of the acid in the pharmaceutical composition is about 2 mM to about 50 mM. In some cases, a concentration of the acid in the pharmaceutical composition is about 2 mM to about 10 mM. In some cases, the concentration of the acid is at most about 50 mM. In some cases, the concentration of the acid is about 20 mM. In some cases, the concentration of the acid is about 5 mM. In some cases, the acid comprises acetic acid. In some cases, the concentration of acetic acid is about 5 mM. In some embodiments, the concentration of citric acid is 3.5 mM. In some cases, the acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid. In some cases, the acid comprises hydrochloric acid. In some cases, the salt of flecainide comprises flecainide acetate, and wherein the acid comprises acetic acid. In some cases, the pH of the solution is from about 4.5 to about 6.5, from about 5 to about 6.5, from about 5 to about 6.2, or from about 5.2 to about 5.9. In some cases, the pH of the solution is at most about 6.5. In some cases, the pH of the solution is from about 5.5 to about 6.5. In some cases, the pH of the solution is about 5.9. In some cases, the pH of the solution is about 5.2. In some cases, the salt of flecainide comprises flecainide acetate. In some cases, the pharmaceutical composition further comprises a sweetener. In some cases, the artificial

sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, alcoholsneotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof. In some cases, the artificial sweetener comprises saccharin. In some cases, the artificial sweetener comprises a salt of saccharin. In some cases, the artificial sweetener comprises saccharin sodium. In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

[0030] Disclosed herein, in some aspects, is a method of manufacturing a liquid formulation for the treatment of treating a human subject suffering from a heart condition, the method comprising a therapeutically effective amount of a salt of flecainide for treating the: administering to the subject via inhalation a pharmaceutical composition described herein.

[0031] Disclosed herein, in some aspects, is a method of treating a human subject suffering from a heart condition, wherein a concentration of the salt of the method comprising: administering to the subject via inhalation a unit dose described herein. In some cases, the heart condition comprises atrial fibrillation. In some cases, atrial fibrillation is recurrent atrial fibrillation. In some cases, the atrial fibrillation is paroxysmal atrial fibrillation. In some cases, the subject has a systolic blood pressure that is greater than about 90 mmHg. In some cases, the subject has a systolic blood pressure that is from about 100 mmHg to about 160 mmHg. In some cases, the subject has a ventricular rate that is no more than 170 BPM. In some cases, the subject has a ventricular rate that is from about 80 BPM to about 155 BPM. In some cases, the subject is no more than 85 years old. In some cases, the subject is from 18 years old to 85 years old. In some cases, the subject has undergone cardiac ablation no less than 3 months prior to the administering. In some cases, the subject has an ongoing prescription for oral flecainide or a pharmaceutically acceptable salt thereof. In some cases, the atrial fibrillation has an onset that occurred no more than about 48 hours prior to the administering. In some cases, the atrial fibrillation has an onset that occurred from about 1 hour to about 48 hours prior to the treating prior to the administering. In some cases, the subject does not exhibit a pathology comprising abnormal left ventricular ejection fraction within 6 months prior to the administering. In some cases, the subject does not exhibit a pathology comprising heart failure that is class 2 or greater as classified by New York Heart Association Functional Classification within 6 months prior to the administering. In some cases, the subject does not exhibit a pathology comprising

myocardial infarction or a history of myocardial infarction. In some cases, the subject does not exhibit a pathology comprising hemodynamic instability or cardiac instability. In some cases, subject does not exhibit a pathology comprising an episode of atrial flutter within 6 months prior to the administering. In some cases, the subject has not undergone cardiac surgery for the pathology within 6 months prior to the administering.

[0032] Disclosed herein, in some aspects, is a method of preparing a liquid pharmaceutical composition, comprising combining: (a) water; (b) a pH adjusting agent; (c) flecainide in the formulation is aboveor a pharmaceutically acceptable salt thereof; and (d) a cyclodextrin. In some cases, (i)a concentration of the flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in the pharmaceutical composition, (ii) a concentration of the cyclodextrin in the pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and (iii) a room-temperature pH in the pharmaceutical composition of from about 5.5 to about 6.5. In some cases, the combining comprises: (a) providing the water; (b) contacting the portion of water with the flecainide or pharmaceutically acceptable salt thereof, the cyclodextrin, and the pH adjusting agent in a vessel; and (c) adding a subsequent portion of the water to the vessel to provide the pharmaceutical composition, wherein: (i) a concentration of the flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in the pharmaceutical composition, (ii) a concentration of the cyclodextrin in the pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and (iii) a room-temperature pH in the pharmaceutical composition of from about 5.5 to about 6.5. In some cases, the pH adjusting agent comprises an ion selected from the group consisting of: acetate, citrate, nitrate, chloride, sulfate, maleate, tartrate, phosphate, aconitate, adipate, ascorbate, benzoate, caprylate, cholate, formate, glutamate, lactate, propionate, sorbate, stearate, and succinate. In some cases, the pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid. In some cases, the pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid. In some cases, the pH adjusting agent comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid. In some cases, a concentration of the pH adjusting agent in the pharmaceutical composition is about 2 mM to about 50 mM. In some cases, a concentration of the pH adjusting agent in the pharmaceutical composition is about 2 mM to about 10 mM. In some cases, the pH adjusting agent comprises acetic acid. In some cases, the concentration in the pharmaceutical

composition of the acetic acid is about 5 mM. In some cases, the pH adjusting agent comprises citric acid. In some cases, the concentration in the pharmaceutical composition of the citric acid is about 5 mM. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins. In some cases, the cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins. In some cases, the cyclodextrin comprises hydroxypropyl-β-cyclodextrin. In some cases, the concentration of the cyclodextrin in the pharmaceutical composition is from about 10% (w/v) to about 30% (w/v). In some cases, the method further comprises adding a sweetener. In some cases, the sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof. In some cases, the sweetener comprises saccharin. In some cases, the sweetener comprises a salt of saccharin. In some cases, the sweetener comprises saccharin sodium. In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v). In some cases, a concentration of the sweetener in the pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v). In some cases, the pharmaceutically acceptable salt of flecainide is added. In some cases, the pharmaceutically acceptable salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate. In some cases, the pharmaceutically acceptable the salt of flecainide comprises flecainide acetate. In some cases, the pharmaceutically acceptable the salt of flecainide comprises flecainide hydrochloride. In some cases, the method further comprises packaging the pharmaceutical composition in unit dose form. In some cases, the method further comprises packaging the pharmaceutical composition in unit dose form, wherein the unit dose form comprises about 50 mg to about 350 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 60 mg/mL to about 150 mg of the

pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 75 mg to about 125 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 250 mg to about 350 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 150 mg to about 250 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 90 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 120 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form comprises about 200 mg of the pharmaceutically acceptable salt of flecainide. In some cases, the unit dose form further comprises a container. In some cases, the container is selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.

INCORPORATION BY REFERENCE

[0033] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0035] FIGURE 1 is a schematic demonstrating the complexation between hydroxypropyl-β-cyclodextrin and flecainide acetate in an exemplary pharmaceutical formulation.

[0036] FIGURE 2 is a chart summarizing pharmacokinetic profiles of three different flecainide formulations when delivered via intravenous infusion in pig model of atrial fibrillation.

[0037] FIGURE 3A is a chart summarizing pharmacokinetic profiles (plasma concentration of flecainide acetate) of two different flecainide formulations when delivered via intratracheal instillation at a dose of 0.75 mg/kg in pig model of atrial fibrillation.

[0038] FIGURE 3B is a chart summarizing pharmacokinetic profiles (plasma concentration of flecainide acetate) of two different flecainide formulations when delivered via intratracheal instillation at a dose of 1 mg/kg in pig model of atrial fibrillation.

[0039] FIGURES 4A and 4B are charts summarizing pharmacodynamic profiles (QRS interval duration and atrial depolarization, respectively) of two different flecainide formulations when delivered via intratracheal instillation at a dose of 0.75 mg/kg in pig model of atrial fibrillation.

[0040] FIGURES 4C and 4D are charts summarizing pharmacodynamic profiles (QRS interval duration and atrial depolarization, respectively) of two different flecainide formulations when delivered via intratracheal instillation at a dose of 1 mg/kg in pig model of atrial fibrillation.

[0041] FIGURE 5 is a schematic of experiment design in Example 9.

[0042] FIGURE 6 is a chart summarizing plasma concentration of flecainide acetate when an exemplary HPβCD-flecainide formulation is delivered via intratracheal instillation at two different doses in pig model of atrial fibrillation.

[0043] FIGURE 7 summarizes atrial fibrillation duration in pig models in response to different treatments.

[0044] FIGURE 8 shows illustrative example of conversion of AF in pig models in response to different treatments.

[0045] FIGURE 9 is a chart summarizing dominant frequency during atrial fibrillation in pig model in response to different treatments.

[0046] FIGURE 10 is a chart summarizing ventricular rate in pig model in response to different treatments.

[0047] FIGURE 11 show two charts summarizing heart rate in pig model of atrial fibrillation in response to intratracheal instillation of an exemplary flecainide formulation at doses of 0.5 mg/kg and 1.0 mg/kg, respectively.

[0048] FIGURE 12 is a chart summarizing atrial fibrillation duration in pig model in response to different treatments.

[0049] FIGURE 13 is a chart summarizing atrial depolarization in pig model in response to different treatments.

[0050] FIGURE 14 is a chart summarizing PR interval in pig model in response to different treatments.

[0051] FIGURE 15 is a chart summarizing QRS duration in pig model in response to different treatments.

[0052] FIGURE 16 is a chart summarizing atrial fibrillation duration when the atrial fibrillation is re-induced in pig model in response to different treatments.

[0053] FIGURE 17 is a chart summarizing ventricular rate in pig model in response to different treatments.

[0054] FIGURE 18 is a chart summarizing mean arterial pressure in pig model in response to different treatments.

[0055] FIGURE 19 is a chart summarizing left ventricular contractility in pig model in response to different treatments.

[0056] FIGURE 20 is a chart summarizing plasma concentration of flecainide acetate in pig model in response to different treatments.

[0057] FIGURE 21 is a chart summarizing the magnitude of the prolongations of the QRS interval duration (ΔQRS_{max}) in individual human subjects after inhalation of the formulations of flecainide described in **TABLE 19**.

[0058] FIGURE 22A is a chart summarizing peak plasma concentration of flecainide (C_{max}) in individual human subjects after inhaling flecainide formulations described in **TABLE 19**. Coefficient of variance (%CV) in Cmax values were 111, 83, 67, and 55 for 60 [65], 90 [45], 120 [75] CD, and 120 [75] iCD-SAC dose cohorts, respectively.

[0059] FIGURE 22B is a chart summarizing peak plasma concentration of flecainide (C_{max}) in individual human subjects after inhaling CD and iCD flecainide formulations described in **TABLE 19**.

[0060] FIGURE 22C is a chart summarizing peak plasma concentration of flecainide (C_{max}) in individual human subjects that underwent cardioversion after inhaling CD and iCD flecainide formulations described in **TABLE 19**.

[0061] FIGURE 23A is a chart summarizing the cardioversion rate in human subjects as categorized according to the administered formulation as described in **TABLE 19.**

[0062] FIGURE 23B is a chart summarizing the cardioversion rate in human subjects as categorized according to the C_{max} of flecainide measured after inhalation of flecainide formulations described in **TABLE 19**.

[0063] FIGURE 23C is a chart summarizing the cardioversion rate in human subjects who had a ventricular rate of $\geq$ 80 and $\leq$ 155 bpm at screening, as categorized according to the C_{max} of flecainide measured after inhalation of flecainide formulations described in **TABLE 19**.

[0064] FIGURE 23D is a chart summarizing the cardioversion rate in human subjects as categorized by observed C_{max} (< 250 ng/mL or > 250 ng/mL) across all dose cohorts.

[0065] FIGURE 24 is a chart summarizing the time to conversion of atrial fibrillation to normal sinus rhythm from the end of flecainide inhalation in human subjects administered the formulations described in **TABLE 19**.

[0066] FIGURE 25 is a chart summarizing the cardioversion rate in human subjects categorized by subjects who had a ventricular rate of <80 PM at screening and those who had a ventricular

rate of ≥ 80 and ≤ 155 bpm at screening, and further categorized according to administered formulation (as described in **TABLE 19**).

[0067] **FIGURE 26A** is a chart summarizing the negative inotropic burden of pulmonary and intravenous delivery of flecainide observed in the animals. **FIGURE 26B** is a chart summarizing the correlation between decrease in left ventricular contractility (LV dP/dt max) and QRS complex prolongation.

DETAILED DESCRIPTION

[0068] As an overview, the present disclosure relates to a novel formulation comprising a relatively high concentration of flecainide to treat a heart condition (*e.g.*, cardiac arrhythmic) in a subject in need thereof. In some aspects, provided herein are methods of treatment comprising administering a novel formulation comprising a relatively high concentration of flecainide to treat a heart condition (*e.g.*, cardiac arrhythmic) in a subject in need thereof.

[0069] In some embodiments, the pharmaceutical composition and the method of treatment provided herein are advantageous in offering fast, efficient, and safe therapeutic solution to heart conditions, such as cardiac arrhythmia, such as atrial arrhythmia. In some embodiments, the present disclosure relates to inhalation administration of a pharmaceutical composition in the form of a solution that comprises a salt of flecainide.

[0070] In some embodiments, the drug mass nebulization rate contributes to the efficiency of the inhalation therapy, as demonstrated in studies in human subjects for the pharmacokinetics and pharmacodynamics of inhalation administration of flecainide acetate (*e.g.*, clinical studies FLE-001, FLE-003 (in healthy subjects) and FLE-002 (patients) sponsored by InCarda Therapeutics, Inc.). In some embodiments, human subjects cannot be expected to inhale the nebulized drug solution continuously for longer than approximately 4.5 minutes without a break. Long inhalation duration (*e.g.*, longer than 5 minutes) can result in fatigue, inadequate or poor compliance with proper inhalation maneuver in some subjects, which can lead to insufficient delivery of drug to the lung, and stress. In some cases, stress in some subjects, *e.g.*, stress induced by long inhalation duration or other discomfort, can lead to a rise in sympathetic tone, which can render cardioversion more difficult.

[0071] In some cases, a fast drug mass nebulization rate minimizes inhalation time for an effective dose. The drug mass nebulization rate can be strongly influenced by the drug concentration in the nebulization solution. In a nebulized product, the drug delivery rate can be constrained by the ability of the device to produce a nebulized cloud with an appropriate droplet size for inhalation (*e.g.*, less than 5 microns). On the other hand, when the aerosolization rate is

too high and the cloud too dense, the small nebulized droplets can coalesce into larger droplets which tend to deposit in the mouth and throat and do not reach the lungs.

[0072] In one aspect, the present disclosure provides a pharmaceutical composition, comprising: a therapeutically effective amount of a salt of flecainide, wherein the pharmaceutical composition is in the form of a liquid solution that has the salt of flecainide at a concentration above 60 mg/mL. In some embodiments, the pharmaceutical composition further comprises a cyclodextrin. In some embodiments, the presence of cyclodextrin increases the solubility of the salt of flecainide as compared to a corresponding formulation without the cyclodextrin. In some embodiments, the solution has pH above 5.5 when the pH is measured at room temperature. In some embodiments, the pharmaceutical composition further comprises a cyclodextrin, and the pH of the solution is above 5.5 when the pH is measured at room temperature. In some embodiments, the presence of cyclodextrin renders it possible to increase pH of the solution without compromising the solubility of the salt of flecainide, as compared to a corresponding solution without the cyclodextrin.

[0073] In some embodiments, the pharmaceutical composition or formulation provided herein enables delivery of more pharmaceutically active ingredient, *e.g.*, flecainide, to the subject. In some embodiments, the subject pharmaceutical composition or formulation has an increased flecainide concentration as compared to a corresponding flecainide formulation (*e.g.*, flecainide acetate water solution which has a solubility around 60 mg/mL). In some cases, the increased flecainide concentration increases the delivery speed when the composition is nebulized and administered via inhalation. In some embodiments, the increased flecainide concentration shortens the inhalation duration as a given dose can be delivered at a higher speed as compared to a corresponding formulation with a lower concentration of flecainide. Shorter inhalation duration can improve subject compliance, which can further increase the delivery efficiency of the drug.

[0074] In some embodiments, the pharmaceutical composition or formulation provided herein reduces adverse cough of the subject while inhaling, has improved organoleptic properties, and improves overall patient experience of inhalation. In some embodiments, the improved overall inhalation experience results in better compliance with the full inhalation program. In some embodiments, more effective drug delivery is achieved when the subject has better inhalation compliance, and thus more drug is delivered.

[0075] In some embodiments, the subject pharmaceutical composition or formulation has improved pharmacokinetics or pharmacodynamics parameter(s), for instance, the peak plasma level of flecainide (C_{max}) can be higher with the subject pharmaceutical composition as

compared to a corresponding pharmaceutical composition in which the concentration of the salt of flecainide is lower. In some embodiments, the C_{max} achieved with the subject pharmaceutical composition is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 or greater fold higher as compared to a corresponding pharmaceutical composition in which the concentration of the salt of flecainide is lower.

[0076] In some embodiments, a pharmaceutical composition with a low concentration of acid or a high pH, *e.g.*, at most about 10 mM acetic acid, *e.g.*, about 5 mM acetic acid, or *e.g.* a pH of higher than 5.5, *e.g.*, a pH of 5.9 when the pH is measured at room temperature, has a higher C_{max} as compared to a corresponding pharmaceutical composition in which the concentration of the acid is higher or the pH is lower, *e.g.*, at least about 50 mM acetic acid, *e.g.*, about 90 mM acetic acid, or *e.g.*, a pH of at most 5.5, *e.g.*, a pH of about 5.2 when the pH is measured at room temperature. In some embodiments, the C_{max} achieved with the subject pharmaceutical composition that has a low concentration of acid or a high pH is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 or greater fold higher as compared to a corresponding pharmaceutical composition in which the concentration of the acid is higher or the pH is lower. In some embodiments, the C_{max} achieved with the subject pharmaceutical composition that has at most about 10 mM acetic acid, *e.g.*, about 5 mM acetic acid, or a pH of higher than 5.5, *e.g.*, a pH of 5.9 when the pH is measured at room temperature is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 or greater fold higher as compared to a corresponding pharmaceutical composition in which the concentration of the acetic acid is about 90 mM, or the pH is about 5.2.

[0077] In one aspect of the present disclosure, provided herein is a unit dose of a pharmaceutical composition provided herein. In some embodiments, the unit dose comprises about 50 mg to about 350 mg of the salt of flecainide. In another aspect, provided herein are kits comprising the pharmaceutical composition or the unit dose provided herein and instructions for use of the pharmaceutical composition for treatment of a heart condition (*e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia).

[0078] In one aspect of the present disclosure, provided is a system comprising a pharmaceutical composition provided herein and a nebulizer. In some embodiments, the system further comprises instructions for use of the nebulizer and the pharmaceutical composition for treatment of a heart condition. In some embodiments, the system comprises: a pharmaceutical composition that comprises a salt of flecainide, a cyclodextrin, and an acid; a nebulizer configured to inhalationally administer the pharmaceutical composition as droplets having a mass median

aerodynamic diameter of less than 10 μm; and instructions for use of the nebulizer to inhalationally administer the pharmaceutical composition in an aerosolized dose that contains from about 50 mg to about 150 mg of the salt of flecainide, wherein the pharmaceutical composition is in the form of a liquid solution that has (i) the salt of flecainide at a concentration of from about 65 mg/mL to about 95 mg/mL, (ii) the cyclodextrin at a concentration of from about 10% (w/v) to about 30% (w/v) of the solution; and (iii) a pH of from about 5.5 to about 6.5 when the pH is measured at room temperature.

[0079] In one aspect of the present disclosure, provided is a method of treating a subject suffering from a heart condition. In some embodiments, the method comprises: administering to the subject via inhalation a pharmaceutical composition in the form of a liquid solution, wherein the pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein a concentration of the salt of flecainide in the pharmaceutical composition is above 60 mg/mL.

[0080] As used herein, "heart condition" can refer to a condition where heart has an abnormal function and/or structure, for example, heart is beating in an irregular rhythm, experiencing arrhythmia, atrial fibrillation, and/or tachycardia, there is myocardial infarction, and/or coronary heart disease. As used herein, "atrial arrhythmia" can refer to an arrhythmia that affects at least one atrium and does not include bradycardia. For instance, atrial arrhythmia may originate in and affect at least one atrium. As used herein, "tachycardia" can refer to an arrhythmia in which the heart beat is too fast. For instance, tachycardia may involve a resting heart rate of over 100 beats per minute, such as greater than 110, greater than 120, or greater than 130 beats minute. In some cases, tachycardia can comprise sinus tachycardia, atrial fibrillation, atrial flutter, AV nodal reentrant tachycardia, accessory pathway mediated tachycardia, atrial tachycardia, multifocal atrial tachycardia, junctional tachycardia, ventricular tachycardia, supraventricular tachycardia, or any combination thereof.

[0081] As used herein, the phrase "heart rhythm arrhythmia" can refer to an arrhythmia in which the heart beat is irregular. As used herein, the term "atrial fibrillation" can refer to an abnormal heart rhythm characterized by rapid and irregular beating of the atria. As used herein, the term "cardioversion" can refer to a process by which an abnormally fast heart rate (tachycardia) or other cardiac arrhythmia is converted to a normal sinus rhythm. Cardioversion can be induced by electricity, drugs, or both.

[0082] As used herein, the singular forms "a," "an," and "the" can include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an antiarrhythmic agent"

can include not only a single active agent but also a combination or mixture of two or more different active agents.

[0083] Reference herein to "one embodiment," "one version," or "one aspect" can include one or more such embodiments, versions or aspects, unless otherwise clear from the context.

[0084] As used herein, the term "pharmaceutically acceptable solvate" can refer to a solvate that retains one or more of the biological activities and/or properties of the antiarrhythmic pharmaceutical agent and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable solvates include, but are not limited to, antiarrhythmic pharmaceutical agents in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, ethanolamine, or combinations thereof.

[0085] As used herein, the term "salt" is equivalent to the term "pharmaceutically acceptable salt," and can refer to those salts that retain one or more of the biological activities and properties of the free acids and bases and that are not biologically or otherwise undesirable. Illustrative examples of pharmaceutically acceptable salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, di nitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenyipropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[0086] The term "about" in relation to a reference numerical value can include a range of values plus or minus 10% from that value. For example, the amount "about 10" includes amounts from 9 to 11, including the reference numbers of 9, 10, and 11. The term "about" in relation to a reference numerical value can also include a range of values plus or minus 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% from that value.

[0087] As used herein, "atrial arrhythmia" can refer to an arrhythmia that affects at least one atrium and does not include bradycardia. For instance, atrial arrhythmia can originate in and affect at least one atrium.

[0088] As used herein, "tachycardia" can mean an arrhythmia in which the heart beat is too fast, e.g., faster than normal. For instance, tachycardia may involve a resting heart rate of over 100 beats per minute, such as greater than 110, greater than 120, or greater than 130 beats minute.

[0089] As used herein, the phrase "heart rhythm arrhythmia" can refer to an arrhythmia in which the heart beat is irregular.

[0090] As used herein, the amount of an agent as described herein in the coronary circulation of the heart" can be measured by extracting a sample from any vascular region of the coronary circulation of the heart (e.g., arteries, veins, including coronary sinus) by using a cannula. The amount of the agent in the sample can then be determined by known means, such as bioanalytical techniques that employ analytical equipment such as LC-MS/MS. Thus, the amount of the agent in the blood in the heart can be measured for any particular time.

[0091] As used herein, the terms "treating" and "treatment" can refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, reduction in likelihood of the occurrence of symptoms and/or underlying cause, and/or remediation of damage. Thus, "treating" a patient with an active agent as provided herein can include prevention of a particular condition, disease, or disorder in a susceptible individual as well as treatment of a clinically symptomatic individual.

[0092] As used herein, "nominal amount" can refer to the amount contained within the unit dose receptacle(s) that are administered.

[0093] As used herein, "effective amount" can refer to an amount covering both therapeutically effective amounts and prophylactically effective amounts.

[0094] As used herein, a "therapeutically effective amount" of an active agent can refer to an amount that is effective to achieve a desired therapeutic result. A therapeutically effective amount of a given active agent can vary with respect to factors such as the type and severity of the disorder or disease being treated and the age, gender, and weight of the patient. In some cases, "inhalation" (e.g., "oral inhalation" or "nasal inhalation") refers to inhalation delivery of a therapeutically effective amount of a pharmaceutical agent contained in one unit dose receptacle, which, in some instance, can require one or more breaths, like 1, 2, 3, 4, 5, 6, 7, 8, 9, or more breaths. For example, if the effective amount is 90 mg, and each unit dose receptacle contains 30 mg, the delivery of the effective amount can require 3 inhalations.

[0095] Unless otherwise specified, the term "therapeutically effective amount" can include a "prophylactically effective amount," e.g., an amount of active agent that is effective to prevent the onset or recurrence of a particular condition, disease, or disorder in a susceptible individual.

[0096] As used herein, the phrase "minimum effective amount" can mean the minimum amount of a pharmaceutical agent necessary to achieve an effective amount.

[0097] As used herein, "mass median diameter" or "MMD" can refer to the median diameter of a plurality of particles, typically in a polydisperse particle population, e.g., consisting of a range

of particle sizes. MMD values as reported herein are determined by laser diffraction (Sympatec Helos, Clausthal-Zellerfeld, Germany), unless the context indicates otherwise. For instance, for powders the samples are added directly to the feeder funnel of the Sympatec RODOS dry powder dispersion unit. This can be achieved manually or by agitating mechanically from the end of a VIBRI vibratory feeder element. Samples are dispersed to primary particles via application of pressurized air (2 to 3 bar), with vacuum depression (suction) maximized for a given dispersion pressure. Dispersed particles are probed with a 632.8 nm laser beam that intersects the dispersed particles' trajectory at right angles. Laser light scattered from the ensemble of particles is imaged onto a concentric array of photomultiplier detector elements using a reverse-Fourier lens assembly. Scattered light is acquired in time-slices of 5 ms. Particle size distributions are back-calculated from the scattered light spatial/intensity distribution using a proprietary algorithm.

[0098] As used herein, "geometric diameter" can refer to the diameter of a single particle, as determined by microscopy, unless the context indicates otherwise.

[0099] As used herein, "mass median aerodynamic diameter" or "MMAD" can refer to the median aerodynamic size of a plurality of particles or particles, typically in a polydisperse population. The "aerodynamic diameter" can be the diameter of a unit density sphere having the same settling velocity, generally in air, as a powder and is therefore a useful way to characterize an aerosolized powder or other dispersed particle or particle formulation in terms of its settling behavior. The aerodynamic diameter encompasses particle or particle shape, density, and physical size of the particle or particle. As used herein, MMAD refers to the median of the aerodynamic particle or particle size distribution of aerosolized particles determined by cascade impaction, unless the context indicates otherwise.

[0100] By a "pharmaceutically acceptable" component is meant a component that is not biologically or otherwise undesirable, e.g., the component may be incorporated into a pharmaceutical formulation of the disclosure and administered to a patient as described herein without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the formulation in which it is contained. When the term "pharmaceutically acceptable" is used to refer to an excipient, it can imply that the component has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration.

[0101] As used herein, "P wave" can represent the wave generated by the electrical depolarization of the atria (right and left) and is usually 0.08 to 0.1 seconds (80-100 ms) in duration.

[0102] As used herein, "room temperature" can refer to a temperature that is from 18 °C to 25 °C.

CYCLODEXTRINS

[0103] In some aspects of the present disclosure, a cyclodextrin is used as a solubility enhancer of a salt of flecainide. Cyclodextrins are cyclic carbohydrates derived from starch. The unmodified cyclodextrins differ by the number of glucopyranose units joined together in the cylindrical structure. The parent cyclodextrins contain 6, 7, or 8 glucopyranose units and are referred to as α-, β-, and γ-cyclodextrin respectively. Each cyclodextrin subunit can have secondary hydroxyl groups at the 2 and 3 positions and a primary hydroxyl group at the 6-position. The cyclodextrins can be pictured as hollow truncated cones with hydrophilic exterior surfaces and hydrophobic interior cavities. In aqueous solutions, these hydrophobic cavities can provide a haven for hydrophobic organic compounds that can fit all or part of their structure into these cavities. This process, known as inclusion complexation, can result in increased apparent aqueous solubility and stability for the complexed drug.

[0104] The cyclodextrin in a pharmaceutical composition provided herein can include, but not limited to, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins. Non-limiting examples of cyclodextrin that can be used in the subject pharmaceutical composition include α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins. In some embodiments, the pharmaceutical composition comprises hydroxypropyl-β-cyclodextrin (HPβCD). In some embodiments, the pharmaceutical composition comprises more than one species of cyclodextrins, such as, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different species of cyclodextrins. In some embodiments, the pharmaceutical composition comprises HPβCD and one or more other cyclodextrins, such as, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more other different species of cyclodextrins.

[0105] The subject pharmaceutical composition can comprise a cyclodextrin at a concentration of at least about 1% (w/v) of the solution, such as at least about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%,

28%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 100%, or more (w/v) of the solution. In some embodiments, the pharmaceutical composition comprises a cyclodextrin at a concentration of from about 1% (w/v) to about 80% (w/v) of the solution, such as from about 2% (w/v) to about 70% (w/v), from about 2% (w/v) to about 60% (w/v), from about 2% (w/v) to about 50% (w/v), from about 2% (w/v) to about 40% (w/v), from about 2% (w/v) to about 30% (w/v), from about 2% (w/v) to about 20% (w/v), from about 2% (w/v) to about 15% (w/v), from about 2% (w/v) to about 10% (w/v), from about 2% (w/v) to about 8% (w/v), from about 2% (w/v) to about 5% (w/v), from about 5% (w/v) to about 80% (w/v), from about 5% (w/v) to about 70% (w/v), from about 5% (w/v) to about 60% (w/v), from about 5% (w/v) to about 50% (w/v), from about 5% (w/v) to about 40% (w/v), from about 5% (w/v) to about 30% (w/v), from about 5% (w/v) to about 20% (w/v), from about 5% (w/v) to about 15% (w/v), from about 5% (w/v) to about 12% (w/v), from about 5% (w/v) to about 10% (w/v), from about 10% (w/v) to about 60% (w/v), from about 10 % (w/v) to about 50% (w/v), from about 10% (w/v) to about 40% (w/v), from about 10% (w/v) to about 30% (w/v), from about 20% (w/v) to about 30% (w/v), from about 10% (w/v) to about 25% (w/v), from about 19% (w/v) to about 25% (w/v), from about 19.5% (w/v) to about 25% (w/v), from about 20% (w/v) to about 25% (w/v), from about 20.5% (w/v) to about 25% (w/v), from about 21% (w/v) to about 25% (w/v), from about 21.5% (w/v) to about 25% (w/v), from about 22% (w/v) to about 25% (w/v), from about 22.5% (w/v) to about 25% (w/v), from about 23% (w/v) to about 25% (w/v), from about 10% (w/v) to about 20% (w/v), or from about 10% (w/v) to about 15% (w/v) of the solution. In some embodiments, the pharmaceutical composition comprises a cyclodextrin at a concentration of about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 20.5%, 21%, 21.5%, 22%, 22.5%, 23%, 23.5%, 24%, 24.5%, 25%, 25.5%, 26%, 26.5%, 27%, 27.5%, 28%, 28.5%, 29%, 29.5%, 30%, 31%, 32%, 33%, 34%, 35%, 38%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% (w/v) of the solution.

[0106] In some embodiments, the concentration of the cyclodextrin contributes to the viscosity of the solution, which can reduce the nebulization efficiency (or rate) of the solution. For instance, in some cases, the higher the concentration of the cyclodextrin is, the higher viscosity of the solution is. In some cases, the concentration of the cyclodextrin in the pharmaceutical composition is controlled so that the viscosity of the solution is not higher than a reference value, such as about 3.1 cP, 3.2 cP, 3.3 cP, 3.4 cP, 3.5 cP, 3.6 cP, 3.7 cP, 3.8 cP, 3.9 cP, 4.0 cP, 4.1 cP, 4.2 cP, 4.3 cP, 4.4 cP, 4.5 cP, 4.6 cP, 4.7 cP, 4.8 cP, 4.9 cP, or 5.0 cP. In some cases, the concentration of the cyclodextrin in the pharmaceutical composition is at most about 2%, 5%, 8%, 10%, 12%, 15%, 18%, 20%, 20.5%, 21%, 21.5%, 22%, 22.5%, 23%, 23.5%, 24%, 24.5%,

25%, 25.5%, 26%, 26.5%, 27%, 27.5%, 28%, 28.5%, 29%, 29.5%, 30%, 31%, 32%, 33%, 34%, 35%, 38%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% (w/v) of the solution.

[0107] In some embodiments, the pharmaceutical composition comprises HPβCD at a concentration of about 20% (w/v) of the solution. In some embodiments, the pharmaceutical composition comprises HPβCD at a concentration of about 22.5% (w/v) of the solution. In some embodiments, the pharmaceutical composition comprises HPβCD at a concentration of about 20% (w/v) of the solution.

ACIDS

[0108] Some aspects of the present disclosure relate to use of one or more acids in the pharmaceutical composition. In some cases, the acid enhances solubility of flecainide. In some cases, flecainide freebase has a low solubility, *e.g.,* in water. In some cases, certain salts of flecainide have higher solubility as compared to other salts of flecainide and flecainide freebase. For instance, flecainide acetate can have a higher solubility as compared to some other flecainide salts, as demonstrated in Example 1. In some cases, acid is provided in the pharmaceutical composition to provide anion for flecainide salt formation and sufficiently low pH to ensure the solubility of the flecainide salt.

[0109] In some cases, a mixture of more than one acid can increase flecainide solubility as compared to a single acid. In some instances, the pharmaceutical composition comprises acetic acid as the single acid. In some instances, the pharmaceutical composition comprises citric acid as the single acid. In some cases, the pharmaceutical composition comprises a mixture of different acids. In some cases, the pharmaceutical composition comprises lactic acid. In some cases, the pharmaceutical composition comprises L-(+)-lactic acid. In some cases, the pharmaceutical composition comprises D-(-)-lactic acid. In some cases, the pharmaceutical composition comprises a mixture of D-(-)-lactic acid and L-(+)-lactic acid, i.e. the pharmaceutical composition comprises DL-lactic acid. In some cases, there are equal amounts of D-(-)-lactic acid and L-(+)-lactic acid in the pharmaceutical composition. In some cases, the pharmaceutical composition comprises ascorbic acid. Non-limiting examples of the acids that can be used in the subject pharmaceutical compositions and methods of treatment include any suitable organic or inorganic acid, such as any GRAS (Generally Recognized As Safe) listed acid, *e.g.*, acetic acid, aconitic acid, adipic acid, alginic acid, benzoic acid, caprylic acid, citric acid, cholic acid, formic acid, lactic acid (*e.g.*, D-(-)-lactic acid or L-(+)-lactic acid), linoleic acid, malic acid, maleic acid, propionic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, tartaric acid, glutamic acid, hydrochloric acid, phosphoric acid, ascorbic acid, erythorbic acid,

sorbic acid, or thiodipropionic acid, or any other acid that is not listed in GRAS but is pharmaceutically acceptable in the subject pharmaceutical composition.

[0110] In some cases, the pharmaceutical composition comprises a mixture of different acids, such as 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different acids. In some cases, the pharmaceutical composition comprises one of the following: acetic acid and nitric acid; acetic acid and sulfuric acid; acetic acid and citric acid; acetic acid, nitric acid, and sulfuric acid; acetic acid, nitric acid, and citric acid; acetic acid, citric acid, and sulfuric acid; or acetic acid, nitric acid, citric acid, and sulfuric acid.

[0111] In some embodiments, the pharmaceutical composition has a pH that is above 5.5 when the pH is measured at room temperature, such as above 5.6, above 5.7, above 5.8, above 5.9, above 6.0, above 6.1, above 6.2, above 6.3, above 6.4, above 6.5, above 6.6, above 6.7, or above 6.8 when the pH is measured at room temperature. In some cases, the pharmaceutical composition is acidic at room temperature, *e.g.*, having a pH at most 6.9, at most 6.8, at most 6.7, at most 6.6, at most 6.5, at most 6.4, at most 6.3, at most 6.2, at most 6.1, at most 6.0, at most 5.9, at most 5.8, at most 5.7, or at most 5.6 when the pH is measured at room temperature. In some cases, the pharmaceutical composition has a pH that is from about 5.5 and about 6.5 when the pH is measured at room temperature, such as from about 5.6 and about 6.4, from about 5.7 and about 6.3, from about 5.8 and about 6.2, or from about 5.9 and about 6.1 when the pH is measured at room temperature. In some instances, the pharmaceutical composition has a pH of about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, or 6.4 when the pH is measured at room temperature. In some examples, the pharmaceutical composition has a pH of about 5.5 when the pH is measured at room temperature. In some embodiments, the pH of the pharmaceutical composition is titrated by a pH buffer as described herein.

[0112] In some embodiments, the concentration of the acid in the pharmaceutical composition is about 2 mM to about 200 mM, such as about 2 mM to about 180 mM, from about 2 mM to about 150 mM, from about 2 mM to about 120 mM, from about 2 mM to about 100 mM, from about 2 mM to about 80 mM, from about 2 mM to about 60 mM, from about 2 mM to about 50 mM, from about 2 mM to about 40 mM, from about 2 mM to about 30 mM, from about 2 mM to about 20 mM, from about 2 mM to about 10 mM, from about 2 mM to about 8 mM, 2 mM to about 6 mM, from about 5 mM to about 200 mM, from about 5 mM to about 150 mM, from about 5 mM to about 120 mM, from about 5 mM to about 100 mM, from about 5 mM to about 80 mM, from about 5 mM to about 60 mM, from about 5 mM to about 50 mM, from about 5 mM to about 40 mM, from about 5 mM to about 30 mM, from about 5 mM to about 20 mM, from about 5 mM to about 10 mM, from about 5 mM to about 8 mM, from about 10 mM to

about 200 mM, from about 10 mM to about 150 mM, from about 10 mM to about 120 mM, from about 10 mM to about 100 mM, from about 10 mM to about 90 mM, from about 10 mM to about 80 mM, from about 10 mM to about 70 mM, from about 10 mM to about 60 mM, from about 10 mM to about 50 mM, from about 10 mM to about 40 mM, from about 10 mM to about 30 mM, from about 10 mM to about 20 mM, from about 20 mM to about 200 mM, from about 20 mM to about 150 mM, from about 20 mM to about 100 mM, from about 20 mM to about 90 mM, from about 20 mM to about 80 mM, from about 20 mM to about 70 mM, from about 20 mM to about 60 mM, from about 20 mM to about 50 mM, from about 20 mM to about 40 mM, from about 20 mM to about 30 mM, from about 40 mM to about 200 mM, from about 40 mM to about 150 mM, from about 40 mM to about 120 mM, from about 40 mM to about 100 mM, from about 40 mM to about 90 mM, from about 40 mM to about 80 mM, from about 40 mM to about 70 mM, from about 40 mM to about 60 mM, or about 40 mM to about 50 mM. In some embodiments, the concentration of the acid in the pharmaceutical composition is at most about 200 mM, such as at most about 180 mM, at most about 160 mM, at most about 150 mM, at most about 140 mM, at most about 120 mM, at most about 100 mM, at most about 90 mM, at most about 80 mM, at most about 70 mM, at most about 60 mM, at most about 50 mM, at most about 40 mM, at most about 30 mM, at most about 20 mM, at most about 10 mM, at most about 9 mM, at most about 8 mM, at most about 7 mM, at most about 6 mM, at most about 5 mM, at most about 4 mM, at most about 3 mM, at most about 2 mM, or at most about 1 mM. In some embodiments, the concentration of the acid in the pharmaceutical composition is about 100 mM, about 90 mM, about 80 mM, about 70 mM, about 60 mM, about 50 mM, about 40 mM, about 30 mM, about 20 mM, about 10 mM, about 9 mM, about 8 mM, about 7 mM, about 6 mM, about 5 mM, about 4 mM, about 3 mM, about 2 mM, or about 1 mM. In some embodiments, the concentration of the acid in the pharmaceutical composition is about 20 mM. In some embodiments, the concentration of the acid in the pharmaceutical composition is about 5 mM.

[0113] Without wishing to be bound to a particular theory, the concentration of the acid in the pharmaceutical composition can contribute to the pharmaceutical application of the composition. In some embodiments, the acid concentration and thus the pH of the solution can influence solubility of the flecainide salt in the formulation, therefore affecting the concentration of the flecainide salt. As discussed above, the concentration of the flecainide salt can contribute to the delivery efficiency and rate of the pharmaceutical composition. In some embodiments, the acid concentration can influence the organoleptic properties of the pharmaceutical composition. For instance, the lower the pH of the solution is, the more irritating the solution can be to the mouth, the nose, the pharynx, or other parts of the respiratory system, particularly the upper respiratory

system. Irritation of the solution can induce cough or other adverse reactions, or reduced compliance of the subject, therefore adversely affecting the delivery efficiency of the pharmaceutical composition.

[0114] In some embodiments, the pharmaceutical composition provided herein does not induce coughing reflex when being inhaled by a subject. In some embodiments, the pharmaceutical composition provided herein induces coughing reflex less frequently when being inhaled by a subject as compared to a corresponding pharmaceutical composition that has a higher acid concentration or lower pH, such as about 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90%, or 100%, or 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 or greater fold lower as compared to the corresponding pharmaceutical composition. In some embodiments, a subject receiving inhalation administration of the pharmaceutical composition reports less severe discomfort when inhaling the composition, or has lower incidence of reporting discomfort when inhaling the composition, as compared to a corresponding pharmaceutical composition that has a higher acid concentration or lower pH, such as about 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90%, or 100%, or 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 or greater fold lower as compared to the corresponding pharmaceutical composition.

[0115] Without wishing to be bound by a certain theory, the presence of a cyclodextrin in the pharmaceutical composition can reduce the concentration of acid that is required to achieve a desirable concentration of flecainide salt according to some aspects of the present disclosure. In some embodiments, the presence of a cyclodextrin (*e.g.*, HPβCD) increases flecainide solubility, *e.g.*, through inclusion complexation that "dissolves" flecainide salt (*e.g.*, flecainide acetate) inside the cavity of the cyclodextrin. The inclusion complexation, on the other hand, can reduce the reliability of flecainide salt on the acid (or the low pH) to be dissolved in the solution. Therefore, as a result, the introduction of cyclodextrin (*e.g.*, HPβCD) can lead to reduction of acid concentration in the solution, both of which synergistically lead to increased flecainide concentration in the solution, improved organoleptic properties, increased delivery speed, and improved delivery efficiency.

SWEETENERS AND ORGANOLEPTIC PROPERTIES

[0116] In some embodiments, the pharmaceutical composition provided herein comprises a sweetener to improve the organoleptic properties of the composition. The sweetener can be a natural sweet substance, *e.g.* certain sugars, or an artificial sweetener. Without wishing to be bound to a certain theory, the presence of the sweetener in the pharmaceutical composition can improve the organoleptic properties of the composition. In some cases, the presence of the sweetener in the pharmaceutical composition can improve the compliance of the subject.

presence of the sweetener in the pharmaceutical composition can increase the delivery efficiency of the composition. In some embodiments, the presence of the sweetener in the pharmaceutical composition can enhance the therapeutic effects of the composition.

[0117] Non-limiting examples of artificial sweeteners that can be used in the pharmaceutical composition include acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, and sugar alcohols (*e.g.*, erythritol, hydrogenated starch hydrolysates, isomalt, lactitol, maltitol, mannitol, sorbitol, and xylitol), such as those used in commercial products, like Sweet n' low powder sweetener, Truvia powder sweetener, Equal (aspartame), Stevia powder sachet, Aspen Naturals liquid stevia, Now Better Stevia liquid sweetener, Sweet N' Low liquid sweetener, Quick Sweet: Neotame liquid sweetener, or Splenda powder sachet, or pharmaceutically acceptable salts thereof In some embodiments, the pharmaceutical composition comprises saccharin. In some embodiments, the pharmaceutical composition comprises a salt of saccharin. In some embodiments, the pharmaceutical composition comprises saccharin sodium.

[0118] Natural sweet substances that can be used in the pharmaceutical composition include, but not limited to, sucrose, agave, brown sugar, confectioner's (powdered) sugar, corn syrup, dextrose, fructose, fruit juice concentrate, glucose, high-fructose corn syrup, honey, invert sugar, lactose, malt sugar, maltose, maple syrup, molasses, nectars, raw sugar, and syrup. Sugars can increase the viscosity of the liquid solution, thus the concentration of any sugar added into the pharmaceutical composition, in some embodiments, is tightly controlled below a certain threshold value.

[0119] In some embodiments, the concentration of the sweetener, *e.g.*, artificial sweetener, in the pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v) of the solution, such as 0.002% to 1%, 0.005% to 1%, 0.01% to 1%, 0.02% to 1%, 0.05% to 1%, 0.08% to 1%, 0.1% to 1%, 0.2% to 1%, 0.5% to 1%, 0.8 to 1%, 0.002% to 0.5%, 0.005% to 0.5%, 0.01% to 0.5%, 0.02% to 0.5%, 0.05% to 0.5%, 0.08% to 0.5%, 0.1% to 0.5%, 0.2% to 0.5%, 0.005% to 0.1%, 0.01% to 0.1%, 0.02% to 0.1%, 0.05% to 0.1%, 0.08% to 0.1%, 0.005% to 0.05%, 0.01% to 0.05%, or 0.02% to 0.05% (w/v) of the solution. In some embodiments, the concentration of the sweetener, *e.g.*, artificial sweetener, in the pharmaceutical composition is at least about 0.001%, at least about 0.002%, at least about 0.005%, at least about 0.01%, at least about 0.02%, at least about 0.05%, at least about 0.08%, at least about 0.1%, at least about 0.2%, at least about 0.5%, or at least about 0.8, or at least about 1% (w/v) of the solution. In some embodiments, the concentration of the sweetener, *e.g.*, artificial sweetener, in the pharmaceutical composition is at most about 0.001%, at most about 0.002%, at most about 0.005%, at most about 0.01%, at most

about 0.02%, at most about 0.05%, at most about 0.08%, at most about 0.1%, at most about 0.2%, at most about 0.5%, or at most about 0.8, or at most about 1% (w/v) of the solution.

PHARMACEUTICAL COMPOSITIONS, FORMULATIONS, AND KITS

[0120] In one aspect, provided herein are pharmaceutical composition for treatment of a heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia.

[0121] The pharmaceutical composition can include a therapeutically effective amount of a salt of flecainide. The therapeutically effective amount of flecainide can be effective for treatment of a heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia, when it is administered to a subject in need thereof via inhalation. In some cases, the therapeutically effective amount of flecainide salt is effective for treatment of atrial arrhythmia by inducing cardioversion when it is administered to a subject in need thereof via inhalation.

[0122] In some cases, provided herein are pharmaceutical composition including a therapeutically effective amount of a salt of flecainide. As described herein, in some embodiments, the pharmaceutical composition is in the form of a liquid solution. In some cases, the concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is about 60 mg/mL to about 200 mg/mL, such as 60 mg/mL to 195 mg/mL, 60 mg/mL to 190 mg/mL, 60 mg/mL to 185 mg/mL, 60 mg/mL to 175 mg/mL, 60 mg/mL to 170 mg/mL, 60 mg/mL to 165 mg/mL, 60 mg/mL to 160 mg/mL, 60 mg/mL to 155 mg/mL, 60 mg/mL to 150 mg/mL, 60 mg/mL to 145 mg/mL, 60 mg/mL to 140 mg/mL, 60 mg/mL to 135 mg/mL, 60 mg/mL to 130 mg/mL, 60 mg/mL to 125 mg/mL, 60 mg/mL to 120 mg/mL, 60 mg/mL to 118 mg/mL, 60 mg/mL to 115 mg/mL, 60 mg/mL to 112 mg/mL, 60 mg/mL to 110 mg/mL, 60 mg/mL to 108 mg/mL, 60 mg/mL to 105 mg/mL, 60 mg/mL to 102 mg/mL, 60 mg/mL to 100 mg/mL, 60 mg/mL to 98 mg/mL, 60 mg/mL to 95 mg/mL, 60 mg/mL to 92 mg/mL, 60 mg/mL to 90mg/mL, 60 mg/mL to 88 mg/mL, 60 mg/mL to 85 mg/mL, 60 mg/mL to 82 mg/mL60 mg/mL to 80 mg/mL, 60 mg/mL to 78 mg/mL, 60 mg/mL to 75 mg/mL, 60 mg/mL to 72 mg/mL, 60 mg/mL to 70 mg/mL, 70 mg/mL to 195 mg/mL, 70 mg/mL to 190 mg/mL, 70 mg/mL to 185 mg/mL, 70 mg/mL to 175 mg/mL, 70 mg/mL to 170 mg/mL, 70 mg/mL to 165 mg/mL, 70 mg/mL to 160 mg/mL, 70 mg/mL to 155 mg/mL, 70 mg/mL to 150 mg/mL, 70 mg/mL to 145 mg/mL, 70 mg/mL to 140 mg/mL, 70 mg/mL to 135 mg/mL, 70 mg/mL to 130 mg/mL, 70 mg/mL to 125 mg/mL, 70 mg/mL to 120 mg/mL, 70 mg/mL to 118 mg/mL, 70 mg/mL to 115 mg/mL, 70 mg/mL to 112 mg/mL, 70 mg/mL to 110 mg/mL, 70 mg/mL to 108 mg/mL, 70 mg/mL to 105 mg/mL, 70 mg/mL to 102 mg/mL, 70 mg/mL to 100 mg/mL, 70 mg/mL to 98 mg/mL, 70 mg/mL to 95 mg/mL, 70 mg/mL to 92 mg/mL, 70 mg/mL to 90mg/mL, 70 mg/mL to 88 mg/mL, 70 mg/mL to

85 mg/mL, 70 mg/mL to 82 mg/mL70 mg/mL to 80 mg/mL, 70 mg/mL to 78 mg/mL, 70 mg/mL to 75 mg/mL, 80 mg/mL to 195 mg/mL, 80 mg/mL to 190 mg/mL, 80 mg/mL to 185 mg/mL, 80 mg/mL to 175 mg/mL, 80 mg/mL to 170 mg/mL, 80 mg/mL to 165 mg/mL, 80 mg/mL to 160 mg/mL, 80 mg/mL to 155 mg/mL, 80 mg/mL to 150 mg/mL, 80 mg/mL to 145 mg/mL, 80 mg/mL to 140 mg/mL, 80 mg/mL to 135 mg/mL, 80 mg/mL to 130 mg/mL, 80 mg/mL to 125 mg/mL, 80 mg/mL to 120 mg/mL, 80 mg/mL to 118 mg/mL, 80 mg/mL to 115 mg/mL, 80 mg/mL to 112 mg/mL, 80 mg/mL to 110 mg/mL, 80 mg/mL to 108 mg/mL, 80 mg/mL to 105 mg/mL, 80 mg/mL to 102 mg/mL, 80 mg/mL to 100 mg/mL, 80 mg/mL to 98 mg/mL, 80 mg/mL to 95 mg/mL, 80 mg/mL to 92 mg/mL, 80 mg/mL to 90mg/mL, 80 mg/mL to 88 mg/mL, 80 mg/mL to 85 mg/mL, 90 mg/mL to 195 mg/mL, 90 mg/mL to 190 mg/mL, 90 mg/mL to 185 mg/mL, 90 mg/mL to 175 mg/mL, 90 mg/mL to 170 mg/mL, 90 mg/mL to 165 mg/mL, 90 mg/mL to 160 mg/mL, 90 mg/mL to 155 mg/mL, 90 mg/mL to 150 mg/mL, 90 mg/mL to 145 mg/mL, 90 mg/mL to 140 mg/mL, 90 mg/mL to 135 mg/mL, 90 mg/mL to 130 mg/mL, 90 mg/mL to 125 mg/mL, 90 mg/mL to 120 mg/mL, 90 mg/mL to 118 mg/mL, 90 mg/mL to 115 mg/mL, 90 mg/mL to 112 mg/mL, 90 mg/mL to 110 mg/mL, 90 mg/mL to 108 mg/mL, 90 mg/mL to 105 mg/mL, 90 mg/mL to 102 mg/mL, 90 mg/mL to 100 mg/mL, 90 mg/mL to 98 mg/mL, 90 mg/mL to 95 mg/mL, 100 mg/mL to 195 mg/mL, 100 mg/mL to 190 mg/mL, 100 mg/mL to 185 mg/mL, 100 mg/mL to 175 mg/mL, 100 mg/mL to 170 mg/mL, 100 mg/mL to 165 mg/mL, 100 mg/mL to 160 mg/mL, 100 mg/mL to 155 mg/mL, 100 mg/mL to 150 mg/mL, 100 mg/mL to 145 mg/mL, 100 mg/mL to 140 mg/mL, 100 mg/mL to 135 mg/mL, 100 mg/mL to 130 mg/mL, 100 mg/mL to 125 mg/mL, 100 mg/mL to 120 mg/mL, 100 mg/mL to 118 mg/mL, or 100 mg/mL to 115 mg/mL.

[0123] In some cases, the concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is at least about 115 mg/mL, at least about 112 mg/mL, at least about 110 mg/mL, at least about 109 mg/mL, at least about 108 mg/mL, at least about 107 mg/mL, at least about 106 mg/mL, at least about 105 mg/mL, at least about 104 mg/mL, at least about 103 mg/mL, at least about 102 mg/mL, at least about 101 mg/mL, at least about 100 mg/mL, at least about 99 mg/mL, at least about 98 mg/mL, at least about 97 mg/mL, at least about 96 mg/mL, at least about 95 mg/mL, at least about 94 mg/mL, at least about 93 mg/mL, at least about 92 mg/mL, at least about 91 mg/mL, at least about 90mg/mL, at least about 89 mg/mL, at least about 88 mg/mL, at least about 87 mg/mL, at least about 86 mg/mL, at least about 85 mg/mL, at least about 84 mg/mL, at least about 83 mg/mL, at least about 82 mg/mL, at least about 81 mg/mL, at least about 80 mg/mL, at least about 79 mg/mL, at least about 78 mg/mL, at least about 77 mg/mL, at least

about 76 mg/mL, at least about 75 mg/mL, at least about 74 mg/mL, at least about 73 mg/mL, at least about 72 mg/mL, at least about 71 mg/mL, at least about 70 mg/mL, at least about 69 mg/mL, at least about 68 mg/mL, at least about 67 mg/mL, at least about 66 mg/mL, at least about 65 mg/mL, at least about 64 mg/mL, at least about 63 mg/mL, at least about 62 mg/mL, at least about 61 mg/mL, or at least about 60 mg/mL.

[0124] In some cases, the concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is about 195 mg/mL, about 190 mg/mL, about 185 mg/mL, about 175 mg/mL, about 170 mg/mL, about 165 mg/mL, about 160 mg/mL, about 155 mg/mL, about 150 mg/mL, about 145 mg/mL, about 140 mg/mL, about 135 mg/mL, about 130 mg/mL, about 125 mg/mL, about 120 mg/mL, about 118 mg/mL, about 115 mg/mL, about 112 mg/mL, about 110 mg/mL, about 109 mg/mL, about 108 mg/mL, about 107 mg/mL, about 106 mg/mL, about 105 mg/mL, about 104 mg/mL, about 103 mg/mL, about 102 mg/mL, about 101 mg/mL, about 100 mg/mL, about 99 mg/mL, about 98 mg/mL, about 97 mg/mL, about 96 mg/mL, about 95 mg/mL, about 94 mg/mL, about 93 mg/mL, about 92 mg/mL, about 91 mg/mL, about 90mg/mL, about 89 mg/mL, about 88 mg/mL, about 87 mg/mL, about 86 mg/mL, about 85 mg/mL, about 84 mg/mL, about 83 mg/mL, about 82 mg/mL, about 81 mg/mL, about 80 mg/mL, about 79 mg/mL, about 78 mg/mL, about 77 mg/mL, about 76 mg/mL, about 75 mg/mL, about 74 mg/mL, about 73 mg/mL, about 72 mg/mL, about 71 mg/mL, about 70 mg/mL, about 69 mg/mL, about 68 mg/mL, about 67 mg/mL, about 66 mg/mL, about 65 mg/mL, about 64 mg/mL, about 63 mg/mL, about 62 mg/mL, or about 61 mg/mL.

[0125] In some cases, the nominal concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is about 125 mM to about 430 mM, such as 125 mM to 420 mM, 125 mM to 400 mM, 125 mM to 390 mM, 125 mM to 380 mM, 125 mM to 370 mM, 125 mM to 360 mM, 125 mM to 350 mM, 125 mM to 340 mM, 125 mM to 330 mM, 125 mM to 320 mM, 125 mM to 310 mM, 125 mM to 300 mM, 125 mM to 290 mM, 125 mM to 280 mM, 125 mM to 270 mM, 125 mM to 260 mM, 125 mM to 250 mM, 125 mM to 240 mM, 125 mM to 230 mM, 125 mM to 220 mM, 125 mM to 210 mM, 125 mM to 200 mM, 125 mM to 190 mM, 125 mM to 180 mM, 125 mM to 170 mM, 125 mM to 160 mM, 125 mM to 155 mM, 125 mM to 150 mM, 125 mM to 145 mM, 125 mM to 140 mM, 125 mM to 135 mM, 125 mM to 130 mM, 140 mM to 420 mM, 140 mM to 400 mM, 140 mM to 390 mM, 140 mM to 380 mM, 140 mM to 370 mM, 140 mM to 360 mM, 140 mM to 350 mM, 140 mM to 340 mM, 140 mM to 330 mM, 140 mM to 320 mM, 140 mM to 310 mM, 140 mM to 300 mM, 140 mM to 290 mM, 140 mM to 280 mM, 140 mM to 270

mM, 140 mM to 260 mM, 140 mM to 250 mM, 140 mM to 240 mM, 140 mM to 230 mM, 140 mM to 220 mM, 140 mM to 210 mM, 140 mM to 200 mM, 140 mM to 190 mM, 140 mM to 180 mM, 140 mM to 170 mM, 140 mM to 160 mM, 140 mM to 155 mM, 140 mM to 150 mM, 140 mM to 145 mM, 160 mM to 420 mM, 160 mM to 400 mM, 160 mM to 390 mM, 160 mM to 380 mM, 160 mM to 370 mM, 160 mM to 360 mM, 160 mM to 350 mM, 160 mM to 340 mM, 160 mM to 330 mM, 160 mM to 320 mM, 160 mM to 310 mM, 160 mM to 300 mM, 160 mM to 290 mM, 160 mM to 280 mM, 160 mM to 270 mM, 160 mM to 260 mM, 160 mM to 250 mM, 160 mM to 240 mM, 160 mM to 230 mM, 160 mM to 220 mM, 160 mM to 210 mM, 160 mM to 200 mM, 160 mM to 190 mM, 160 mM to 180 mM, 160 mM to 170 mM, 180 mM to 420 mM, 180 mM to 400 mM, 180 mM to 390 mM, 180 mM to 380 mM, 180 mM to 370 mM, 180 mM to 360 mM, 180 mM to 350 mM, 180 mM to 340 mM, 180 mM to 330 mM, 180 mM to 320 mM, 180 mM to 310 mM, 180 mM to 300 mM, 180 mM to 290 mM, 180 mM to 280 mM, 180 mM to 270 mM, 180 mM to 260 mM, 180 mM to 250 mM, 180 mM to 240 mM, 180 mM to 230 mM, 180 mM to 220 mM, 180 mM to 210 mM, 180 mM to 200 mM, 180 mM to 190 mM, 200 mM to 420 mM, 200 mM to 400 mM, 200 mM to 390 mM, 200 mM to 380 mM, 200 mM to 370 mM, 200 mM to 360 mM, 200 mM to 350 mM, 200 mM to 340 mM, 200 mM to 330 mM, 200 mM to 320 mM, 200 mM to 310 mM, 200 mM to 300 mM, 200 mM to 290 mM, 200 mM to 280 mM, 200 mM to 270 mM, 200 mM to 260 mM, 200 mM to 250 mM, 200 mM to 240 mM, 200 mM to 230 mM, 200 mM to 220 mM, or 200 mM to 210 mM.

[0126] In some cases, the nominal concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is at least about 400 mM, at least about 390 mM, at least about 380 mM, at least about 370 mM, at least about 360 mM, at least about 350 mM, at least about 340 mM, at least about 330 mM, at least about 320 mM, at least about 310 mM, at least about 300 mM, at least about 290 mM, at least about 280 mM, at least about 270 mM, at least about 260 mM, at least about 255 mM, at least about 250 mM, at least about 245 mM, at least about 240 mM, at least about 235 mM, at least about 230 mM, at least about 225 mM, at least about 220 mM, at least about 215 mM, at least about 210 mM, at least about 200 mM, at least about 190 mM, at least about 180 mM, at least about 170 mM, at least about 160 mM, at least about 155 mM, at least about 150 mM, at least about 145 mM, at least about 140 mM, at least about 135 mM, at least about 130 mM, or at least about 125 mM.

[0127] In some cases, the concentration of flecainide or the salt of flecainide (*e.g.*, flecainide acetate or flecainide hydrochloride) in the pharmaceutical compositions or formulations is about 420 mM, about 400 mM, about 390 mM, about 380 mM, about 370 mM, about 360 mM, about

350 mM, about 340 mM, about 330 mM, about 320 mM, about 310 mM, about 300 mM, about 290 mM, about 280 mM, about 270 mM, about 260 mM, about 255 mM, about 250 mM, about 245 mM, about 240 mM, about 235 mM, about 230 mM, about 225 mM, about 220 mM, about 215 mM, about 210 mM, about 200 mM, about 190 mM, about 180 mM, about 170 mM, about 160 mM, about 155 mM, about 150 mM, about 145 mM, about 140 mM, about 135 mM, about 130 mM, or about 125 mM.

[0128] In some aspects, also provided herein are unit doses of pharmaceutical compositions described herein for treatment of heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia, via oral or nasal inhalation.

[0129] In one version, a unit dose of the pharmaceutical composition provided herein includes at least about 50 mg, such as at least about 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 450 mg, 500 mg or more of flecainide or a flecainide salt, *e.g.*, flecainide acetate or flecainide hydrochloride. A unit dose of the pharmaceutical composition provided herein can include flecainide or the flecainide salt in the range of about 50 mg to about 500 mg, such as 50 mg to 60 mg, 50 mg to 70 mg, 50 mg to 80 mg, 50 mg to 90 mg, 50 mg to 100 mg, 50 mg to 110 mg, 50 mg to 120 mg, 50 mg to 130 mg, 50 mg to 140 mg, 50 mg to 150 mg, 50 mg to 160 mg, 50 mg to 170 mg, 50 mg to 180 mg, 50 mg to 190 mg, 50 mg to 200 mg, 50 mg to 210 mg, 50 mg to 220 mg, 50 mg to 230 mg, 50 mg to 240 mg, 50 mg to 250 mg, 50 mg to 260 mg, 50 mg to 270 mg, 50 mg to 280 mg, 50 mg to 290 mg, 50 mg to 300 mg, 50 mg to 310 mg, 50 mg to 320 mg, 50 mg to 330 mg, 50 mg to 340 mg, 50 mg to 350 mg, 50 mg to 360 mg, 50 mg to 370 mg, 50 mg to 380 mg, 50 mg to 390 mg, 50 mg to 400 mg, 50 mg to 450 mg, 50 mg to 500 mg, 80 mg to 90 mg, 80 mg to 100 mg, 80 mg to 110 mg, 80 mg to 120 mg, 80 mg to 130 mg, 80 mg to 140 mg, 80 mg to 150 mg, 80 mg to 160 mg, 80 mg to 170 mg, 80 mg to 180 mg, 80 mg to 190 mg, 80 mg to 200 mg, 80 mg to 210 mg, 80 mg to 220 mg, 80 mg to 230 mg, 80 mg to 240 mg, 80 mg to 250 mg, 80 mg to 260 mg, 80 mg to 270 mg, 80 mg to 280 mg, 80 mg to 290 mg, 80 mg to 300 mg, 80 mg to 310 mg, 80 mg to 320 mg, 80 mg to 330 mg, 80 mg to 340 mg, 80 mg to 350 mg, 80 mg to 360 mg, 80 mg to 370 mg, 80 mg to 380 mg, 80 mg to 390 mg, 80 mg to 400 mg, 80 mg to 450 mg, 80 mg to 500 mg, 120 mg to 140 mg, 120 mg to 150 mg, 120 mg to 160 mg, 120 mg to 170 mg, 120 mg to 180 mg, 120 mg to 190 mg, 120 mg to 200 mg, 120 mg to 210 mg, 120 mg to 220 mg, 120 mg to 230 mg, 120 mg to 240 mg, 120 mg to 250 mg, 120 mg to 260 mg, 120 mg to 270 mg, 120 mg to 280 mg, 120 mg to 290 mg, 120 mg to 300 mg, 120 mg to 310 mg, 120 mg to 320 mg, 120 mg to 330 mg, 120

mg to 340 mg, 120 mg to 350 mg, 120 mg to 360 mg, 120 mg to 370 mg, 120 mg to 380 mg, 120 mg to 390 mg, 120 mg to 400 mg, 120 mg to 450 mg, 120 mg to 500 mg, 150 mg to 160 mg, 150 mg to 170 mg, 150 mg to 180 mg, 150 mg to 190 mg, 150 mg to 200 mg, 150 mg to 210 mg, 150 mg to 220 mg, 150 mg to 230 mg, 150 mg to 240 mg, 150 mg to 250 mg, 150 mg to 260 mg, 150 mg to 270 mg, 150 mg to 280 mg, 150 mg to 290 mg, 150 mg to 300 mg, 150 mg to 310 mg, 150 mg to 320 mg, 150 mg to 330 mg, 150 mg to 340 mg, 150 mg to 350 mg, 150 mg to 360 mg, 150 mg to 370 mg, 150 mg to 380 mg, 150 mg to 390 mg, 150 mg to 400 mg, 150 mg to 450 mg, 150 mg to 500 mg, 180 mg to 200 mg, 180 mg to 210 mg, 180 mg to 220 mg, 180 mg to 230 mg, 180 mg to 240 mg, 180 mg to 250 mg, 180 mg to 260 mg, 180 mg to 270 mg, 180 mg to 280 mg, 180 mg to 290 mg, 180 mg to 300 mg, 180 mg to 310 mg, 180 mg to 320 mg, 180 mg to 330 mg, 180 mg to 340 mg, 180 mg to 350 mg, 180 mg to 360 mg, 180 mg to 370 mg, 180 mg to 380 mg, 180 mg to 390 mg, 180 mg to 400 mg, 180 mg to 450 mg, 180 mg to 500 mg, 200 mg to 220 mg, 200 mg to 230 mg, 200 mg to 240 mg, 200 mg to 250 mg, 200 mg to 260 mg, 200 mg to 270 mg, 200 mg to 280 mg, 200 mg to 290 mg, 200 mg to 300 mg, 200 mg to 310 mg, 200 mg to 320 mg, 200 mg to 330 mg, 200 mg to 340 mg, 200 mg to 350 mg, 200 mg to 360 mg, 200 mg to 370 mg, 200 mg to 380 mg, 200 mg to 390 mg, 200 mg to 400 mg, 200 mg to 450 mg, 200 mg to 500 mg, 220 mg to 240 mg, 220 mg to 250 mg, 220 mg to 260 mg, 220 mg to 270 mg, 220 mg to 280 mg, 220 mg to 290 mg, 220 mg to 300 mg, 220 mg to 310 mg, 220 mg to 320 mg, 220 mg to 330 mg, 220 mg to 340 mg, 220 mg to 350 mg, 220 mg to 360 mg, 220 mg to 370 mg, 220 mg to 380 mg, 220 mg to 390 mg, 220 mg to 400 mg, 220 mg to 450 mg, 220 mg to 500 mg, 250 mg to 260 mg, 250 mg to 270 mg, 250 mg to 280 mg, 250 mg to 290 mg, 250 mg to 300 mg, 250 mg to 310 mg, 250 mg to 320 mg, 250 mg to 330 mg, 250 mg to 340 mg, 250 mg to 350 mg, 250 mg to 360 mg, 250 mg to 370 mg, 250 mg to 380 mg, 250 mg to 390 mg, 250 mg to 400 mg, 250 mg to 450 mg, 250 mg to 500 mg, 280 mg to 260 mg, 280 mg to 270 mg, 280 mg to 280 mg, 280 mg to 290 mg, 280 mg to 300 mg, 280 mg to 310 mg, 280 mg to 320 mg, 280 mg to 330 mg, 280 mg to 340 mg, 280 mg to 350 mg, 280 mg to 360 mg, 280 mg to 370 mg, 280 mg to 380 mg, 280 mg to 390 mg, 280 mg to 400 mg, 280 mg to 450 mg, 280 mg to 500 mg, 300 mg to 320 mg, 300 mg to 330 mg, 300 mg to 340 mg, 300 mg to 350 mg, 300 mg to 360 mg, 300 mg to 370 mg, 300 mg to 380 mg, 300 mg to 390 mg, 300 mg to 400 mg, 300 mg to 450 mg, 300 mg to 500 mg, 320 mg to 330 mg, 320 mg to 340 mg, 320 mg to 350 mg, 320 mg to 360 mg, 320 mg to 370 mg, 320 mg to 380 mg, 320 mg to 390 mg, 320 mg to 400 mg, 320 mg to 450 mg, 320 mg to 500 mg, 340 mg to 360 mg, 340 mg to 370 mg, 340 mg to 380 mg, 340 mg to 390 mg, 340 mg to 400 mg, 340 mg to 450 mg, or 340 mg to 500 mg.

[0130] In one version, a unit dose as provided herein includes flecainide or a flecainide salt of about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 450 mg, or about 500 mg.

[0131] In one aspect, provided herein are formulations for treatment of a heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia. The formulations can include the pharmaceutical compositions provided herein and a pharmaceutically acceptable carrier, excipient, diluent, or any other suitable component for the intended administration routes, such as oral or nasal inhalation. Examples of pharmaceutically acceptable excipients include, but are not limited to, lipids, metal ions, surfactants, amino acids, carbohydrates, buffers, salts, polymers, and the like, and combinations thereof.

[0132] The pharmaceutical formulation according to one or more embodiments of the disclosure may comprise a salt of flecainide and, optionally, one or more other active ingredients and, optionally, one or more pharmaceutically acceptable excipients. For example, the pharmaceutical formulation can comprise particles of the flecainide salt with no other ingredients added (neat particles), may comprise neat particles of antiarrhythmic pharmaceutical agent together with other particles, and/or may comprise particles comprising antiarrhythmic pharmaceutical agent and one or more active ingredients and/or one or more pharmaceutically acceptable excipients.

[0133] In one aspect, also provided herein are kits for treatment of heart conditions via inhalation. The kits can include one or more pharmaceutical agents, for instance, a salt of flecainide, or some additional active agent(s) as described herein. In some cases, the kits include container for the pharmaceutical agents or compositions. In some cases, unit doses of the pharmaceutical agents as discussed above are provided in the kits. In some cases, the kits also include containers/receptacles for containing the pharmaceutical agents.

[0134] In some cases, the kits include separate containers/receptacles for containing the pharmaceutical composition as described herein. In some cases, the kits include an aerosolization device for forming an aerosol of the pharmaceutical compositions. The aerosolization device can be any device as provided herein, and in some cases, used for inhalation of the pharmaceutical compositions. In some cases, the kits include nasal spray device as provided herein. In some cases, the pharmaceutical composition(s) is/are present in aerosol form in the kits. In some other cases, the kits include a single container for containing

the pharmaceutical composition. The kits can further include instructions for methods of using the kit. The instructions can be presented in the form of a data sheet, a manual, in a piece of paper, printed on one or more containers or devices of the kit. Alternatively, the instructions can be provided in electronic form, for instance, available in a disc or online with a weblink available from the kit. The instructions for use of the kit can comprise instructions for use of the pharmaceutical composition and the aerosolization device (*e.g.*, a nebulizer) to treat any applicable indication, *e.g.*, a heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia. The instructions for use of the kit can comprise instructions for use of the pharmaceutical composition and the aerosolization device (*e.g.*, a nebulizer) to treat atrial fibrillation. In some cases, the kits include a nose clip. A nose clip can be used to hinder passage of air through a nose of a subject during inhalation and increase the proportion of a total inhaled volume that is the aerosol issued by the nebulizer.

[0135] Examples of carbohydrates include, but are not limited to, monosaccharides, disaccharides, and polysaccharides. For example, monosaccharides such as dextrose (anhydrous and monohydrate), galactose, mannitol, D-mannose, sorbitol, sorbose and the like; disaccharides such as lactose, maltose, sucrose, trehalose, and the like; trisaccharides such as raffinose and the like; and other carbohydrates such as starches (hydroxyethylstarch), and maltodextrins.

[0136] Non-limiting examples of lipids include phospholipids, glycolipids, ganglioside GM1, sphingomyelin, phosphatidic acid, cardiolipin; lipids bearing polymer chains such as polyethylene glycol, chitin, hyaluronic acid, or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, and polysaccharides; fatty acids such as palmitic acid, stearic acid, and oleic acid; cholesterol, cholesterol esters, and cholesterol hemisuccinate.

[0137] In some cases, the phospholipid comprises a saturated phospholipid, such as one or more phosphatidylcholines. Exemplary acyl chain lengths are 16:0 and 18:0 (e.g., palmitoyl and stearoyl). The phospholipid content can be determined by the active agent activity, the mode of delivery, and other factors.

[0138] Phospholipids from both natural and synthetic sources can be used in varying amounts. When phospholipids are present, the amount is typically sufficient to coat the active agent(s) with at least a single molecular layer of phospholipid. In general, the phospholipid content ranges from about 5 wt% to about 99.9 wt%, such as about 20 wt% to about 80 wt%.

[0139] Generally, compatible phospholipids can comprise those that have a gel to liquid crystal phase transition greater than about 40° C., such as greater than about 60° C., or greater than about 80° C. The incorporated phospholipids can be relatively long chain (e.g., C_{16}-C_{22}) saturated lipids. Exemplary phospholipids useful in the present disclosure include, but are not

limited to, phosphoglycerides such as dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerols, short-chain phosphatidylcholines, hydrogenated phosphatidylcholine, E-100-3 (available from Lipoid KG, Ludwigshafen, Germany), long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, long-chain saturated phosphatidylinositols, phosphatidic acid, phosphatidylinositol, and sphingomyelin.

[0140] Examples of metal ions include, but are not limited to, divalent cations, including calcium, magnesium, zinc, iron, and the like. For instance, when phospholipids are used, the pharmaceutical composition can also comprise a polyvalent cation, as disclosed in WO 01/85136 and WO 01/85137, which are incorporated herein by reference in their entireties. The polyvalent cation can be present in an amount effective to increase the melting temperature (T_m) of the phospholipid such that the pharmaceutical composition exhibits a T_m which is greater than its storage temperature (T_m) by at least about 20° C., such as at least about 40° C. The molar ratio of polyvalent cation to phospholipid can be at least about 0.05:1, such as about 0.05:1 to about 2.0:1 or about 0.25:1 to about 1.0:1. An example of the molar ratio of polyvalent cation: phospholipid is about 0.50:1. When the polyvalent cation is calcium, it can be in the form of calcium chloride. Although metal ion, such as calcium, is often included with phospholipid, none is required.

[0141] The pharmaceutical composition can include one or more surfactants. For instance, one or more surfactants can be in the liquid phase with one or more being associated with solid particles or particles of the composition. By "associated with" it is meant that the pharmaceutical compositions can incorporate, adsorb, absorb, be coated with, or be formed by the surfactant. Surfactants include, but are not limited to, fluorinated and nonfluorinated compounds, such as saturated and unsaturated lipids, nonionic detergents, nonionic block copolymers, ionic surfactants, and combinations thereof. It should be emphasized that, in addition to the aforementioned surfactants, suitable fluorinated surfactants are compatible with the teachings herein and can be used to provide the desired preparations.

[0142] Examples of nonionic detergents include, but are not limited to, sorbitan esters including sorbitan trioleate (Span™ 85), sorbitan sesquioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, and polyoxyethylene (20) sorbitan monooleate, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, glycerol esters, and sucrose esters. Other suitable nonionic detergents can be easily identified

using McCutcheon's Emulsifiers and Detergents (McPublishing Co., Glen Rock, N.J.), which is incorporated herein by reference in its entirety.

[0143] Examples of block copolymers include, but are not limited to, diblock and triblock copolymers of polyoxyethylene and polyoxypropylene, including poloxamer 188 (Pluronic™ F-68), poloxamer 407 (Pluronic™ F-127), and poloxamer 338. Examples of ionic surfactants include, but are not limited to, sodium sulfosuccinate, and fatty acid soaps. Examples of amino acids include, but are not limited to hydrophobic amino acids. Use of amino acids as pharmaceutically acceptable excipients is known in the art as disclosed in WO 95/31479, WO 96/32096, and WO 96/32149, which are incorporated herein by reference in their entireties.

[0144] Examples of buffers include, but are not limited to, acetate, tris, or citrate. Examples of acids include, but are not limited to, carboxylic acids. Examples of salts include, but are not limited to, sodium chloride, salts of carboxylic acids, (e.g., sodium citrate, sodium ascorbate, magnesium gluconate, sodium gluconate, tromethamine hydrochloride, etc.), ammonium carbonate, ammonium acetate, ammonium chloride, and the like. Examples of organic solids include, but are not limited to, camphor, and the like. The pharmaceutical composition of one or more embodiments of the present disclosure can also include a biocompatible, such as biodegradable polymer, copolymer, or blend or other combination thereof. In this respect useful polymers comprise polylactides, polylactide-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.). Those skilled in the art will appreciate that, by selecting the appropriate polymers, the delivery efficiency of the composition and/or the stability of the dispersions can be tailored to optimize the effectiveness of the antiarrhythmic pharmaceutical agent(s).

[0145] For solutions, the compositions can include one or more osmolality adjuster, such as sodium chloride. For instance, sodium chloride can be added to solutions to adjust the osmolality of the solution. In one or more embodiments, an aqueous composition consists essentially of the antiarrhythmic pharmaceutical agent, the osmolality adjuster, and water.

[0146] Solutions can also comprise a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers comprise organic acid salts of citric acid, lactic acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers. Thus, the buffers can include citrates, phosphates, phthalates, and lactates.

[0147] Besides the above mentioned pharmaceutically acceptable excipients, it can be desirable to add other pharmaceutically acceptable excipients to the pharmaceutical composition to improve particle rigidity, production yield, emitted dose and deposition, shelf-life, and patient acceptance. Such optional pharmaceutically acceptable excipients include, but are not limited to: coloring agents, taste masking agents, buffers, hygroscopic agents, antioxidants, and chemical stabilizers. Further, various pharmaceutically acceptable excipients can be used to provide structure and form to the particle compositions (e.g., latex particles). In this regard, it will be appreciated that the rigidifying components can be removed using a post-production technique such as selective solvent extraction.

[0148] The pharmaceutical compositions of one or more embodiments of the present disclosure can lack taste. In this regard, although taste masking agents are optionally included within the composition, the compositions in some embodiments do not include a taste masking agent other than a cyclodextrin and lack taste even without a taste masking agent.

[0149] The pharmaceutical compositions can also include mixtures of pharmaceutically acceptable excipients. For instance, mixtures of carbohydrates and amino acids are within the scope of the present disclosure.

[0150] The compositions of one or more embodiments of the present disclosure can take various forms, such as solutions, dry powders, reconstituted powders, suspensions, or dispersions comprising a non-aqueous phase, such as propellants (e.g., chlorofluorocarbon, hydrofluoroalkane).

[0151] The solutions of the present disclosure are typically clear. In this regard, many of the antiarrhythmic pharmaceutical agents of the present disclosure are water soluble.

[0152] In some embodiments, the isotonicity of the solution ranges from isotonic to physiologic isotonicity. Physiologic isotonicity is the isotonicity of physiological fluids.

[0153] In some versions, the pharmaceutical composition is a nebulized aerosol and comprises liquid droplets having a mass median diameter less than about 20 μm, such as less than about 10 μm, less than about 7 μm, or less than about 5 μm. The droplets can have a mass median aerodynamic diameter ranging from about 1 μm to about 6 μm, such as about 1.5 μm to about 5 μm, or about 2 μm to about 4 μm. If the droplets are too large, a larger percentage of the particles cannot reach the lungs. If the droplets are too small, a larger percentage of the droplets can be exhaled.

[0154] Unit doses of the pharmaceutical compositions can be placed in a container. Examples of containers include, but are not limited to, syringes, capsules, blow fill seal, blisters, vials, ampoules, cartridges, or container closure systems made of metal, polymer (e.g., plastic,

elastomer), glass, or the like. For instance, the vial can be a colorless Type I borosilicate glass ISO 4R 6 mL vial with a chlorobutyl rubber siliconized stopper, and flip-off type aluminum cap with colored plastic cover. In some embodiments, the vial can be a colorless Type I borosilicate glass ISO 6R 10 mL vial with a chlorobutyl rubber siliconized stopper, and flip-off type aluminum cap with colored plastic cover.

[0155] The container can be inserted into an aerosolization device. The container can be of a suitable shape, size, and material to contain the pharmaceutical composition and to provide the pharmaceutical composition in a usable condition. For example, the capsule or blister can comprise a wall which comprises a material that does not adversely react with the pharmaceutical composition. In addition, the wall can comprise a material that allows the capsule to be opened to allow the pharmaceutical composition to be aerosolized. In one version, the wall comprises one or more of gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxyproplycellulose, agar, aluminum foil, or the like. In one version, the capsule can comprise telescopically adjoining sections, as described for example in U.S. Pat. No. 4,247,066 which is incorporated herein by reference in its entirety. The size of the capsule can be selected to adequately contain the dose of the pharmaceutical composition. The sizes generally range from size 5 to size 000 with the outer diameters ranging from about 4.91 mm to 9.97 mm, the heights ranging from about 11.10 mm to about 26.14 mm, and the volumes ranging from about 0.10 ml to about 1.37 mL, respectively. Suitable capsules are available commercially from, for example, Shionogi Qualicaps Co. in Nara, Japan and Capsugel in Greenwood, S.C. After filling, a top portion can be placed over the bottom portion to form a capsule shape and to contain the powder within the capsule, as described in U.S. Pat. Nos. 4,846,876 and 6,357,490, and in WO 00/07572, which are incorporated herein by reference in their entireties. After the top portion is placed over the bottom portion, the capsule can optionally be banded.

[0156] For solutions, the amount of the composition in the unit dose can range from about 0.5 mL to about 15 mL, such as 1 mL to 15 mL, 2 mL to 15 mL, 3 mL to 15 mL, 4 mL to 15 mL, 5 mL to 15 mL, 6 mL to 15 mL, 7 mL to 15 mL, 8 mL to 15 mL, 9 mL to 15 mL, 10 mL to 15 mL, 11 mL to 15 mL, 12 mL to 15 mL, 10 mL to 15 mL, 14 mL to 15 mL, 1 mL to 13 mL, 2 mL to 13 mL, 3 mL to 13 mL, 4 mL to 13 mL, 5 mL to 13 mL, 6 mL to 13 mL, 7 mL to 13 mL, 8 mL to 13 mL, 9 mL to 13 mL, 10 mL to 13 mL, 11 mL to 13 mL, 12 mL to 13 mL, 1 mL to 10 mL, 2 mL to 10 mL, 3 mL to 10 mL, 4 mL to 10 mL, 5 mL to 10 mL, 6 mL to 10 mL, 7 mL to 10 mL, 8 mL to 10 mL, 9 mL to 10 mL, 1 mL to 8 mL, 2 mL to 8 mL, 3 mL to 8 mL, 4 mL to 8 mL, 5 mL to 8 mL, 6 mL to 8 mL, 7 mL to 8 mL, 1 mL to 5 mL, 2 mL to 5 mL, 3 mL to 5 mL, 4 mL to 5 mL, or 1 mL to 3 mL. In some embodiments, the amount of the composition in a unit dose is

about 1 mL, about 2 mL, about 3 mL, about 4 mL, about 5 mL, about 6 mL, about 7 mL, about 8 mL, about 9 mL, about 10 mL, about 11 mL, about 12 mL, about 10 mL, about 14 mL, or about 15 mL. In some embodiments, the amount of the composition in a unit dose is at most about 2 mL, at most about 3 mL, at most about 4 mL, at most about 5 mL, at most about 6 mL, at most about 7 mL, at most about 8 mL, at most about 9 mL, at most about 10 mL, at most about 11 mL, at most about 12 mL, at most about 10 mL, at most about 14 mL, or at most about 15 mL.

[0157] The compositions of the present disclosure can be made by any of the various methods and techniques known and available to those skilled in the art.

[0158] For instance, a solution of antiarrhythmic pharmaceutical agent can be made using the following procedure. Typically, manufacturing equipment is sterilized before use. A portion of the final volume, e.g., 70%, of solvent, e.g., water for injection, can be added into a suitable container. Some or all of other additional pharmaceutically acceptable carrier or excipient, solubilizer, or other additional ingredients of the pharmaceutical composition (*e.g.*, cyclodextrin, *e.g.*, HPβCD; *e.g.*, acids, *e.g.*, acetic acid, hydrochloric acid, nitric acid, or citric acid; *e.g.*, saccharin, *e.g.*, saccharin sodium) can be added either before or after addition of the antiarrhythmic agent, *e.g.*, the flecainide salt, *e.g.*, flecainide acetate. Antiarrhythmic pharmaceutical agent, *e.g.*, a salt of flecainide can then be added. The antiarrhythmic pharmaceutical agent can be mixed until dissolved. Additional solvent can be added to make up the final batch volume. The batch can be filtered, e.g., through a 0.2 μm filter into a sterilized receiving vessel. Filling components can be sterilized before use in filling the batch into vials, e.g., 10 mL vials.

[0159] As an example, the above-noted sterilizing can include the following. A 5 liter type 1 glass bottle and lid can be placed in an autoclave bag and sterilized at elevated temperature, e.g., 121° C. for 15 minutes, using an autoclave. Similarly, vials can be placed into suitable racks, inserted into an autoclave bag, and sterilized at elevated temperature, e.g., 121° C. for 15 minutes, using an autoclave. Also, similarly, stoppers can be placed in an autoclave bag and sterilized at elevated temperature, e.g., 121° C. for 15 minutes, using an autoclave. Before sterilization, sterilizing filters can be attached to tubing, e.g., a 2 mm length of 7 mm x 13 mm silicone tubing. A filling line can be prepared by placed in an autoclave bag and sterilized at elevated temperature, e.g., 121° C. for 15 minutes, using an autoclave.

[0160] The above-noted filtration can involve filtration into a laminar flow work area. The receiving bottle and filters can be set up in the laminar flow work area.

[0161] The above-noted filling can also be conducted under laminar flow protection. The filling line can be unwrapped and placed into the receiving bottle. The sterilized vials and stoppers can

be unwrapped under laminar flow protection. Each vial can be filled, e.g., to a target fill of 5 g, and stoppered. A flip off collar can be applied to each vial. The sealed vials can be inspected for vial leakage, correct overseals, and cracks.

[0162] The pharmaceutical composition according to one or more embodiments of the disclosure may, if desired, contain a combination of antiarrhythmic pharmaceutical agent (*e.g.*, flecainide salt) and one or more additional active agents. Examples of additional active agents include, but are not limited to, agents that may be delivered through the lungs.

[0163] Additional active agents may comprise, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, additional anti-infectives (antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, antiepileptics, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxidants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitic, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The additional active agent, when administered by inhalation, may act locally or systemically.

[0164] The additional active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

[0165] Examples of additional active agents suitable for use in this disclosure include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Pat. No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle

stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFFR) gene, deoxyribonuclease (DNase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefinetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the disclosure is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments, derivatives, and analogs thereof.

[0166] Additional active agents for use in the disclosure can further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, e.g.,

suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition), which is incorporated herein by reference in its entirety.

[0167] When a combination of active agents is used, the agents may be provided in combination in a single species of pharmaceutical composition or individually in separate species of pharmaceutical compositions.

PREPARATION

[0168] In some aspects, the present disclosure provides a method of preparing a liquid pharmaceutical composition that comprises an antiarrhythmic pharmaceutical agent. In some cases, the method comprises combining: (a) water; (b) a pH adjusting agent; (c) flecainide or a pharmaceutically ac-ceptable salt thereof; and (d) a cyclodextrin. In some cases, the water used in preparing the for-mulation is sterilized. In some cases, the water used in preparing the formulation is water for in-jection. In some cases, all the starting materials are sterilized by established technologies that meet the standards for medical use.

[0169] In some cases, the method of preparation includes (a) providing the water; (b) contacting the portion of water with the flecainide or pharmaceutically acceptable salt thereof, the cyclodex-trin, and the pH adjusting agent in a vessel; and (c) adding a subsequent portion of the water to the vessel to provide the pharmaceutical composition.

[0170] In some cases, in the composition prepared by the method provided herein, a concentration of the flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in the pharmaceutical composition, a concentration of the cyclodextrin in the pharma-ceutical composition is from about 10% (w/v) to about 30% (w/v); and a room-temperature pH in the pharmaceutical composition of from about 5.5 to about 6.5.

[0171] In some cases, the pH adjusting agent comprises an ion selected from the group consisting of: acetate, citrate, nitrate, chloride, sulfate, maleate, tartrate, phosphate, aconitate, adipate, ascor-bate, benzoate, caprylate, cholate, formate, glutamate, lactate, propionate, sorbate, stearate, and succinate. In some cases, the pH adjusting agent comprises a pH buffer. In some cases, the pH adjusting agent comprises an acid or a base. In some cases, the pH adjusting agent comprises an acid. In some cases, the pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glu-tamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid. In some cases, the pH adjusting agent is selected from the group consisting of: acetic acid,

citric acid, nitric ac-id, hydrochloric acid, and sulfuric acid. In some cases, the pH adjusting agent comprises a mix-ture of acids, including, but not limited to, acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid. In some cases, the pH adjusting agent comprises acetic acid. In some cases, the pH adjusting agent comprises citric acid.

[0172] In some cases, the pH adjusting agent is added to a concentration at about 2 mM to about 50 mM. In some cases, the pH adjusting agent is added to a concentration at about 2 mM to about 10 mM. In some cases, the pH adjusting agent comprises acetic acid. In some cases, the concen-tration in the pharmaceutical composition of the acetic acid is about 5 mM. In some cases, the pH adjusting agent comprises citric acid. In some cases, the concentration in the pharmaceutical composition of the citric acid is about 5 mM.

[0173] In some cases, the method of preparation includes adding cyclodextrin to the solution. In some cases, the cyclodextrin to be added comprises α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, or derivatized γ-cyclodextrins. In some cases, the cyclodextrin comprises α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutyl-ether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, or sulfoal-kylether-γ-cyclodextrins. In some cases, the cyclodextrin comprises hydroxypropyl-β-cyclodextrin. In some cases, the concentration of the cyclodextrin in the pharmaceutical com-position is from about 10% (w/v) to about 30% (w/v).

[0174] In some cases, the method of preparation includes adding a sweetener to the solution. In some cases, the sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof. In some cases, the sweetener comprises saccharin. In some cases, the sweetener comprises a salt of saccharin. In some cases, the sweetener comprises saccharin sodium. In some cases, the sweetener is added to a concentra-tion at from about 0.001% (w/v) to about 1% (w/v). In some cases, the sweetener is added to a concentration at from about 0.001% (w/v) to about 0.05% (w/v). In some cases, the sweetener is added to a concentration at from about 0.001% (w/v) to about 0.01% (w/v).

[0175] In some cases, the method of preparation includes adding a pharmaceutically acceptable salt of flecainide, such as, flecainide acetate, flecainide hydrochloride, flecainide citrate,

flecainide phosphate, or flecainide nitrate. In some cases, the pharmaceutically acceptable the salt of flecainide comprises flecainide acetate. In some cases, the pharmaceutically acceptable the salt of flecainide comprises flecainide hydrochloride.

[0176] In some cases, the method of preparation further includes packaging the pharmaceutical composi-tion in unit dose form. For instance, the unit dose form can include about 50 mg to about 350 mg of the pharmaceutically acceptable salt of flecainide. For instance, the unit dose form comprises about 60 mg to about 150 mg of the pharmaceutically acceptable salt of flecainide, such as about 75 mg to about 125 mg, about 250 mg to about 350 mg, or about 150 mg to about 250 mg, such as about 90 mg, about 120 mg, or about 200 mg of the pharmaceutically acceptable salt of flecainide.

METHODS OF TREATMENT

[0177] The methods, compositions, and kits provided herein can include administration of the pharmaceutical composition via inhalation, *e.g.*, oral or nasal inhalation.

[0178] The therapy provided herein can comprise or be suitable for inhalation, *e.g.*, oral or nasal inhalation. In some cases, during administration via oral inhalation, the pharmaceutical agent is inhaled by the patient through the mouth and absorbed by the lungs. In some cases, during administration via nasal inhalation, the pharmaceutical agent is inhaled by the patient through the nose and absorbed by the nasal mucous and/or the lungs.

[0179] The inhalation route can avoid first-pass hepatic metabolism, hence dosing variability can be eliminated. Unlike the case for oral tablets or pills, the patient's metabolic rates may not matter as the administration is independent of the metabolic paths experienced when a drug is administered via oral route through gastrointestinal tract, e.g., as tablets, pills, solution, or suspension. A fast onset of action, a potential improvement in efficacy, and/or a reduction in dose can be achieved with the fast absorption of drugs from the nasal mucosa and/or lungs.

[0180] The fast absorption rate of drugs through the lungs can be achieved because of the large surface area available in the lungs for aerosols small enough to penetrate central and peripheral lung regions. Consequently, the rate and extent of absorption of drugs delivered via inhalation can yield plasma concentrations vs. time profiles that are comparable with the IV route of administration.

[0181] The time for onset of action can be short. For instance, the patient may have normal sinus rhythm within 20 minutes of initiating the administering, such as within 15 minutes, within 10 minutes, or within 5 minutes of initiating the administering. In some cases, the rapid onset of action is advantageous because the longer a patient remains in arrhythmia (*i.e.* atrial fibrillation), the more difficult it will be to restore normal sinus rhythm.

[0182] In some embodiments, the method of the present disclosure allows the patient to avoid other therapies, such as ablation and/or electrical cardioversion. In other embodiments, the method of the present disclosure is used in combination with other therapies, such as before or after electrical cardioversion and/or ablation therapy.

[0183] In some aspects of the present disclosure, the compositions or formulations of the pharmaceutical composition via inhalation. The pharmaceutical compositions can be aerosolized prior to administration or can be presented to a user in the form of an aerosol.

[0184] The pharmaceutical compositions can be administered using an aerosolization device. The aerosolization device can be a nebulizer, a metered dose inhaler, or a liquid dose instillation device. The aerosolization device can comprise the extrusion of the pharmaceutical preparation through micron or submicron-sized holes with subsequent Rayleigh break-up into fine droplets. The pharmaceutical composition can be delivered by a nebulizer as described in WO 99/16420, by a metered dose inhaler as described in WO 99/16422, by a liquid dose instillation apparatus as described in WO 99/16421, and by a dry powder inhaler as described in U.S. Published Application Nos. 20020017295 and 20040105820, WO 99/16419, WO 02/83220, and U.S. Pat. No. 6,546,929, which are incorporated herein by reference in their entireties. As such, an inhaler can comprise a canister containing the particles or particles and propellant, and wherein the inhaler comprises a metering valve in communication with an interior of the canister. The propellant can be a hydrofluoroalkane.

[0185] For instance, the pharmaceutical formulation can be in liquid solution, and can be administered with nebulizers, such as that disclosed in PCT WO 99/16420, the disclosure of which is hereby incorporated in its entirety by reference, in order to provide an aerosolized medicament that can be administered to the pulmonary air passages of a patient in need thereof. Nebulizers known in the art can easily be employed for administration of the claimed formulations. Breath-activated or breath-actuated nebulizers, as well as those comprising other types of improvements which have been, or will be, developed are also compatible with the formulations of the present disclosure and are contemplated as being within the scope thereof.

[0186] In some cases, the nebulizer is a breath activated or breath-actuated nebulizer. In some cases, the nebulizer is a hand-held inhaler device (e.g., AeroEclipse® II Breath Actuated Nebulizer (BAN)). In some cases, the nebulizer has a compressed air source. In some cases, the nebulizer converts liquid medication into an aerosol. In some cases, the nebulizer converts liquid medication into an aerosol by extruding the pharmaceutical preparation through micron or submicron-sized holes. In some cases, the nebulizer converts liquid medication into an aerosol so it can be inhaled into the lungs. In some cases, the nebulizer is a small volume nebulizer. In

some cases, the nebulizer is a small volume jet nebulizer. In some cases, aerosolized medication is only produced when inhaled through the device. In some cases, the medication is contained in the cup between breaths or during breaks in treatment. In some cases, the medication is contained in the cup until ready to be inhaled.

[0187] Nebulizers can impart energy into a liquid pharmaceutical formulation to aerosolize the liquid, and to allow delivery to the pulmonary system, e.g., the lungs, of a patient. A nebulizer comprises a liquid delivery system, such as a container having a reservoir that contains a liquid pharmaceutical formulation. The liquid pharmaceutical formulation generally comprises an active agent that is either in solution or suspended within a liquid medium.

[0188] In one type of nebulizer that can be used in the subject methods and kits, generally referred to as a jet nebulizer, compressed gas is forced through an orifice in the container. The compressed gas forces liquid to be withdrawn through a nozzle, and the withdrawn liquid can mix with the flowing gas to form aerosol droplets. A cloud of droplets can then be administered to the patients respiratory tract.

[0189] In another type of nebulizer that can be used in the subject methods and kits, generally referred to as a vibrating mesh nebulizer, energy, such as mechanical energy, vibrates a mesh. This vibration of the mesh aerosolizes the liquid pharmaceutical formulation to create an aerosol cloud that is administered to the patient's lungs. In another type of nebulizer that can be used in the subject methods and kits, the nebulizing comprises extrusion through micron or submicron-sized holes followed by Rayleigh break-up into fine droplets.

[0190] Alternatively or additionally, the pharmaceutical formulation may be in a liquid form and may be aerosolized using a nebulizer as described in WO 2004/071368, which is herein incorporated by reference in its entirety, as well as U.S. Published application Nos. 2004/0011358 and 2004/0035413, which are both herein incorporated by reference in their entireties. Other examples of nebulizers include, but are not limited to, the Aeroneb®Go or Aeroneb®Pro nebulizers, available from Aerogen Ltd. of Galway, Ireland; the PARI eFlow and other PARI nebulizers available from PARI Respiratory Equipment, Inc. of Midlothian, Va.; the Lumiscope® Nebulizer 6600 or 6610 available from Lumiscope Company, Inc. of East Brunswick, N.J.; and the Omron NE-U22 available from Omron Healthcare, Inc. of Kyoto, Japan. Other examples of nebulizers include devices produced by Medspray (Enschede, The Netherlands).

[0191] It has been found that a nebulizer of the vibrating mesh type, such as one that that forms droplets without the use of compressed gas, such as the Aeroneb® Pro provides unexpected improvement in dosing efficiency and consistency. By generating fine droplets by using a

vibrating perforated or unperforated membrane, rather than by introducing compressed air, the aerosolized pharmaceutical formulation can be introduced without substantially affecting the flow characteristics. In addition, the generated droplets when using a nebulizer of this type are introduced at a low velocity, thereby decreasing the likelihood of the droplets being driven to an undesired region. It has been found that when using a nebulizer of the extrusion/Rayleigh jet breakup type, the generated droplets are also introduced at a low velocity, thereby decreasing the likelihood of the droplets being driven to an undesired region.

[0192] In some cases, the nebulizer that can be used in the subject methods and kits is of the vibrating mesh type. In some cases, the nebulizer that can be used in the subject methods and kits is of the pressurized jet type. In some cases, the nebulizer that can be used in the subject methods and kits is of the extrusion/Rayleigh breakup type. In some cases, the nebulizer is lightweight (at most 60 g, at most 100 g, at most 200 g, at most 250 g) and nearly silent. In some cases, the nebulizer has a sound level less than 35 A-weighted decibels (dBA) at 1 meter. In some cases, the nebulizer has a medication cup capacity of 6 mL. In some cases, the nebulizer has a residual volume of less than 0.3 mL. In some cases, the nebulizer generates an average flow rate of 0.4 mL/min. In some cases, the nebulizer generates an average flow rate of 0.5 mL/min. In some cases, the nebulizer generates an average flow rate of 0.6 mL/min. In some cases, the nebulizer generates an average flow rate of 0.7 mL/min. In some cases, the nebulizer generates an average flow rate of 0.8 mL/min. In some cases, the nebulizer generates an average flow rate of 0.9 mL/min. In some cases, the nebulizer generates an average flow rate of 1.0 mL/min. In some cases, the nebulizer generates an average flow rate of 1.1 mL/min. In some cases, the nebulizer generates an average flow rate of 1.2 mL/min. In some cases, the nebulizer generates an average particle size of 3.0 μm MMAD. In some cases, the nebulizer generates an average particle size between 3.0 μm MMAD and 4.0 μm MMAD. In some cases, the nebulizer generates an average particle size of 3.0 μm MMAD. In some cases, the nebulizer generates an average particle size between 3.0 μm MMAD and 5.0 μm MMAD. In some cases, the nebulizer generates an average particle size of 3.0 μm MMAD. In some cases, the nebulizer generates an average particle size between 3.0 μm MMAD and 6.0 μm MMAD.

[0193] In still another type of nebulizer that can be used in the subject methods and kits, ultrasonic waves are generated to directly vibrate and aerosolize the pharmaceutical formulation.

[0194] The pharmaceutical formulations disclosed herein can also be administered to the lungs of a patient via aerosolization, such as with a metered dose inhaler. The use of such formulations provides for superior dose reproducibility and improved lung deposition as disclosed in WO 99/16422, hereby incorporated in its entirety by reference. Metered dose inhalers (MDIs) known

in the art can be employed for administration of the claimed pharmaceutical compositions. Breath-activated or breath-actuated MDIs and pressurized MDIs (pMDIs), as well as those comprising other types of improvements which have been, or will be, developed are also compatible with the formulations of the present disclosure and, as such, are contemplated as being within the scope thereof.

[0195] Along with MDIs and nebulizers, it will be appreciated that the formulations of one or more embodiments of the present disclosure can be used in conjunction with liquid dose instillation or LDI techniques as disclosed in, for example, WO 99/16421, which is incorporated herein by reference in its entirety. Liquid dose instillation involves the direct administration of a formulation to the lung. With respect to LDI the formulations are preferably used in conjunction with partial liquid ventilation or total liquid ventilation. Moreover, one or more embodiments of the present disclosure may further comprise introducing a therapeutically beneficial amount of a physiologically acceptable gas (such as nitric oxide or oxygen) into the pharmaceutical microdispersion prior to, during or following administration.

[0196] The pharmaceutical composition of one or more embodiments of the present disclosure can have improved emitted dose efficiency. Accordingly, high doses of the pharmaceutical composition can be delivered using a variety of aerosolization devices and techniques.

[0197] The emitted dose (ED) of the particles of the present disclosure may be greater than about 30%, such as greater than about 40%, greater than about 50%, greater than about 60%, or greater than about 70%.

[0198] The pharmaceutical composition can be administered to the patient on an as-needed basis. For instance, the methods, kits, and compositions can find particular use in treating a subject experiencing a heart condition, *e.g.*, cardiac arrhythmia, *e.g.*, atrial arrhythmia. In some cases, a subject is administered with the therapy described herein when he/she is experiencing atrial arrhythmia. In some cases, the pharmaceutical composition is administered to a subject after the onset of an episode of cardiac arrhythmia. In other cases, the subject is treated between episodes of cardiac arrhythmias.

[0199] The dose of the antiarrhythmic agent, *e.g.*, flecainide salt, *e.g.*, flecainide acetate, can be administered during a single inhalation or can be administered during several inhalations. The fluctuations of antiarrhythmic pharmaceutical agent concentration can be reduced by administering the pharmaceutical composition more often or can be increased by administering the pharmaceutical composition less often. Therefore, the pharmaceutical composition provided herein can be administered from about four times daily to about once a month, such as about

once daily to about once every two weeks, about once every two days to about once a week, and about once per week.

[0200] . In some cases, the antiarrhythmic pharmaceutical agent is delivered over two or more inhalations. In some cases, time between the two or more inhalations is from about 0.1 to 10 minutes. The antiarrhythmic pharmaceutical agent is administered in the described dose in less than 60 minutes, less than 50 minutes, less than 40 minutes, less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 10 minutes, less than 7 minutes, less than 5 minutes, in less than 3 minutes, in less than 2 minutes, or in less than 1 minute. In some cases, delivery of the required dose of antiarrhythmic pharmaceutical agent is completed with 1, 2, 3, 4, 5, or 6 inhalations. In some cases, each inhalation is performed for about 0.5, 1, 1.2, 1.5, 1.8, 2, 2.2, 2.5, 2.8, 3, 3.2, 3.5, 3.8, 4, 4.2, 4.5, 4.8, or 5 minutes. In some cases, each inhalation is performed for longer than 5 minutes. In some cases, each inhalation is performed for up to 4.5 minutes. In some cases, each inhalation comprises at least 60 inhalation breaths, 50 inhalation breaths, 40 inhalation breaths, 30 inhalation breaths, 20 inhalation breaths, 10 inhalation breaths, 8 inhalation breaths, 6 inhalation breaths, 4 inhalation breaths, 3 inhalation breaths, 2 inhalation breaths or 1 inhalation breath. In some cases, each inhalation comprises no more than 100 inhalation breaths, 90 inhalation breaths, 80 inhalation breaths, 70 inhalation breaths, 60 inhalation breaths, 50 inhalation breaths, 40 inhalation breaths, 30 inhalation breaths, or 20 inhalation breaths. In some cases, inhalation of the antiarrhythmic pharmaceutical agent is performed with deep lung breath that lasts for longer than 1 second, 2 seconds, 3 seconds, or 4 seconds. In some cases, inhalation of the antiarrhythmic pharmaceutical agent is performed with deep lung breath that lasts for about 1 second, 2 seconds, 3 seconds, or 4 seconds.

[0201] In some embodiments, during inhalational delivery of the antiarrhythmic pharmaceutical agent, the subject takes, or is instructed to take, a break between two inhalations. In such embodiments, the break between two inhalations lasts for about 0.1 to 10 minutes, such as, 0.2 to 5, 1 to 5, 1.5 to 5, 2 to 5, 3 to 5, 4 to 5, 1 to 1.5, 1 to 2, 1 to 2.5, 1 to 3, 1 to 3.5 , 1 to 4, 1.5 to 2, 1.5 to 2.5, or 1.5 to 3 minutes. In some cases, the subject takes, or is instructed to take, a break for about 1 minute between two inhalations. In some cases, the inhalation pattern for delivery of a single dose goes as follows: a first inhalation for about 4 to 4.5 minutes, a break for about 1 minute, and a second inhalation for about 4 to 4.5 minutes; a first inhalation for about 4 to 4.5 minutes, a break for about 30 seconds, and a second inhalation for about 4 to 4.5 minutes; a first inhalation for about 4 to 4.5 minutes, a first break for about 1 minute, and a second inhalation for about 4 to 4.5 minutes; a second break for about 1 minutes, and a third inhalation for about 4 to 4.5 minutes; or a first inhalation for about 4 to 4.5 minutes, a first break for about 30 seconds,

and a second inhalation for about 4 to 4.5 minutes; a second break for about 30 seconds, and a third inhalation for about 4 to 4.5 minutes.

[0202] In one version, the antiarrhythmic can be administered daily. In this case, the daily dosage of the flecainide acetate ranges from about 0.1 mg to about 600 mg, such as about 0.5 mg to about 500 mg, about 1 mg to about 400 mg, about 2 mg to about 300 mg, and about 3 mg to about 200 mg.

[0203] In some cases, the therapy provided herein is provided to a subject for more than once on an as-needed basis. For instance, the present disclosure may involve a follow-up inhalation if no cardioversion occurs after an initial inhalation. In some instances, if no cardioversion occurs within 30 minutes of the initial inhalation, the follow-up dosage is higher or the same as the initial dosage.

[0204] The dosing can be guided by how the patient feels. Additionally or alternatively, dosing can be guided by using a portable/mobile ECG device. For instance, the dosing may be guided by using a Holter monitor.

[0205] In another version, the pharmaceutical composition is administered prophylactically to a subject who is likely to develop an arrhythmia. For example, a patient who has a history of arrhythmias can be prophylactically treated with a pharmaceutical composition comprising antiarrhythmic pharmaceutical agent to reduce the likelihood of developing an arrhythmia.

[0206] The pharmaceutical composition can be administered to a patient in any regimen which is effective to prevent an arrhythmia. Illustrative prophylactic regimes include administering an antiarrhythmic pharmaceutical agent as described herein 1 to 21 times per week.

[0207] In some cases, patient receiving administration of pharmaceutical composition according to the method described herein needs to meet one or more of the following ECG criteria: P waves not seen on the ECG; fibrillatory waves are coarse; there are varying RR intervals; there are irregular-irregular QRS complexes; or there is an elevated ventricular rate. In some cases, method of treatment disclosed herein comprises confirming a patient in atrial fibrillation episode via ECG. In some cases, the method comprises confirming a patient having the following ECG features before administering the pharmaceutical composition as described herein: P waves not seen on the ECG; fibrillatory waves are coarse; there are varying RR intervals; there are irregular-irregular QRS complexes; and there is an elevated ventricular rate. In some cases, a patient receiving administration of pharmaceutical composition according to the method described herein has a medical history that is current within predetermined time period and qualifies the patient to receive flecainide safely. In some cases, the patient's current AF episode

has had a duration of less than 48 hours. In some cases, total flecainide exposure the patient receives within past 24 hour period does not exceed 320 mg.

[0208] The amount of the flecainide salt that is delivered to the subject (*e.g.*, approximately the amount of the flecainide salt exiting a mouthpiece when being inhaled by the subject) for the treatment of arrhythmia, *e.g.*, atrial arrhythmia, *e.g.*, atrial fibrillation, can be from about 50 mg to about 300 mg, such as 50 mg to 60 mg, 50 mg to 70 mg, 50 mg to 80 mg, 50 mg to 90 mg, 50 mg to 100 mg, 50 mg to 110 mg, 50 mg to 120 mg, 50 mg to 130 mg, 50 mg to 140 mg, 50 mg to 150 mg, 50 mg to 160 mg, 50 mg to 170 mg, 50 mg to 180 mg, 50 mg to 190 mg, 50 mg to 200 mg, 50 mg to 210 mg, 50 mg to 220 mg, 50 mg to 230 mg, 50 mg to 240 mg, 50 mg to 250 mg, 50 mg to 260 mg, 50 mg to 270 mg, 50 mg to 280 mg, 50 mg to 290 mg, 70 mg to 80 mg, 70 mg to 90 mg, 70 mg to 100 mg, 70 mg to 110 mg, 70 mg to 120 mg, 70 mg to 130 mg, 70 mg to 140 mg, 70 mg to 170 mg, 70 mg to 160 mg, 70 mg to 170 mg, 70 mg to 180 mg, 70 mg to 190 mg, 70 mg to 200 mg, 70 mg to 210 mg, 70 mg to 220 mg, 70 mg to 230 mg, 70 mg to 240 mg, 70 mg to 270 mg, 70 mg to 260 mg, 70 mg to 270 mg, 70 mg to 280 mg, 70 mg to 290 mg, 70 mg to 300 mg, 80 mg to 90 mg, 80 mg to 100 mg, 80 mg to 110 mg, 80 mg to 120 mg, 80 mg to 130 mg, 80 mg to 140 mg, 80 mg to 150 mg, 80 mg to 160 mg, 80 mg to 170 mg, 80 mg to 180 mg, 80 mg to 190 mg, 80 mg to 200 mg, 80 mg to 210 mg, 80 mg to 220 mg, 80 mg to 230 mg, 80 mg to 240 mg, 80 mg to 250 mg, 80 mg to 260 mg, 80 mg to 270 mg, 80 mg to 280 mg, 80 mg to 290 mg, 80 mg to 300 mg, 100 mg to 110 mg, 100 mg to 120 mg, 100 mg to 130 mg, 100 mg to 140 mg, 100 mg to 150 mg, 100 mg to 160 mg, 100 mg to 170 mg, 100 mg to 180 mg, 100 mg to 190 mg, 100 mg to 200 mg, 100 mg to 210 mg, 100 mg to 220 mg, 100 mg to 230 mg, 100 mg to 240 mg, 100 mg to 250 mg, 100 mg to 260 mg, 100 mg to 270 mg, 100 mg to 280 mg, 100 mg to 290 mg, 100 mg to 300 mg, 120 mg to 140 mg, 120 mg to 150 mg, 120 mg to 160 mg, 120 mg to 170 mg, 120 mg to 180 mg, 120 mg to 190 mg, 120 mg to 200 mg, 120 mg to 210 mg, 120 mg to 220 mg, 120 mg to 230 mg, 120 mg to 240 mg, 120 mg to 250 mg, 120 mg to 260 mg, 120 mg to 270 mg, 120 mg to 280 mg, 120 mg to 290 mg, 120 mg to 300 mg, 150 mg to 160 mg, 150 mg to 170 mg, 150 mg to 180 mg, 150 mg to 190 mg, 150 mg to 200 mg, 150 mg to 210 mg, 150 mg to 220 mg, 150 mg to 230 mg, 150 mg to 240 mg, 150 mg to 250 mg, 150 mg to 260 mg, 150 mg to 270 mg, 150 mg to 280 mg, 150 mg to 290 mg, 150 mg to 300 mg, 180 mg to 200 mg, 180 mg to 210 mg, 180 mg to 220 mg, 180 mg to 230 mg, 180 mg to 240 mg, 180 mg to 250 mg, 180 mg to 260 mg, 180 mg to 270 mg, 180 mg to 280 mg, 180 mg to 290 mg, 180 mg to 300 mg, 200 mg to 220 mg, 200 mg to 230 mg, 200 mg to 240 mg, 200 mg to 250 mg, 200 mg to 260 mg, 200 mg to 270 mg, 200 mg to 280 mg, 200 mg to 290 mg, 200 mg to 300 mg, 220 mg to 240 mg, 220 mg to 250 mg, 220 mg to 260 mg, 220 mg to 270 mg, 220 mg to 280 mg, 220 mg to 290 mg, 220 mg to

300 mg, 250 mg to 260 mg, 250 mg to 270 mg, 250 mg to 280 mg, 250 mg to 290 mg, 250 mg to 300 mg, 280 mg to 260 mg, 280 mg to 270 mg, 280 mg to 280 mg, 280 mg to 290 mg, or 280 mg to 300 mg.

[0209] In one version, the amount of the flecainide salt that is delivered to the subject (*e.g.*, approximately the amount of the flecainide salt exiting the aerosolization device when being inhaled by the subject) for the treatment of arrhythmia, *e.g.*, atrial arrhythmia, *e.g.*, atrial fibrillation, is at least about 50 mg, at least about 60 mg, at least about 70 mg, at least about 80 mg, at least about 90 mg, at least about 100 mg, at least about 110 mg, at least about 120 mg, at least about 130 mg, at least about 140 mg, at least about 150 mg, at least about 160 mg, at least about 170 mg, at least about 180 mg, at least about 190 mg, at least about 200 mg, at least about 210 mg, at least about 220 mg, at least about 230 mg, at least about 240 mg, at least about 250 mg, at least about 260 mg, at least about 270 mg, at least about 280 mg, or at least about 290 mg.

[0210] In one version, the amount of the flecainide salt that is delivered to the subject (*e.g.*, approximately the amount of the flecainide salt exiting a mouthpiece when being inhaled by the subject) for the treatment of arrhythmia, *e.g.*, atrial arrhythmia, *e.g.*, atrial fibrillation, is at most about 100 mg, at most about 110 mg, at most about 120 mg, at most about 130 mg, at most about 140 mg, at most about 150 mg, at most about 160 mg, at most about 170 mg, at most about 180 mg, at most about 190 mg, at most about 200 mg, at most about 210 mg, at most about 220 mg, at most about 230 mg, at most about 240 mg, at most about 250 mg, at most about 260 mg, at most about 270 mg, at most about 280 mg, or at most about 290 mg.

[0211] In some cases, the amount of the flecainide salt that is delivered to the subject (*e.g.*, approximately the amount of the flecainide salt exiting a mouthpiece when being inhaled by the subject) for the treatment of arrhythmia, *e.g.*, atrial arrhythmia, *e.g.*, atrial fibrillation, is about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, or about 290 mg.

[0212] There can be loss of a pharmaceutical composition along the respiratory pathway when the pharmaceutical composition is inhaled by a subject, so that not all the pharmaceutical composition reaches the lung for absorption into the systemic circulation. In some embodiments, the estimated total lung dose (eTLD, *e.g.*, a theoretical value that measures the dose of the pharmaceutical active ingredient that reaches the lung, *e.g.*, about 70% of the dose exiting the aerosolization device) of the flecainide acetate that is delivered according to the methods provided herein is from about 40 mg to about 180 mg, such as 40 mg to 60 mg, 40 mg to 70 mg,

40 mg to 80 mg, 40 mg to 90 mg, 40 mg to 100 mg, 40 mg to 110 mg, 40 mg to 120 mg, 40 mg to 130 mg, 40 mg to 140 mg, 40 mg to 150 mg, 40 mg to 160 mg, 40 mg to 170 mg, 40 mg to 180 mg, 50 mg to 60 mg, 50 mg to 70 mg, 50 mg to 80 mg, 50 mg to 90 mg, 50 mg to 100 mg, 50 mg to 110 mg, 50 mg to 120 mg, 50 mg to 130 mg, 50 mg to 140 mg, 50 mg to 150 mg, 50 mg to 160 mg, 50 mg to 170 mg, 50 mg to 180 mg, 70 mg to 80 mg, 70 mg to 90 mg, 70 mg to 100 mg, 70 mg to 110 mg, 70 mg to 120 mg, 70 mg to 130 mg, 70 mg to 140 mg, 70 mg to 170 mg, 70 mg to 160 mg, 70 mg to 170 mg, 70 mg to 180 mg, 80 mg to 90 mg, 80 mg to 100 mg, 80 mg to 110 mg, 80 mg to 120 mg, 80 mg to 130 mg, 80 mg to 140 mg, 80 mg to 150 mg, 80 mg to 160 mg, 80 mg to 170 mg, 80 mg to 180 mg, 90 mg to 100 mg, 90 mg to 110 mg, 90 mg to 120 mg, 90 mg to 130 mg, 90 mg to 140 mg, 90 mg to 150 mg, 90 mg to 160 mg, 90 mg to 170 mg, 90 mg to 180 mg, 100 mg to 110 mg, 100 mg to 120 mg, 100 mg to 130 mg, 100 mg to 140 mg, 100 mg to 150 mg, 100 mg to 160 mg, 100 mg to 170 mg, 100 mg to 180 mg, 120 mg to 140 mg, 120 mg to 150 mg, 120 mg to 160 mg, 120 mg to 170 mg, 120 mg to 180 mg, 150 mg to 160 mg, 150 mg to 170 mg, or 150 mg to 180 mg.

[0213] In some cases, the eTLD of the flecainide acetate that is delivered according to the methods provided herein is at least about 40 mg, at least about 60 mg, at least about 70 mg, at least about 80 mg, at least about 90 mg, at least about 100 mg, at least about 110 mg, at least about 120 mg, at least about 130 mg, at least about 140 mg, at least about 150 mg, at least about 160 mg, or at least about 170 mg. In some cases, the eTLD of the flecainide acetate that is delivered according to the methods provided herein is at most about 60 mg, at most about 70 mg, at most about 80 mg, at most about 90 mg, at most about 100 mg, at most about 110 mg, at most about 120 mg, at most about 130 mg, at most about 140 mg, at most about 150 mg, at most about 160 mg, at most about 170 mg, or at most about 180 mg. In some cases, the eTLD of the flecainide acetate that is delivered according to the methods provided herein is 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, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 160 mg, about 170 mg, or about 180 mg.

[0214] This method of treatment results in a pulsatile pharmacokinetic profile and transient pharmacodynamic effect mimicking the effect of an IV. This method delivers high drug concentrations that are safe and effective to the heart, while the distribution to the rest of the body results in the drug being diluted to sub-therapeutic levels. This method is the shortest route of delivery to the heart next to intra-cardial injection. This provides the convenience of self-administration like the “pill-in-the-pocket” approach, but the effectiveness and fast onset of

action of an IV. Although the delivery of medications through the lung for systemic effect is not new, it was thought it wouldn't be effective to the heart, because of the fast passage of drug through it. The animal and human PK/PD data in this study show that the drug exposure is sufficient for therapeutic effect at a much lower dose compared to other routes of administration. This method ensures dug concentrations in overall plasma are much lower than what is achieved by oral/IV hence minimizing drug-drug interactions and side effects.

[0215] In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be within about 30 min, such as within about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 15, 20, 25, or 30 minutes. In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation is within about 5 minutes. In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 0.1 minute to about 30 minutes, such as 0.1-0.5, 0.1-1, 0.1-1.5, 0.1-2, 0.1-2.5, 0.1-3, 0.1-3.5, 0.1-4, 0.1-4.5, 0.1-5, 0.1-6, 0.1-8, 0.1-10, 0.1-15, 0.1-20, 0.1-25, 0.1-30, 0.2-0.5, 0.2-1, 0.2-1.5, 0.2-2, 0.2-2.5, 0.2-3, 0.2-3.5, 0.2-4, 0.2-4.5, 0.2-5, 0.2-6, 0.2-8, 0.2-10, 0.2-15, 0.2-20, 0.2-25, 0.2-30, 0.3-0.5, 0.3-1, 0.3-1.5, 0.3-2, 0.3-2.5, 0.3-3, 0.3-3.5, 0.3-4, 0.3-4.5, 0.3-5, 0.3-6, 0.3-8, 0.3-10, 0.3-15, 0.3-20, 0.3-25, 0.3-30, 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3, 0.5-3.5, 0.5-4, 0.5-4.5, 0.5-5, 0.5-6, 0.5-8, 0.5-10, 0.5-15, 0.5-20, 0.5-25, 0.5-30, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1-6, 1-8, 1-10, 1-15, 1-20, 1-25, 1-30, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 1.5-6, 1.5-8, 1.5-10, 1.5-15, 1.5-20, 1.5-25, 1.5-30, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2-6, 2-8, 2-10, 2-15, 2-20, 2-25, 2-30, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 2.5-6, 2.5-8, 2.5-10, 2.5-15, 2.5-20, 2.5-25, 2.5-30, 3-3.5, 3-4, 3-4.5, 3-5, 3-6, 3-8, 3-10, 3-15, 3-20, 3-25, 3-30, 3.5-4, 3.5-4.5, 3.5-5, 3.5-6, 3.5-8, 3.5-10, 3.5-15, 3.5-20, 3.5-25, 3.5-30, 4-4.5, 4-5, 4-6, 4-8, 4-10, 4-15, 4-20, 4-25, 4-30, 4.5-5, 4.5-6, 4.5-8, 4.5-10, 4.5-15, 4.5-20, 4.5-25, 4.5-30, 5-6, 5-8, 5-10, 5-15, 5-20, 5-25, 5-30, 5.5-6, 5.5-8, 5.5-10, 5.5-15, 5.5-20, 5.5-25, 5.5-30, 6-8, 6-10, 6-15, 6-20, 6-25, 6-30, 8-10, 8-15, 8-20, 8-25, 8-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30, or 25-30 min. A range given out in the present disclosure can be a range between two accurate numerical values, in some cases, a range in the present disclosure can also refer to a range between two approximate numerical values. For instance, "1-10" can refer to "from 1 to 10" in some cases, while in other case, "1-10" can refer to "from about 1 to about 10". In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be 0.01-5, 0.02-5, 0.03-5, 0.04- 5, 0.05-5, 0.06-5, 0.07-5, 0.08-5, 0.09-5, 0.12-5, 0.14-5, 0.15-5, 0.16-5, 0.18-5, 0.2-5, 0.24-5, 0.26-5, 0.28-5, 0.3-5, 0.35-5, 0.4-5, 0.5-5, 0.6-5, 0.7-5, 0.8-5, 0.9-5, or 1-5 min. In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 0.1 to about 3 min. In some cases, the T_{max} of the antiarrhythmic pharmaceutical

agent administered via inhalation can be from about 0.1 to about 5 min. In some cases, the T_{max} of the antiarrhythmic pharmaceutical agent (e.g., flecainide) administered via inhalation can be from about 0.2 to about 5 min. In one or more embodiments, the antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0216] In some cases, the T_{max} is calculated as the amount of time at which the maximum plasma concentration of the antiarrhythmic pharmaceutical agent is observed. In some cases, the T_{max} can be calculated as the amount of time after administration of the antiarrhythmic pharmaceutical agent when the maximum plasma concentration is reached. In some cases, the T_{max} can be calculated as the amount of time after the initiation of the administration of the antiarrhythmic pharmaceutical agent when the maximum plasma concentration is reached. In some cases, the T_{max} can be calculated as the amount of time after the completion of the administration of the antiarrhythmic pharmaceutical agent when the maximum plasma concentration is reached. In some cases, the T_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the left ventricular chamber. In some cases, the T_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the pulmonary artery. In some cases, the T_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the vein (e.g., femoral vein). In some cases, the T_{max} can be measured in a human PK/ PD study.

[0217] The term "human PK/PD study" as used herein can refer to any settings where a human subject receives administration of a single dose of the antiarrhythmic agent as provided herein and a pharmacokinetic (PK) or pharmacodynamic (PD) parameter is measured from the human subject after the administration of the antiarrhythmic agent. In some cases, a human PK/PD study as provided herein can refer to a clinical study performed in a clinic or hospital settings. In some cases, the human PK/PD study can be a single center or multi-center study. A human PK/PD study can be performed on healthy human subjects or human cardiovascular patients. In some cases, the patients with cardiovascular disease experience arrhythmia as described herein. In some cases, a human PK/PD study can be a single-dose study, in other cases, a human PK/PD study can be a multi-dose (e.g. escalating doses) study.

[0218] Pharmacokinetics (PK) as described herein is concerned with the time course of a therapeutic agent, such as an antiarrhythmic pharmaceutical agent, *e.g.*, flecainide, in the body. Pharmacodynamics (PD) is concerned with the relationship between pharmacokinetics and

efficacy *in vivo*. PK/PD parameters correlate the therapeutic agent, such as an antiarrhythmic pharmaceutical agent, *e.g.*, flecainide, with efficacious activity.

[0219] Any standard pharmacokinetic protocol can be used in a human PK/PD study to determine blood plasma concentration profile in humans following administration of a formulation described herein, such as an inhalable formulation comprising flecainide, and thereby establish whether that formulation meets the pharmacokinetic criteria set out herein. For example, but in no way limiting, a type of a randomized single-dose crossover study can be utilized using a group of healthy adult human subjects. The number of subjects can be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 8 or greater, *e.g.*, about 10, 12, 14, 16, 18, 20, or 25. In certain embodiments a smaller group can be used. In one embodiment, a subject receives administration, at time zero, a single dose of an inhalable formulation described herein, *e.g.*, an inhalable formulation comprising flecainide. Blood samples are collected from each subject prior to administration and at several intervals after administration. Plasma can be separated from the blood samples by centrifugation and the separated plasma is analyzed, for example, by a validated high performance liquid chromatography/tandem weight spectrometry (LC/APCI-MS/MS) procedure such as, for example, those described in Ramu et al., Journal of Chromatography B, 751:49-59 (2001). In other embodiments, data from a single subject may be collected and may be used to construct a PK profile and may be indicative of an enhanced pharmacokinetic profile.

[0220] In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 10 ng/mL to about 5000 ng/mL, such as from about 10-30, 10-50, 10-70, 10-80, 10-90, 10-100, 10-110, 10-120, 10-130, 10-140, 10-150, 10-160, 10-170, 10-180, 10-190, 10-200, 10-250, 10-300, 10-350, 10-400, 10-450, 10-500, 10-550, 10-600, 10-650, 10-700, 10-800, 10-900, 10-1000, 10-1500, 10-2000, 10-3000, 10-4000, 10-5000, 20-30, 20-50, 20-70, 20-80, 20-90, 20-100, 20-110, 20-120, 20-130, 20-140, 20-150, 20-160, 20-170, 20-180, 20-190, 20-200, 20-250, 20-300, 20-350, 20-400, 20-450, 20-500, 20-550, 20-600, 20-650, 20-700, 20-800, 20-900, 20-1000, 20-1500, 20-2000, 20-3000, 20-4000, 20-5000, 30-50, 30-70, 30-80, 30-90, 30-100, 30-110, 30-120, 30-130, 30-140, 30-150, 30-160, 30-170, 30-180, 30-190, 30-200, 30-250, 30-300, 30-350, 30-400, 30-450, 30-500, 30-550, 30-600, 30-650, 30-700, 30-800, 30-900, 30-1000, 30-1500, 30-2000, 30-3000, 30-4000, 30-5000, 50-70, 50-80, 50-90, 50-100, 50-110, 50-120, 50-130, 50-140, 50-150, 50-160, 50-170, 50-180, 50-190, 50-200, 50-250, 50-300, 50-350, 50-400, 50-450, 50-500, 50-550, 50-600, 50-650, 50-700, 50-800, 50-900, 50-1000, 50-1500, 50-2000, 50-3000, 50-4000, 50-5000, 70-80, 70-90, 70-100, 70-110, 70-120, 70-130, 70-140, 70-150, 70-160, 70-170, 70-180, 70-190, 70-200, 70-250, 70-300, 70-350, 70-400, 70-

450, 70-500, 70-550, 70-600, 70-650, 70-700, 70-800, 70-900, 70-1000, 70-1500, 70-2000, 70-3000, 70-4000, 70-5000, 80-90, 80-100, 80-110, 80-120, 80-130, 80-140, 80-150, 80-160, 80-170, 80-180, 80-190, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 80-550, 80-600, 80-650, 80-700, 80-800, 80-900, 80-1000, 80-1500, 80-2000, 80-3000, 80-4000, 80-5000, 90-100, 90-110, 90-120, 90-130, 90-140, 90-150, 90-160, 90-170, 90-180, 90-190, 90-200, 90-250, 90-300, 90-350, 90-400, 90-450, 90-500, 90-550, 90-600, 90-650, 90-700, 90-800, 90-900, 90-1000, 90-1500, 90-2000, 90-3000, 90-4000, 90-5000, 100-110, 100-120, 100-130, 100-140, 100-150, 100-160, 100-170, 100-180, 100-190, 100-200, 100-250, 100-300, 100-350, 100-400, 100-450, 100-500, 100-550, 100-600, 100-650, 100-700, 100-800, 100-900, 100-1000, 100-1500, 100-2000, 100-3000, 100-4000, 100-5000, 110-120, 110-130, 110-140, 110-150, 110-160, 110-170, 110-180, 110-190, 110-200, 110-250, 110-300, 110-350, 110-400, 110-450, 110-500, 110-550, 110-600, 110-650, 110-700, 110-800, 110-900, 110-1000, 110-1500, 110-2000, 110-3000, 110-4000, 110-5000, 120-130, 120-140, 120-150, 120-160, 120-170, 120-180, 120-190, 120-200, 120-250, 120-300, 120-350, 120-400, 120-450, 120-500, 120-550, 120-600, 120-650, 120-700, 120-800, 120-900, 120-1000, 120-1500, 120-2000, 120-3000, 120-4000, 120-5000, 130-140, 130-150, 130-160, 130-170, 130-180, 130-190, 130-200, 130-250, 130-300, 130-350, 130-400, 130-450, 130-500, 130-550, 130-600, 130-650, 130-700, 130-800, 130-900, 130-1000, 130-1500, 130-2000, 130-3000, 130-4000, 130-5000, 140-150, 140-160, 140-170, 140-180, 140-190, 140-200, 140-250, 140-300, 140-350, 140-400, 140-450, 140-500, 140-550, 140-600, 140-650, 140-700, 140-800, 140-900, 140-1000, 140-1500, 140-2000, 140-3000, 140-4000, 140-5000, 150-160, 150-170, 150-180, 150-190, 150-200, 150-250, 150-300, 150-350, 150-400, 150-450, 150-500, 150-550, 150-600, 150-650, 150-700, 150-800, 150-900, 150-1000, 150-1500, 150-2000, 150-3000, 150-4000, 150-5000, 160-170, 160-180, 160-190, 160-200, 160-250, 160-300, 160-350, 160-400, 160-450, 160-500, 160-550, 160-600, 160-650, 160-700, 160-800, 160-900, 160-1000, 160-1500, 160-2000, 160-3000, 160-4000, 160-5000, 170-180, 170-190, 170-200, 170-250, 170-300, 170-350, 170-400, 170-450, 170-500, 170-550, 170-600, 170-650, 170-700, 170-800, 170-900, 170-1000, 170-1500, 170-2000, 170-3000, 170-4000, 170-5000, 180-190, 180-200, 180-250, 180-300, 180-350, 180-400, 180-450, 180-500, 180-550, 180-600, 180-650, 180-700, 180-800, 180-900, 180-1000, 180-1500, 180-2000, 180-3000, 180-4000, 180-5000, 190-200, 190-250, 190-300, 190-350, 190-400, 190-450, 190-500, 190-550, 190-600, 190-650, 190-700, 190-800, 190-900, 190-1000, 190-1500, 190-2000, 190-3000, 190-4000, 190-5000, 200-250, 200-300, 200-350, 200-400, 200-450, 200-500, 200-550, 200-600, 200-650, 200-700, 200-800, 200-900, 200-1000, 200-1500, 200-2000, 200-3000, 200-4000, 200-5000, 250-300, 250-350, 250-400, 250-450, 250-500, 250-550, 250-600, 250-650, 250-700, 250-800, 250-900,

250-1000, 250-1500, 250-2000, 250-3000, 250-4000, 250-5000, 300-350, 300-400, 300-450, 300-500, 300-550, 300-600, 300-650, 300-700, 300-800, 300-900, 300-1000, 300-1500, 300-2000, 300-3000, 300-4000, 300-5000, 350-400, 350-450, 350-500, 350-550, 350-600, 350-650, 350-700, 350-800, 350-900, 350-1000, 350-1500, 350-2000, 350-3000, 350-4000, 350-5000, 400-450, 400-500, 400-550, 400-600, 400-650, 400-700, 400-800, 400-900, 400-1000, 400-1500, 400-2000, 400-3000, 400-4000, 400-5000, 450-500, 450-550, 450-600, 450-650, 450-700, 450-800, 450-900, 450-1000, 450-1500, 450-2000, 450-3000, 450-4000, 450-5000, 500-550, 500-600, 500-650, 500-700, 500-800, 500-900, 500-1000, 500-1500, 500-2000, 500-3000, 500-4000, 500-5000, 550-600, 550-650, 550-700, 550-800, 550-900, 550-1000, 550-1500, 550-2000, 550-3000, 550-4000, 550-5000, 600-650, 600-700, 600-800, 600-900, 600-1000, 600-1500, 600-2000, 600-3000, 600-4000, 600-5000, 650-700, 650-800, 650-900, 650-1000, 650-1500, 650-2000, 650-3000, 650-4000, 650-5000, 700-800, 700-900, 700-1000, 700-1500, 700-2000, 700-3000, 700-4000, 700-5000, 800-900, 800-1000, 800-1500, 800-2000, 800-3000, 800-4000, 800-5000, 900-1000, 900-1500, 900-2000, 900-3000, 900-4000, 900-5000, 1000-1500, 1000-2000, 1000-3000, 1000-4000, 1000-5000, 1500-2000, 1500-3000, 1500-4000, 1500-5000, 2000-3000, 2000-4000, 2000-5000, 3000-4000, 3000-5000, or 4000-5000 ng/mL. In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 20 ng/mL to about 500 ng/mL, such as 20-500, 30-500, 40-500, 50-500, 60-500, 70-500, 80-500, 90-500, 100-500, 150-500, 200-500, or 250-500 ng/mL. In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 50 to about 500 ng/mL. In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 200 to about 500 ng/mL. In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation is at least about 200 ng/mL. In some cases, the C_{max} of the antiarrhythmic pharmaceutical agent administered via inhalation is at least about 250 ng/mL. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0221] In some cases, the C_{max} can be calculated as the maximum plasma concentration of the antiarrhythmic pharmaceutical agent observed. In some cases, the C_{max} can be calculated as the peak plasma concentration that the antiarrhythmic pharmaceutical agent achieves after the drug has been administrated. In some cases, the C_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the left ventricular chamber. In some cases, the C_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent

measured in the pulmonary artery. In some cases, the C_{max} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the vein (e.g., femoral vein). In some cases, the C_{max} can be measured in a human PK/ PD study.

[0222] In some cases, the AUC_{Last} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 100 hr*ng/mL to about 10000 hr*ng/mL, such as from 100-200, 100-300, 100-400, 100-420, 100-440, 100-460, 100-480, 100-500, 100-520, 100-540, 100-560, 100-580, 100-600, 100-620, 100-640, 100-660, 100-680, 100-700, 100-800, 100-900, 100-1000, 100-1500, 100-2000, 100-3000, 100-3500, 100-4000, 100-4500, 100-5000, 100-5500, 100-6000, 100-6500, 100-7000, 100-8000, 100-9000, 100-10000, 200-300, 200-400, 200-420, 200-440, 200-460, 200-480, 200-500, 200-520, 200-540, 200-560, 200-580, 200-600, 200-620, 200-640, 200-660, 200-680, 200-700, 200-800, 200-900, 200-1000, 200-1500, 200-2000, 200-3000, 200-3500, 200-4000, 200-4500, 200-5000, 200-5500, 200-6000, 200-6500, 200-7000, 200-8000, 200-9000, 200-10000, 300-400, 300-420, 300-440, 300-460, 300-480, 300-500, 300-520, 300-540, 300-560, 300-580, 300-600, 300-620, 300-640, 300-660, 300-680, 300-700, 300-800, 300-900, 300-1000, 300-1500, 300-2000, 300-3000, 300-3500, 300-4000, 300-4500, 300-5000, 300-5500, 300-6000, 300-6500, 300-7000, 300-8000, 300-9000, 300-10000, 400-420, 400-440, 400-460, 400-480, 400-500, 400-520, 400-540, 400-560, 400-580, 400-600, 400-620, 400-640, 400-660, 400-680, 400-700, 400-800, 400-900, 400-1000, 400-1500, 400-2000, 400-3000, 400-3500, 400-4000, 400-4500, 400-5000, 400-5500, 400-6000, 400-6500, 400-7000, 400-8000, 400-9000, 400-10000, 420-440, 420-460, 420-480, 420-500, 420-520, 420-540, 420-560, 420-580, 420-600, 420-620, 420-640, 420-660, 420-680, 420-700, 420-800, 420-900, 420-1000, 420-1500, 420-2000, 420-3000, 420-3500, 420-4000, 420-4500, 420-5000, 420-5500, 420-6000, 420-6500, 420-7000, 420-8000, 420-9000, 420-10000, 440-460, 440-480, 440-500, 440-520, 440-540, 440-560, 440-580, 440-600, 440-620, 440-640, 440-660, 440-680, 440-700, 440-800, 440-900, 440-1000, 440-1500, 440-2000, 440-3000, 440-3500, 440-4000, 440-4500, 440-5000, 440-5500, 440-6000, 440-6500, 440-7000, 440-8000, 440-9000, 440-10000, 460-480, 460-500, 460-520, 460-540, 460-560, 460-580, 460-600, 460-620, 460-640, 460-660, 460-680, 460-700, 460-800, 460-900, 460-1000, 460-1500, 460-2000, 460-3000, 460-3500, 460-4000, 460-4500, 460-5000, 460-5500, 460-6000, 460-6500, 460-7000, 460-8000, 460-9000, 460-10000, 480-500, 480-520, 480-540, 480-560, 480-580, 480-600, 480-620, 480-640, 480-660, 480-680, 480-700, 480-800, 480-900, 480-1000, 480-1500, 480-2000, 480-3000, 480-3500, 480-4000, 480-4500, 480-5000, 480-5500, 480-6000, 480-6500, 480-7000, 480-8000, 480-9000, 480-10000, 500-520, 500-540, 500-560, 500-580, 500-600, 500-620, 500-640, 500-660, 500-680, 500-700, 500-800, 500-900, 500-1000, 500-1500, 500-2000, 500-3000, 500-3500, 500-4000, 500-4500, 500-5000, 500-5500,

500-6000, 500-6500, 500-7000, 500-8000, 500-9000, 500-10000, 520-540, 520-560, 520-580, 520-600, 520-620, 520-640, 520-660, 520-680, 520-700, 520-800, 520-900, 520-1000, 520-1500, 520-2000, 520-3000, 520-3500, 520-4000, 520-4500, 520-5000, 520-5500, 520-6000, 520-6500, 520-7000, 520-8000, 520-9000, 520-10000, 540-560, 540-580, 540-600, 540-620, 540-640, 540-660, 540-680, 540-700, 540-800, 540-900, 540-1000, 540-1500, 540-2000, 540-3000, 540-3500, 540-4000, 540-4500, 540-5000, 540-5500, 540-6000, 540-6500, 540-7000, 540-8000, 540-9000, 540-10000, 560-580, 560-600, 560-620, 560-640, 560-660, 560-680, 560-700, 560-800, 560-900, 560-1000, 560-1500, 560-2000, 560-3000, 560-3500, 560-4000, 560-4500, 560-5000, 560-5500, 560-6000, 560-6500, 560-7000, 560-8000, 560-9000, 560-10000, 580-600, 580-620, 580-640, 580-660, 580-680, 580-700, 580-800, 580-900, 580-1000, 580-1500, 580-2000, 580-3000, 580-3500, 580-4000, 580-4500, 580-5000, 580-5500, 580-6000, 580-6500, 580-7000, 580-8000, 580-9000, 580-10000, 600-620, 600-640, 600-660, 600-680, 600-700, 600-800, 600-900, 600-1000, 600-1500, 600-2000, 600-3000, 600-3500, 600-4000, 600-4500, 600-5000, 600-5500, 600-6000, 600-6500, 600-7000, 600-8000, 600-9000, 600-10000, 620-640, 620-660, 620-680, 620-700, 620-800, 620-900, 620-1000, 620-1500, 620-2000, 620-3000, 620-3500, 620-4000, 620-4500, 620-5000, 620-5500, 620-6000, 620-6500, 620-7000, 620-8000, 620-9000, 620-10000, 640-660, 640-680, 640-700, 640-800, 640-900, 640-1000, 640-1500, 640-2000, 640-3000, 640-3500, 640-4000, 640-4500, 640-5000, 640-5500, 640-6000, 640-6500, 640-7000, 640-8000, 640-9000, 640-10000, 660-680, 660-700, 660-800, 660-900, 660-1000, 660-1500, 660-2000, 660-3000, 660-3500, 660-4000, 660-4500, 660-5000, 660-5500, 660-6000, 660-6500, 660-7000, 660-8000, 660-9000, 660-10000, 680-700, 680-800, 680-900, 680-1000, 680-1500, 680-2000, 680-3000, 680-3500, 680-4000, 680-4500, 680-5000, 680-5500, 680-6000, 680-6500, 680-7000, 680-8000, 680-9000, 680-10000, 700-800, 700-900, 700-1000, 700-1500, 700-2000, 700-3000, 700-3500, 700-4000, 700-4500, 700-5000, 700-5500, 700-6000, 700-6500, 700-7000, 700-8000, 700-9000, 700-10000, 800-900, 800-1000, 800-1500, 800-2000, 800-3000, 800-3500, 800-4000, 800-4500, 800-5000, 800-5500, 800-6000, 800-6500, 800-7000, 800-8000, 800-9000, 800-10000, 900-1000, 900-1500, 900-2000, 900-3000, 900-3500, 900-4000, 900-4500, 900-5000, 900-5500, 900-6000, 900-6500, 900-7000, 900-8000, 900-9000, 900-10000, 1000-1500, 1000-2000, 1000-3000, 1000-3500, 1000-4000, 1000-4500, 1000-5000, 1000-5500, 1000-6000, 1000-6500, 1000-7000, 1000-8000, 1000-9000, 1000-10000, 1500-2000, 1500-3000, 1500-3500, 1500-4000, 1500-4500, 1500-5000, 1500-5500, 1500-6000, 1500-6500, 1500-7000, 1500-8000, 1500-9000, 1500-10000, 2000-3000, 2000-3500, 2000-4000, 2000-4500, 2000-5000, 2000-5500, 2000-6000, 2000-6500, 2000-7000, 2000-8000, 2000-9000, 2000-10000, 2500-3000, 2500-3500, 2500-4000, 2500-4500, 2500-5000, 2500-5500, 2500-6000, 2500-6500,

2500-7000, 2500-8000, 2500-9000, 2500-10000, 3000-3500, 3000-4000, 3000-4500, 3000-5000, 3000-5500, 3000-6000, 3000-6500, 3000-7000, 3000-8000, 3000-9000, 3000-10000, 3500-4000, 3500-4500, 3500-5000, 3500-5500, 3500-6000, 3500-6500, 3500-7000, 3500-8000, 3500-9000, 3500-10000, 4000-4500, 4000-5000, 4000-5500, 4000-6000, 4000-6500, 4000-7000, 4000-8000, 4000-9000, 4000-10000, 4500-5000, 4500-5500, 4500-6000, 4500-6500, 4500-7000, 4500-8000, 4500-9000, 4500-10000, 5000-5500, 5000-6000, 5000-6500, 5000-7000, 5000-8000, 5000-9000, 5000-10000, 5500-6000, 5500-6500, 5500-7000, 5500-8000, 5500-9000, 5500-10000, 6000-6500, 6000-7000, 6000-8000, 6000-9000, 6000-10000, 6500-7000, 6500-8000, 6500-9000, 6500-10000, 7000-8000, 7000-9000, 7000-10000, 8000-9000, 8000-10000, or 9000-10000 hr*ng/mL. In some cases, the AUC_{Last} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 200 to about 2000 hr*ng/mL. In some cases, the AUC_{Last} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 500 to about 800 hr*ng/mL. In some cases, the AUC_{Last} of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 400 to about 600 hr*ng/mL. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0223] In some cases, the AUC_{Last} can be calculated as the area under the concentration-time curve up to the last measurable concentration. In some cases, the AUC_{Last} can be calculated as the total drug exposure over time. In some cases, the AUC_{Last} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the left ventricular chamber. In some cases, the AUC_{Last} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the pulmonary artery. In some cases, the AUC_{Last} can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the vein (e.g., femoral vein). In some cases, the AUC_{Last} can be measured in a human PK/ PD study.

[0224] In some cases, the distribution $t_{1/2}$ of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 0.1 minute to about 15 minutes, such as from about 0.1-0.5, 0.1-1, 0.1-1.5, 0.1-2, 0.1-2.5, 0.1-2.6, 0.1-2.7, 0.1-2.8, 0.1-2.9, 0.1-3, 0.1-3.1, 0.1-3.2, 0.1-3.3, 0.1-3.4, 0.1-3.5, 0.1-3.6, 0.1-3.7, 0.1-3.8, 0.1-3.9, 0.1-4, 0.1-4.1, 0.1-4.2, 0.1-4.3, 0.1-4.4, 0.1-4.5, 0.1-5, 0.1-5.5, 0.1-6, 0.1-7, 0.1-8, 0.1-9, 0.1-10, 0.1-11, 0.1-12, 0.1-13, 0.1-14, 0.1-15, 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-2.6, 0.5-2.7, 0.5-2.8, 0.5-2.9, 0.5-3, 0.5-3.1, 0.5-3.2, 0.5-3.3, 0.5-3.4, 0.5-3.5, 0.5-3.6, 0.5-3.7, 0.5-3.8, 0.5-3.9, 0.5-4, 0.5-4.1, 0.5-4.2, 0.5-4.3, 0.5-

4.4, 0.5-4.5, 0.5-5, 0.5-5.5, 0.5-6, 0.5-7, 0.5-8, 0.5-9, 0.5-10, 0.5-11, 0.5-12, 0.5-13, 0.5-14, 0.5-15, 1-1.5, 1-2, 1-2.5, 1-2.6, 1-2.7, 1-2.8, 1-2.9, 1-3, 1-3.1, 1-3.2, 1-3.3, 1-3.4, 1-3.5, 1-3.6, 1-3.7, 1-3.8, 1-3.9, 1-4, 1-4.1, 1-4.2, 1-4.3, 1-4.4, 1-4.5, 1-5, 1-5.5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-14, 1-15, 1.5-2, 1.5-2.5, 1.5-2.6, 1.5-2.7, 1.5-2.8, 1.5-2.9, 1.5-3, 1.5-3.1, 1.5-3.2, 1.5-3.3, 1.5-3.4, 1.5-3.5, 1.5-3.6, 1.5-3.7, 1.5-3.8, 1.5-3.9, 1.5-4, 1.5-4.1, 1.5-4.2, 1.5-4.3, 1.5-4.4, 1.5-4.5, 1.5-5, 1.5-5.5, 1.5-6, 1.5-7, 1.5-8, 1.5-9, 1.5-10, 1.5-11, 1.5-12, 1.5-13, 1.5-14, 1.5-15, 2-2.5, 2-2.6, 2-2.7, 2-2.8, 2-2.9, 2-3, 2-3.1, 2-3.2, 2-3.3, 2-3.4, 2-3.5, 2-3.6, 2-3.7, 2-3.8, 2-3.9, 2-4, 2-4.1, 2-4.2, 2-4.3, 2-4.4, 2-4.5, 2-5, 2-5.5, 2-6, 2-7, 2-8, 2-9, 2-10, 2-11, 2-12, 2-13, 2-14, 2-15, 2.5-2.6, 2.5-2.7, 2.5-2.8, 2.5-2.9, 2.5-3, 2.5-3.1, 2.5-3.2, 2.5-3.3, 2.5-3.4, 2.5-3.5, 2.5-3.6, 2.5-3.7, 2.5-3.8, 2.5-3.9, 2.5-4, 2.5-4.1, 2.5-4.2, 2.5-4.3, 2.5-4.4, 2.5-4.5, 2.5-5, 2.5-5.5, 2.5-6, 2.5-7, 2.5-8, 2.5-9, 2.5-10, 2.5-11, 2.5-12, 2.5-13, 2.5-14, 2.5-15, 2.6-2.7, 2.6-2.8, 2.6-2.9, 2.6-3, 2.6-3.1, 2.6-3.2, 2.6-3.3, 2.6-3.4, 2.6-3.5, 2.6-3.6, 2.6-3.7, 2.6-3.8, 2.6-3.9, 2.6-4, 2.6-4.1, 2.6-4.2, 2.6-4.3, 2.6-4.4, 2.6-4.5, 2.6-5, 2.6-5.5, 2.6-6, 2.6-7, 2.6-8, 2.6-9, 2.6-10, 2.6-11, 2.6-12, 2.6-13, 2.6-14, 2.6-15, 2.7-2.8, 2.7-2.9, 2.7-3, 2.7-3.1, 2.7-3.2, 2.7-3.3, 2.7-3.4, 2.7-3.5, 2.7-3.6, 2.7-3.7, 2.7-3.8, 2.7-3.9, 2.7-4, 2.7-4.1, 2.7-4.2, 2.7-4.3, 2.7-4.4, 2.7-4.5, 2.7-5, 2.7-5.5, 2.7-6, 2.7-7, 2.7-8, 2.7-9, 2.7-10, 2.7-11, 2.7-12, 2.7-13, 2.7-14, 2.7-15, 2.8-2.9, 2.8-3, 2.8-3.1, 2.8-3.2, 2.8-3.3, 2.8-3.4, 2.8-3.5, 2.8-3.6, 2.8-3.7, 2.8-3.8, 2.8-3.9, 2.8-4, 2.8-4.1, 2.8-4.2, 2.8-4.3, 2.8-4.4, 2.8-4.5, 2.8-5, 2.8-5.5, 2.8-6, 2.8-7, 2.8-8, 2.8-9, 2.8-10, 2.8-11, 2.8-12, 2.8-13, 2.8-14, 2.8-15, 2.9-3, 2.9-3.1, 2.9-3.2, 2.9-3.3, 2.9-3.4, 2.9-3.5, 2.9-3.6, 2.9-3.7, 2.9-3.8, 2.9-3.9, 2.9-4, 2.9-4.1, 2.9-4.2, 2.9-4.3, 2.9-4.4, 2.9-4.5, 2.9-5, 2.9-5.5, 2.9-6, 2.9-7, 2.9-8, 2.9-9, 2.9-10, 2.9-11, 2.9-12, 2.9-13, 2.9-14, 2.9-15, 3-3.1, 3-3.2, 3-3.3, 3-3.4, 3-3.5, 3-3.6, 3-3.7, 3-3.8, 3-3.9, 3-4, 3-4.1, 3-4.2, 3-4.3, 3-4.4, 3-4.5, 3-5, 3-5.5, 3-6, 3-7, 3-8, 3-9, 3-10, 3-11, 3-12, 3-13, 3-14, 3-15, 3.1-3.2, 3.1-3.3, 3.1-3.4, 3.1-3.5, 3.1-3.6, 3.1-3.7, 3.1-3.8, 3.1-3.9, 3.1-4, 3.1-4.1, 3.1-4.2, 3.1-4.3, 3.1-4.4, 3.1-4.5, 3.1-5, 3.1-5.5, 3.1-6, 3.1-7, 3.1-8, 3.1-9, 3.1-10, 3.1-11, 3.1-12, 3.1-13, 3.1-14, 3.1-15, 3.2-3.3, 3.2-3.4, 3.2-3.5, 3.2-3.6, 3.2-3.7, 3.2-3.8, 3.2-3.9, 3.2-4, 3.2-4.1, 3.2-4.2, 3.2-4.3, 3.2-4.4, 3.2-4.5, 3.2-5, 3.2-5.5, 3.2-6, 3.2-7, 3.2-8, 3.2-9, 3.2-10, 3.2-11, 3.2-12, 3.2-13, 3.2-14, 3.2-15, 3.3-3.4, 3.3-3.5, 3.3-3.6, 3.3-3.7, 3.3-3.8, 3.3-3.9, 3.3-4, 3.3-4.1, 3.3-4.2, 3.3-4.3, 3.3-4.4, 3.3-4.5, 3.3-5, 3.3-5.5, 3.3-6, 3.3-7, 3.3-8, 3.3-9, 3.3-10, 3.3-11, 3.3-12, 3.3-13, 3.3-14, 3.3-15, 3.4-3.5, 3.4-3.6, 3.4-3.7, 3.4-3.8, 3.4-3.9, 3.4-4, 3.4-4.1, 3.4-4.2, 3.4-4.3, 3.4-4.4, 3.4-4.5, 3.4-5, 3.4-5.5, 3.4-6, 3.4-7, 3.4-8, 3.4-9, 3.4-10, 3.4-11, 3.4-12, 3.4-13, 3.4-14, 3.4-15, 3.5-3.6, 3.5-3.7, 3.5-3.8, 3.5-3.9, 3.5-4, 3.5-4.1, 3.5-4.2, 3.5-4.3, 3.5-4.4, 3.5-4.5, 3.5-5, 3.5-5.5, 3.5-6, 3.5-7, 3.5-8, 3.5-9, 3.5-10, 3.5-11, 3.5-12, 3.5-13, 3.5-14, 3.5-15, 3.6-3.7, 3.6-3.8, 3.6-3.9, 3.6-4, 3.6-4.1, 3.6-4.2, 3.6-4.3, 3.6-4.4, 3.6-4.5, 3.6-5, 3.6-5.5, 3.6-6, 3.6-7, 3.6-8, 3.6-9, 3.6-10, 3.6-11, 3.6-12, 3.6-13, 3.6-14, 3.6-15, 3.7-3.8, 3.8-3.9, 3.8-4, 3.8-4.1, 3.8-4.2, 3.8-4.3, 3.8-4.4, 3.8-4.5, 3.8-5,

3.8-5.5, 3.8-6, 3.8-7, 3.8-8, 3.8-9, 3.8-10, 3.8-11, 3.8-12, 3.8-13, 3.8-14, 3.8-15, 3.9-4, 3.9-4.1, 3.9-4.2, 3.9-4.3, 3.9-4.4, 3.9-4.5, 3.9-5, 3.9-5.5, 3.9-6, 3.9-7, 3.9-8, 3.9-9, 3.9-10, 3.9-11, 3.9-12, 3.9-13, 3.9-14, 3.9-15, 4-4.1, 4-4.2, 4-4.3, 4-4.4, 4-4.5, 4-5, 4-5.5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-14, 4-15, 4.1-4.2, 4.1-4.3, 4.1-4.4, 4.1-4.5, 4.1-5, 4.1-5.5, 4.1-6, 4.1-7, 4.1-8, 4.1-9, 4.1-10, 4.1-11, 4.1-12, 4.1-13, 4.1-14, 4.1-15, 4.2-4.3, 4.2-4.4, 4.2-4.5, 4.2-5, 4.2-5.5, 4.2-6, 4.2-7, 4.2-8, 4.2-9, 4.2-10, 4.2-11, 4.2-12, 4.2-13, 4.2-14, 4.2-15, 4.3-4.4, 4.3-4.5, 4.3-5, 4.3-5.5, 4.3-6, 4.3-7, 4.3-8, 4.3-9, 4.3-10, 4.3-11, 4.3-12, 4.3-13, 4.3-14, 4.3-15, 4.4-4.5, 4.4-5, 4.4-5.5, 4.4-6, 4.4-7, 4.4-8, 4.4-9, 4.4-10, 4.4-11, 4.4-12, 4.4-13, 4.4-14, 4.4-15, 4.5-5, 4.5-5.5, 4.5-6, 4.5-7, 4.5-8, 4.5-9, 4.5-10, 4.5-11, 4.5-12, 4.5-13, 4.5-14, 4.5-15, 5-5.5, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-15, 5.5-6, 5.5-7, 5.5-8, 5.5-9, 5.5-10, 5.5-11, 5.5-12, 5.5-13, 5.5-14, 5.5-15, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-14, 6-15, 7-8, 7-9, 7-10, 7-11, 7-12, 7-13, 7-14, 7-15, 8-9, 8-10, 8-11, 8-12, 8-13, 8-14, 8-15, 9-10, 9-11, 9-12, 9-13, 9-14, 9-15, 10-11, 10-12, 10-13, 10-14, 10-15, 11-12, 11-13, 11-14, 11-15, 12-13, 12-14, 12-15, 13-14, 13-15, or 14-15 min. In some cases, the distribution $t_{1/2}$ of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 3 to about 5 minutes. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0225] In some cases, the distribution $t_{1/2}$ can be calculated as the time at which the antiarrhythmic pharmaceutical agent plasma levels decreased to half of what they were at equilibrium due to distribution to tissues throughout the body. In some cases, the distribution $t_{1/2}$ can be calculated as the time it takes for an antiarrhythmic pharmaceutical agent to lose half of its pharmacologic activity. In some cases, the distribution $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the left ventricular chamber. In some cases, the distribution $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the pulmonary artery. In some cases, the distribution $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the vein (e.g., femoral vein). In some cases, the distribution $t_{1/2}$ can be measured in a human PK/ PD study.

[0226] In some cases, the elimination $t_{1/2}$ of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 1 hour to about 25 hours, such as from about 1-3, 1-5, 1-7, 1-7.5, 1-8, 1-8.5, 1-8.7, 1-8.9, 1-9.1, 1-9.3, 1-9.5, 1-9.7, 1-9.9, 1-10.1, 1-10.3, 1-10.5, 1-10.7, 1-10.9, 1-11.1, 1-11.3, 1-11.5, 1-11.7, 1-11.9, 1-12.1, 1-12.5, 1-13, 1-13.5, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-25, 3-5, 3-7, 3-7.5, 3-8, 3-8.5, 3-8.7, 3-8.9, 3-9.1, 3-9.3, 3-9.5, 3-

9.7, 3-9.9, 3-10.1, 3-10.3, 3-10.5, 3-10.7, 3-10.9, 3-11.1, 3-11.3, 3-11.5, 3-11.7, 3-11.9, 3-12.1, 3-12.5, 3-13, 3-13.5, 3-14, 3-15, 3-16, 3-17, 3-18, 3-19, 3-20, 3-25, 5-7, 5-7.5, 5-8, 5-8.5, 5-8.7, 5-8.9, 5-9.1, 5-9.3, 5-9.5, 5-9.7, 5-9.9, 5-10.1, 5-10.3, 5-10.5, 5-10.7, 5-10.9, 5-11.1, 5-11.3, 5-11.5, 5-11.7, 5-11.9, 5-12.1, 5-12.5, 5-13, 5-13.5, 5-14, 5-15, 5-16, 5-17, 5-18, 5-19, 5-20, 5-25, 7-7.5, 7-8, 7-8.5, 7-8.7, 7-8.9, 7-9.1, 7-9.3, 7-9.5, 7-9.7, 7-9.9, 7-10.1, 7-10.3, 7-10.5, 7-10.7, 7-10.9, 7-11.1, 7-11.3, 7-11.5, 7-11.7, 7-11.9, 7-12.1, 7-12.5, 7-13, 7-13.5, 7-14, 7-15, 7-16, 7-17, 7-18, 7-19, 7-20, 7-25, 7.5-8, 7.5-8.5, 7.5-8.7, 7.5-8.9, 7.5-9.1, 7.5-9.3, 7.5-9.5, 7.5-9.7, 7.5-9.9, 7.5-10.1, 7.5-10.3, 7.5-10.5, 7.5-10.7, 7.5-10.9, 7.5-11.1, 7.5-11.3, 7.5-11.5, 7.5-11.7, 7.5-11.9, 7.5-12.1, 7.5-12.5, 7.5-13, 7.5-13.5, 7.5-14, 7.5-15, 7.5-16, 7.5-17, 7.5-18, 7.5-19, 7.5-20, 7.5-25, 8-8.5, 8-8.7, 8-8.9, 8-9.1, 8-9.3, 8-9.5, 8-9.7, 8-9.9, 8-10.1, 8-10.3, 8-10.5, 8-10.7, 8-10.9, 8-11.1, 8-11.3, 8-11.5, 8-11.7, 8-11.9, 8-12.1, 8-12.5, 8-13, 8-13.5, 8-14, 8-15, 8-16, 8-17, 8-18, 8-19, 8-20, 8-25, 8.5-8.7, 8.5-8.9, 8.5-9.1, 8.5-9.3, 8.5-9.5, 8.5-9.7, 8.5-9.9, 8.5-10.1, 8.5-10.3, 8.5-10.5, 8.5-10.7, 8.5-10.9, 8.5-11.1, 8.5-11.3, 8.5-11.5, 8.5-11.7, 8.5-11.9, 8.5-12.1, 8.5-12.5, 8.5-13, 8.5-13.5, 8.5-14, 8.5-15, 8.5-16, 8.5-17, 8.5-18, 8.5-19, 8.5-20, 8.5-25, 8.7-8.9, 8.7-9.1, 8.7-9.3, 8.7-9.5, 8.7-9.7, 8.7-9.9, 8.7-10.1, 8.7-10.3, 8.7-10.5, 8.7-10.7, 8.7-10.9, 8.7-11.1, 8.7-11.3, 8.7-11.5, 8.7-11.7, 8.7-11.9, 8.7-12.1, 8.7-12.5, 8.7-13, 8.7-13.5, 8.7-14, 8.7-15, 8.7-16, 8.7-17, 8.7-18, 8.7-19, 8.7-20, 8.7-25, 8.9-9.1, 8.9-9.3, 8.9-9.5, 8.9-9.7, 8.9-9.9, 8.9-10.1, 8.9-10.3, 8.9-10.5, 8.9-10.7, 8.9-10.9, 8.9-11.1, 8.9-11.3, 8.9-11.5, 8.9-11.7, 8.9-11.9, 8.9-12.1, 8.9-12.5, 8.9-13, 8.9-13.5, 8.9-14, 8.9-15, 8.9-16, 8.9-17, 8.9-18, 8.9-19, 8.9-20, 8.9-25, 9.1-9.3, 9.1-9.5, 9.1-9.7, 9.1-9.9, 9.1-10.1, 9.1-10.3, 9.1-10.5, 9.1-10.7, 9.1-10.9, 9.1-11.1, 9.1-11.3, 9.1-11.5, 9.1-11.7, 9.1-11.9, 9.1-12.1, 9.1-12.5, 9.1-13, 9.1-13.5, 9.1-14, 9.1-15, 9.1-16, 9.1-17, 9.1-18, 9.1-19, 9.1-20, 9.1-25, 9.3-9.5, 9.3-9.7, 9.3-9.9, 9.3-10.1, 9.3-10.3, 9.3-10.5, 9.3-10.7, 9.3-10.9, 9.3-11.1, 9.3-11.3, 9.3-11.5, 9.3-11.7, 9.3-11.9, 9.3-12.1, 9.3-12.5, 9.3-13, 9.3-13.5, 9.3-14, 9.3-15, 9.3-16, 9.3-17, 9.3-18, 9.3-19, 9.3-20, 9.3-25, 9.5-9.7, 9.5-9.9, 9.5-10.1, 9.5-10.3, 9.5-10.5, 9.5-10.7, 9.5-10.9, 9.5-11.1, 9.5-11.3, 9.5-11.5, 9.5-11.7, 9.5-11.9, 9.5-12.1, 9.5-12.5, 9.5-13, 9.5-13.5, 9.5-14, 9.5-15, 9.5-16, 9.5-17, 9.5-18, 9.5-19, 9.5-20, 9.5-25, 9.7-9.9, 9.7-10.1, 9.7-10.3, 9.7-10.5, 9.7-10.7, 9.7-10.9, 9.7-11.1, 9.7-11.3, 9.7-11.5, 9.7-11.7, 9.7-11.9, 9.7-12.1, 9.7-12.5, 9.7-13, 9.7-13.5, 9.7-14, 9.7-15, 9.7-16, 9.7-17, 9.7-18, 9.7-19, 9.7-20, 9.7-25, 9.9-10.1, 9.9-10.3, 9.9-10.5, 9.9-10.7, 9.9-10.9, 9.9-11.1, 9.9-11.3, 9.9-11.5, 9.9-11.7, 9.9-11.9, 9.9-12.1, 9.9-12.5, 9.9-13, 9.9-13.5, 9.9-14, 9.9-15, 9.9-16, 9.9-17, 9.9-18, 9.9-19, 9.9-20, 9.9-25, 10.1-10.3, 10.1-10.5, 10.1-10.7, 10.1-10.9, 10.1-11.1, 10.1-11.3, 10.1-11.5, 10.1-11.7, 10.1-11.9, 10.1-12.1, 10.1-12.5, 10.1-13, 10.1-13.5, 10.1-14, 10.1-15, 10.1-16, 10.1-17, 10.1-18, 10.1-19, 10.1-20, 10.1-25, 10.3-10.5, 10.3-10.7, 10.3-10.9, 10.3-11.1, 10.3-11.3, 10.3-11.5, 10.3-11.7, 10.3-11.9, 10.3-12.1, 10.3-12.5, 10.3-13, 10.3-13.5, 10.3-14, 10.3-15, 10.3-16, 10.3-17, 10.3-18, 10.3-19,

10.3-20, 10.3-25, 10.5-10.7, 10.5-10.9, 10.5-11.1, 10.5-11.3, 10.5-11.5, 10.5-11.7, 10.5-11.9, 10.5-12.1, 10.5-12.5, 10.5-13, 10.5-13.5, 10.5-14, 10.5-15, 10.5-16, 10.5-17, 10.5-18, 10.5-19, 10.5-20, 10.5-25, 10.7-10.9, 10.7-11.1, 10.7-11.3, 10.7-11.5, 10.7-11.7, 10.7-11.9, 10.7-12.1, 10.7-12.5, 10.7-13, 10.7-13.5, 10.7-14, 10.7-15, 10.7-16, 10.7-17, 10.7-18, 10.7-19, 10.7-20, 10.7-25, 10.9-11.1, 10.9-11.3, 10.9-11.5, 10.9-11.7, 10.9-11.9, 10.9-12.1, 10.9-12.5, 10.9-13, 10.9-13.5, 10.9-14, 10.9-15, 10.9-16, 10.9-17, 10.9-18, 10.9-19, 10.9-20, 10.9-25, 11.1-11.3, 11.1-11.5, 11.1-11.7, 11.1-11.9, 11.1-12.1, 11.1-12.5, 11.1-13, 11.1-13.5, 11.1-14, 11.1-15, 11.1-16, 11.1-17, 11.1-18, 11.1-19, 11.1-20, 11.1-25, 11.3-11.5, 11.3-11.7, 11.3-11.9, 11.3-12.1, 11.3-12.5, 11.3-13, 11.3-13.5, 11.3-14, 11.3-15, 11.3-16, 11.3-17, 11.3-18, 11.3-19, 11.3-20, 11.3-25, 11.5-11.7, 11.5-11.9, 11.5-12.1, 11.5-12.5, 11.5-13, 11.5-13.5, 11.5-14, 11.5-15, 11.5-16, 11.5-17, 11.5-18, 11.5-19, 11.5-20, 11.5-25, 11.7-11.9, 11.7-12.1, 11.7-12.5, 11.7-13, 11.7-13.5, 11.7-14, 11.7-15, 11.7-16, 11.7-17, 11.7-18, 11.7-19, 11.7-20, 11.7-25, 11.9-12.1, 11.9-12.5, 11.9-13, 11.9-13.5, 11.9-14, 11.9-15, 11.9-16, 11.9-17, 11.9-18, 11.9-19, 11.9-20, 11.9-25, 12.1-12.5, 12.1-13, 12.1-13.5, 12.1-14, 12.1-15, 12.1-16, 12.1-17, 12.1-18, 12.1-19, 12.1-20, 12.1-25, 12.5-13, 12.5-13.5, 12.5-14, 12.5-15, 12.5-16, 12.5-17, 12.5-18, 12.5-19, 12.5-20, 12.5-25, 13-13.5, 13-14, 13-15, 13-16, 13-17, 13-18, 13-19, 13-20, 13-25, 13.5-14, 13.5-15, 13.5-16, 13.5-17, 13.5-18, 13.5-19, 13.5-20, 13.5-25, 14-15, 14-16, 14-17, 14-18, 14-19, 14-20, 14-25, 15-16, 15-17, 15-18, 15-19, 15-20, 15-25, 16-17, 16-18, 16-19, 16-20, 16-25, 17-18, 17-19, 17-20, 17-25, 18-19, 18-20, 18-25, 19-20, 19-25, or 20-25 hours. In some cases, the elimination $t_{1/2}$ of the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 8.5 to about 10.5 hours. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0227] In some cases, the elimination $t_{1/2}$ can be calculated as the time at which the antiarrhythmic pharmaceutical agent plasma levels decreased to half of what they were at equilibrium due to metabolism and elimination. In some cases, the elimination $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the left ventricular chamber. In some cases, the elimination $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the pulmonary artery. In some cases, the elimination $t_{1/2}$ can be calculated from plasma concentration of the antiarrhythmic pharmaceutical agent measured in the vein (e.g., femoral vein). In some cases, the elimination $t_{1/2}$ can be measured in a human PK/ PD study.

[0228] In some cases, the maximum change in QRS interval duration (ΔQRS) following the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 0.01 msec to about 100 msec, such as from about 0.01-0.1, 0.01-0.5, 0.01-1, 0.01-1.5, 0.01-2, 0.01-2.5, 0.01-3, 0.01-3.5, 0.01-4, 0.01-4.5, 0.01-5, 0.01-5.5, 0.01-6, 0.01-8, 0.01-10, 0.01-15, 0.01-20, 0.01-25, 0.01-30, 0.01-40, 0.01-50, 0.01-60, 0.01-70, 0.01-80, 0.01-90, 0.01-100, 0.1-0.5, 0.1-1, 0.1-1.5, 0.1-2, 0.1-2.5, 0.1-3, 0.1-3.5, 0.1-4, 0.1-4.5, 0.1-5, 0.1-5.5, 0.1-6, 0.1-8, 0.1-10, 0.1-15, 0.1-20, 0.1-25, 0.1-30, 0.1-40, 0.1-50, 0.1-60, 0.1-70, 0.1-80, 0.1-90, 0.1-100, 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3, 0.5-3.5, 0.5-4, 0.5-4.5, 0.5-5, 0.5-5.5, 0.5-6, 0.5-8, 0.5-10, 0.5-15, 0.5-20, 0.5-25, 0.5-30, 0.5-40, 0.5-50, 0.5-60, 0.5-70, 0.5-80, 0.5-90, 0.5-100, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1-5.5, 1-6, 1-8, 1-10, 1-15, 1-20, 1-25, 1-30, 1-40, 1-50, 1-60, 1-70, 1-80, 1-90, 1-100, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 1.5-5.5, 1.5-6, 1.5-8, 1.5-10, 1.5-15, 1.5-20, 1.5-25, 1.5-30, 1.5-40, 1.5-50, 1.5-60, 1.5-70, 1.5-80, 1.5-90, 1.5-100, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2-5.5, 2-6, 2-8, 2-10, 2-15, 2-20, 2-25, 2-30, 2-40, 2-50, 2-60, 2-70, 2-80, 2-90, 2-100, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 2.5-5.5, 2.5-6, 2.5-8, 2.5-10, 2.5-15, 2.5-20, 2.5-25, 2.5-30, 2.5-40, 2.5-50, 2.5-60, 2.5-70, 2.5-80, 2.5-90, 2.5-100, 3-3.5, 3-4, 3-4.5, 3-5, 3-5.5, 3-6, 3-8, 3-10, 3-15, 3-20, 3-25, 3-30, 3-40, 3-50, 3-60, 3-70, 3-80, 3-90, 3-100, 3.5-4, 3.5-4.5, 3.5-5, 3.5-5.5, 3.5-6, 3.5-8, 3.5-10, 3.5-15, 3.5-3.20, 3.5-3.25, 3.5-3.30, 3.5-40, 3.5-50, 3.5-60, 3.5-70, 3.5-80, 3.5-90, 3.5-100, 4-4.5, 4-5, 4-5.5, 4-6, 4-8, 4-10, 4-15, 4-20, 4-25, 4-30, 4-40, 4-50, 4-60, 4-70, 4-80, 4-90, 4-100, 4.5-5, 4.5-5.5, 4.5-6, 4.5-8, 4.5-10, 4.5-15, 4.5-20, 4.5-25, 4.5-30, 4.5-4.50, 4.5-50, 4.5-60, 4.5-70, 4.5-80, 4.5-90, 4.5-100, 5-5.5, 5-6, 5-8, 5-10, 5-15, 5-20, 5-25, 5-30, 5-40, 5-50, 5-60, 5-70, 5-80, 5-90, 5-100, 5.5-6, 5.5-8, 5.5-10, 5.5-15, 5.5-20, 5.5-25, 5.5-30, 5.5-40, 5.5-50, 5.5-60, 5.5-70, 5.5-80, 5.5-90, 5.5-100, 6-8, 6-10, 6-15, 6-20, 6-25, 6-30, 6-40, 6-50, 6-60, 6-70, 6-80, 6-90, 6-100, 8-10, 8-15, 8-20, 8-25, 8-30, 8-40, 8-50, 8-60, 8-70, 8-80, 8-90, 8-100, 10-15, 10-20, 10-25, 10-30, 10-40, 10-50, 10-60, 10-70, 10-80, 10-90, 10-100, 15-20, 15-25, 15-30, 15-40, 15-50, 15-60, 15-70, 15-80, 15-90, 15-100, 20-25, 20-30, 20-40, 20-50, 20-60, 20-70, 20-80, 20-90, 20-100, 25-30, 25-40, 25-50, 25-60, 25-70, 25-80, 25-90, 25-100, 30-40, 30-50, 30-60, 30-70, 30-80, 30-90, 30-100, 40-50, 40-60, 40-70, 40-80, 40-90, 40-100, 50-60, 50-70, 50-80, 50-90, 50-100, 60-70, 60-80, 60-90, 60-100, 70-80, 70-90, 70-100, 80-90, 80-100, or 90-100 msec. In some cases, the maximum change in QRS interval duration (ΔQRS) following the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 1 to about 10 msec. In some cases, the maximum change in QRS interval duration (ΔQRS) following the antiarrhythmic pharmaceutical agent administered via inhalation can be from about 5 to about 20 msec. In some cases, the ΔQRS can be measured in a human PK/ PD study. In the present disclosure, the term "ΔQRS", if not referred to with reference to time post-administration

of the antiarrhythmic agent, can be used interchangeably with the term "maximum ΔQRS", e.g. meaning the maximum change in QRS following administration of the antiarrhythmic agent as provided herein. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0229] In some cases, the time point at which the QRS interval is measured following the antiarrhythmic pharmaceutical agent administration via inhalation to determine the ΔQRS relative to pre-dose can be from about 0.1 minute to about 450 minutes, such as from about 0.1-1, 0.1-3, 0.1-5, 0.1-10, 0.1-15, 0.1-30, 0.1-45, 0.1-60, 0.1-90, 0.1-120, 0.1-150, 0.1-180, 0.1-210, 0.1-240, 0.1-270, 0.1-300, 0.1-330, 0.1-360, 0.1-390, 0.1-410, 0.1-450, 1-3, 1-5, 1-10, 1-15, 1-30, 1-45, 1-60, 1-90, 1-120, 1-150, 1-180, 1-210, 1-240, 1-270, 1-300, 1-330, 1-360, 1-390, 1-410, 1-450, 3-5, 3-10, 3-15, 3-30, 3-45, 3-60, 3-90, 3-120, 3-150, 3-180, 3-210, 3-240, 3-270, 3-300, 3-330, 3-360, 3-390, 3-410, 3-450, 5-10, 5-15, 5-30, 5-45, 5-60, 5-90, 5-120, 5-150, 5-180, 5-210, 5-240, 5-270, 5-300, 5-330, 5-360, 5-390, 5-410, 5-450, 10-15, 10-30, 10-45, 10-60, 10-90, 10-120, 10-150, 10-180, 10-210, 10-240, 10-270, 10-300, 10-330, 10-360, 10-390, 10-410, 10-450, 15-30, 15-45, 15-60, 15-90, 15-120, 15-150, 15-180, 15-210, 15-240, 15-270, 15-300, 15-330, 15-360, 15-390, 15-410, 15-450, 30-45, 30-60, 30-90, 30-120, 30-150, 30-180, 30-210, 30-240, 30-270, 30-300, 30-330, 30-360, 30-390, 30-410, 30-450, 45-60, 45-90, 45-120, 45-150, 45-180, 45-210, 45-240, 45-270, 45-300, 45-330, 45-360, 45-390, 45-410, 45-450, 60-90, 60-120, 60-150, 60-180, 60-210, 60-240, 60-270, 60-300, 60-330, 60-360, 60-390, 60-410, 60-450, 90-120, 90-150, 90-180, 90-210, 90-240, 90-270, 90-300, 90-330, 90-360, 90-390, 90-410, 90-450, 120-150, 120-180, 120-210, 120-240, 120-270, 120-300, 120-330, 120-360, 120-390, 120-410, 120-450, 150-180, 150-210, 150-240, 150-270, 150-300, 150-330, 150-360, 150-390, 150-410, 150-450, 180-210, 180-240, 180-270, 180-300, 180-330, 180-360, 180-390, 180-410, 180-450, 210-240, 210-270, 210-300, 210-330, 210-360, 210-390, 210-410, 210-450, 240-270, 240-300, 240-330, 240-360, 240-390, 240-410, 240-450, 270-300, 270-330, 270-360, 270-390, 270-410, 270-450, 300-330, 300-360, 300-390, 300-410, 300-450, 330-360, 330-390, 330-410, 330-450, 360-390, 360-410, 360-450, 390-410, 390-450, or 410-450 min.

[0230] The antiarrhythmic activity of pharmaceutical agent can be correlated with QRS interval duration. In some examples, the antiarrhythmic pharmaceutical agent administered via inhalation can have higher antiarrhythmic activity as compared to the antiarrhythmic pharmaceutical agent administered by intravenous delivery (e.g., intravenous infusion). In some cases, such a higher antiarrhythmic activity is reflected by a higher ratio of maximum ΔQRS to

C_{max}. For example, given the same C_{max}, e.g., peak plasma concentration of the antiarrhythmic pharmaceutic agent, inhalation delivery of the antiarrhythmic agent as provided herein can have a higher maximum ΔQRS as compared to intravenous delivery of the same agent. In some cases, the comparison may not be made between corresponding doses via the two different administration routes, for example, inhalation of a first dose of the agent can have a first C_{max} (C_{max1}) and a first maximum ΔQRS (ΔQRS_{max1}), and intravenous administration of a second dose of the agent can have a second C_{max} (C_{max2}) and a second maximum ΔQRS (ΔQRS_{max2}). In some cases, C_{max1} and C_{max2} can be similar. In other case, C_{max1} and C_{max2} can be dissimilar. In some examples of the present disclosure, the ratio of ΔQRS_{max1} versus C_{max1} can be higher than ΔQRS_{max2} versus C_{max2}, i.e., $\Delta QRS_{max1}/C_{max1} > \Delta QRS_{max2}/C_{max2}$. In some cases, $\Delta QRS_{max1}/C_{max1}$ is at least 1.1 folds, at least 1.2 folds, at least 1.3 folds, at least 1.4 folds, at least 1.5 folds, at least 1.6 folds, at least 1.7 folds, at least 1.8 folds, at least 1.9 folds, at least 2.0 folds, at least 2.1 folds, at least 2.2 folds, at least 2.3 folds, at least 2.4 folds, at least 2.5 folds, at least 2.6 folds, at least 2.7 folds, at least 2.8 folds, at least 2.9 folds, at least 3.0 folds, at least 3.1 folds, at least 3.2 folds, at least 3.3 folds, at least 3.4 folds, at least 3.5 folds, at least 3.6 folds, at least 3.7 folds, at least 3.8folds, at least 3.9 folds, at least 4.0 folds, at least 4.2 folds, at least 4.4 folds, at least 4.6 folds, at least 4.8 folds, at least 5.0 folds, at least 5.5 folds, at least 6 folds, at least 7 folds, at least 8 folds, at least 9 folds, at least 10 folds, at least 12 folds, at least 15 folds, at least 20 folds, at least 25 folds, or at least 50 folds greater than $\Delta QRS_{max2}/C_{max2}$. In some cases, $\Delta QRS_{max1}/C_{max1}$ is at least 2 folds greater than $\Delta QRS_{max2}/C_{max2}$. In one or more embodiments antiarrhythmic pharmaceutical agent is a class I, class II, class III, or class IV antiarrhythmic. In some embodiments, the antiarrhythmic pharmaceutical agent is a class Ic, antiarrhythmic. In other embodiments, the antiarrhythmic pharmaceutical agent is flecainide or a pharmaceutically acceptable salt thereof.

[0231] In some cases, the compositions and methods provided herein confer a reduced negative inotropic burden to the subject receiving inhalational delivery of the antiarrhythmic pharmaceutical agent, *e.g.*, flecainide, as compared to receiving delivery of a corresponding dose of the same agent via a different route (*e.g.*, oral or intravenous delivery). Certain antiarrhythmic drugs can have negative inotropic effect, which can limit their use for acute cardioversion of new-onset paroxysmal atrial fibrillation (AF). For instance, intravenous delivery of flecainide can exert negative inotropic burden to the subject's heart, which can be measured by left ventricular (LV) contractility. In some cases, the negative inotropic burden can be measured by the area under the curve (AUC) of a curve depicting the magnitude of LV contractility (*e.g.*, measured by dP/dt max) and time that it remain below baseline (*e.g.*, baseline level before drug

administration or at rest). In some embodiments, the negative inotropic burden of inhalational delivery of a therapeutically effective dose of antiarrhythmic pharmaceutical agent according to the methods described herein is lower than that of a corresponding therapeutically effective dose of the same agent delivered via a different route (*e.g.*, oral or intravenous delivery). For instance, in such embodiments, the negative inotropic burden of inhalational delivery of a therapeutically effective dose of antiarrhythmic pharmaceutical agent according to the methods described herein is at most 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of that of a corresponding therapeutically effective dose of the same agent delivered via a different route (*e.g.*, oral or intravenous delivery). In some embodiments, the negative inotropic burden of inhalational delivery of a therapeutically effective dose of antiarrhythmic pharmaceutical agent according to the methods described herein is about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of that of a corresponding therapeutically effective dose of the same agent delivered via a different route (*e.g.*, oral or intravenous delivery). the negative inotropic burden of inhalational delivery of a therapeutically effective dose of antiarrhythmic pharmaceutical agent according to the methods described herein is about 30% of that of a corresponding therapeutically effective dose of the same agent delivered via a different route (*e.g.*, oral or intravenous delivery). In such embodiments, the corresponding therapeutically effective dose of the antiarrhythmic pharmaceutical agent delivered via the other route can have a similar conversion rate (a percentage of number of effective conversion of arrhythmia to sinus rhythm), *e.g.*, with a variation of less than 20% or 10%, as compared to the therapeutically effective inhalational dose of the same agent.

Indications and Subjects

[0232] Examples of cardiac arrhythmias the methods, compositions, and kits provided herein can treat include, but are not limited to, tachycardia, supraventricular tachycardia (SVT), paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (AF), paroxysmal atrial fibrillation (PAF), persistent atrial fibrillation, permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, and lone atrial fibrillation. In some cases, the methods, compositions, and kits provided herein find use in treating a subject suffering from atrial arrhythmia, *e.g.*, atrial fibrillation.

[0233] Thus, the pharmaceutical compositions according to some examples of the present disclosure can be used to treat and/or provide prophylaxis for a broad range of patients. A suitable patient for, receiving treatment and/or prophylaxis as described herein is any mammalian patient in need thereof, preferably such mammal is a human. Examples of subjects include, but are not limited to, pediatric patients, adult patients, and geriatric patients. In some cases, the composition is intended only as a treatment for rapid resolution of symptoms and

restoration of normal sinus rhythm, and is not taken as a preventative, e.g., when the patient is well, there is no need for drug--this can increase the benefit-risk ratio of the therapy and overall safety due to the sporadic or intermittent dosing, and the focus on reducing disabling symptoms and restoring sinus rhythm only when needed.

[0234] The dosage necessary and the frequency of dosing of the antiarrhythmic pharmaceutical agent depend on the composition and concentration of the antiarrhythmic pharmaceutical agent within the composition. In some cases, the dose is less than about 10%, 20 %, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% of its normal intravenous dose. In some cases, the dose is about 5% to about 10%, is about 10% to about 20%, is about 20% to about 30%, is about 30% to about 40%, is about 50% to about 60%, is about 60% to about 70%, is about 70% to about 80%, is about 80% to about 90%, or is about 90% to about 95% of the intravenous dose.

[0235] Pharmaceutical compositions disclosed herein can be more effective in subjects that include or lack certain physiological or demographic factors, such as, for example, age at clinical presentation, certain hemodynamic criteria, electrophysiological features, and prior treatments. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure suffers from an atrial fibrillation with an onset that occurred within 48 hours prior to the treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure suffers from an atrial fibrillation with an onset that occurred from 1 hour to 48 hours prior to the treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure suffers from recurrent atrial fibrillation. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has undergone cardiac ablation no less than 3 months prior to the treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has an ongoing prescription for an oral antiarrhythmic medication for atrial fibrillation. In some embodiments, the oral antiarrhythmic medication is flecainide, or a pharmaceutically acceptable salt thereof.

[0236] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is over 17 years in age. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is no more than 85 years in age. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is from 18 years old to 85 years old.

[0237] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a systolic blood pressure that is below 180 mmHg, below 175 mmHg, below 170 mmHg, below 165 mmHg, below 160 mmHg, below 155 mmHg, or below 150 mmHg at the time of the treating. In some cases, when referring to a physiological measurement of the subject, for instance, blood pressure, *e.g.*, systolic blood pressure or diastolic blood pressure, or

heart rate, *e.g.*, ventricular rate, the term "at the time of treating" means the measurement is taken from 1 min to 6 hr prior to the treating, for instance, when measured 1 min to 10 min, 1 min to 30 min, 1 min to 60 min, 1 min to 90 min, 1 min to 2 hr, 1 min to 3 hr, 1 min to 4 hr, 1 min to 5 hr, 10 min to 30 min, 10 min to 60 min, 30 min to 60 min, 30 min to 90 min, 30 min to 2 hr, 1 hr to 2 hr, or 2 hr to 3 hr prior to the treating. In some cases, the physiological measurement, for instance, the measurement of the systolic blood pressure or the ventricular rate of the subject provides a basis for an informed decision as to whether or not the subject is to be treated with the subject pharmaceutical composition and method. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a systolic blood pressure that is greater than 70 mmHg, greater than 75 mmHg, greater than 80 mmHg, greater than 85 mmHg, greater than 90 mmHg, greater than 95 mmHg, greater than 100 mmHg, greater than 105 mmHg, greater than 110 mmHg, greater than 115 mmHg, or greater than 120 mmHg at the time of the treating.

[0238] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a systolic blood pressure that is from about 60 mmHg to about 180 mmHg, from about 65 mmHg to about 180 mmHg, from about 70 mmHg to about 180 mmHg, from about 75 mmHg to about 180 mmHg, from about 80 mmHg to about 180 mmHg, from about 85 mmHg to about 180 mmHg, from about 90 mmHg to about 180 mmHg, from about 95 mmHg to about 180 mmHg, from about 100 mmHg to about 180 mmHg, from about 105 mmHg to about 180 mmHg, from about 110 mmHg to about 180 mmHg, from about 115 mmHg to about 180 mmHg, from about 120 mmHg to about 180 mmHg, from about 70 mmHg to about 175 mmHg, from about 70 mmHg to about 170 mmHg, from about 70 mmHg to about 165 mmHg, from about 70 mmHg to about 160 mmHg, from about 70 mmHg to about 155 mmHg, from about 70 mmHg to about 150 mmHg, from about 80 mmHg to about 165 mmHg, from about 90 mmHg to about 165 mmHg, from about 100 mmHg to about 165 mmHg, from about 70 mmHg to about 160 mmHg, from about 70 mmHg to about 160 mmHg, from about 75 mmHg to about 160 mmHg, from about 80 mmHg to about 160 mmHg, from about 85 mmHg to about 160 mmHg, from about 90 mmHg to about 160 mmHg, from about 95 mmHg to about 160 mmHg, from about 100 mmHg to about 160 mmHg, from about 70 mmHg to about 155 mmHg, from about 75 mmHg to about 155 mmHg, or from about 80 mmHg to about 155 mmHg at the time of treating.

[0239] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a ventricular rate that is at least about 50 BPM, at least about 55 BPM, at least about 60 BPM, at least about 65 BPM, at least about 70 BPM, at least about 75 BPM, at least about 80 BPM, at least about 85 BPM, at least about 90 BPM, at least about 95 BPM, or at least

about 100 BPM at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a ventricular rate that is no greater than about 200 BPM, no greater than about 190 BPM, no greater than about 180 BPM, no greater than about 175 BPM, no greater than about 170 BPM, no greater than about 165 BPM, no greater than about 160 BPM, no greater than about 155 BPM, no greater than about 150 BPM, no greater than about 145 BPM, or no greater than about 140 BPM at the time of treating.

[0240] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has a ventricular rate that is from about 50 BPM to about 200 BPM, 50 BPM to about 180 BPM, from about 55 BPM to about 180 BPM, from about 60 BPM to about 180 BPM, from about 65 BPM to about 180 BPM, from about 70 BPM to about 180 BPM, from about 75 BPM to about 180 BPM, from about 80 BPM to about 180 BPM, about 85 BPM to about 180 BPM, about 95 BPM to about 180 BPM, about 100 BPM to about 180 BPM, from about 50 BPM to about 175 BPM, from about 50 BPM to about 170 BPM, from about 50 BPM to about 165 BPM, from about 50 BPM to about 160 BPM, from about 50 BPM to about 155 BPM, from about 70 BPM to about 175 BPM, about 70 BPM to about 170 BPM, about 70 BPM to about 165 BPM, about 70 BPM to about 160 BPM, about 70 BPM to about 155 BPM, about 75 BPM to about 180 BPM, about 75 BPM to about 175 BPM, about 75 BPM to about 170 BPM, about 75 BPM to about 165 BPM, about 75 BPM to about 160 BPM, about 75 BPM to about 155 BPM, about 80 BPM to about 175 BPM, about 80 BPM to about 170 BPM, about 80 BPM to about 165 BPM, about 80 BPM to about 160 BPM, about 80 BPM to about 155 BPM, about 80 BPM to about 150BPM, about 80 BPM to about 145 BPM, about 85 BPM to about 155 BPM, about 90 BPM to about 155 BPM, about 95 BPM to about 155 BPM, or about 100 BPM to about 155 BPM at the time of treating.

[0241] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not been treated with antiarrhythmic drugs or electrical cardioversion since onset of an episode of atrial arrhythmia for which the pharmaceutical composition is being administered. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit acute decompensated heart failure at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have heart failure with reduced ejection fraction or a history thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have myocardial ischemia or a history thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have myocardial infarction or a history thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not

exhibited myocardial infarction (MI) within 3 months prior to administration of the pharmaceutical composition. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit uncorrected severe aortic or mitral stenosis at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit hypertrophic cardiomyopathy with outflow tract obstruction at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have persistent atrial fibrillation or a history thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit atrial flutter at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not exhibited an episode of atrial flutter within 6 months prior to the treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit abnormal left ventricular ejection fraction at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit heart failure that is class 2 or greater as according to New York Heart Association Functional Classification at the time of treating.

[0242] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is hemodynamically stable, has a systolic blood pressure that is greater than about 90 mmHg, has ventricular rate from about 70 BPM to about 170 BPM at the time of treating, and does not have a condition or a history of a condition that is: myocardial infarction, myocardial ischemia, atrial stenosis, hypertrophic cardiomyopathy, and heart failure with reduced ejection fraction.

[0243] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have Long QT syndrome, Conduction disease (e.g. second- or third- degree heart block, bundle branch block), Sick sinus syndrome, Brugada Syndrome, Torsades de pointed (TdP), or a histories thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit at the time of treating an ECG-related feature that is: a QTc interval greater than 480 msec (estimated by the Fridericia's formula); a QRS duration greater than 105 ms; monomorphic or polymorphic ventricular tachycardias that are either sustained or not sustained; and excessive premature ventricular contractions greater than 20 multi-focal PVC's per hour (ventricular extrasystoles); or a predominantly paced heart rhythm.

[0244] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit severe renal impairment, wherein a eGFR of the subject is less than 30 mL/min/1.73 m2 at the time of treating. In some embodiments, a subject treated with a

pharmaceutical composition of the disclosure is not on dialysis at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit abnormal liver function at the time of treating. In some embodiments, the abnormal liver function is hepatic disease or biochemical evidence of significant liver derangement. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit uncorrected hypokalemia at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit a serum potassium less than 3.6 mEq/L at the time of treating.

[0245] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit an established pulmonary disease in need of inhalation medication at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not have a hypersensitivity to flecainide acetate or any of its active metabolites, or a history thereof. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is not concomitantly administered a systemic drug that is an inhibitor of CYP 2D6. In some embodiments, the inhibitor of CYP 2D6 is an antidepressant, a neuroleptic, or an antihistamine. In some embodiments, the inhibitor of CYP 2D6 is propranolol or ritonavir. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is not concomitantly administered a systemic drug that is a CYP 2D6 inducer. In some embodiments, the CYP 2D6 inducer is phenytoin, phenobarbital, or carbamazepine.

[0246] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not been treated with a Class I or a Class II antiarrhythmic drug within a week prior to administration of the pharmaceutical composition. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure with an ongoing episode of atrial fibrillation has not been treated with a Class I or a Class III antiarrhythmic drug since onset of the ongoing episode. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure is administered no more than 320 mg flecainide or a pharmaceutically acceptable salt thereof per day from any source. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure with an ongoing episode of atrial fibrillation has not been treated with electrical cardioversion since onset of the ongoing episode. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not been treated with amiodarone within 12 weeks prior to administration of the pharmaceutical composition. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not been considered high risk for stroke based on screening coagulation panel. In

some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit a CHA2DS2-VASc score greater than 2.

[0247] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit a congenital heart disease at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit a history of refractory atrial fibrillation that has been pharmacologically or electrically cardioverted. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit atrial fibrillation that is secondary to electrolyte imbalance, thyroid disease, or a non-cardiovascular cause at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit syncope at the time of treating.

[0248] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit any serious or life threatening medical condition other than cardiac arrhythmia at the time of treating. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit an acute pathogenic infection at the time of treating.

[0249] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure has not exhibited a drug or alcohol dependence within 12 months prior to administration of the pharmaceutical composition. In some embodiments, a subject treated with a pharmaceutical composition of the disclosure does not exhibit a body mass index greater than 40 Kg/m^2 at the time of treating.

[0250] In some embodiments, a subject treated with a pharmaceutical composition of the disclosure:

(i) suffers from an atrial fibrillation with an onset that occurred from 1 hour to 48 hours prior to the treating;

(ii) has undergone cardiac ablation no less than 3 months prior to the treating, has an ongoing prescription for oral flecainide or a pharmaceutically acceptable salt thereof, or suffers from recurrent atrial fibrillation;

(iii) is from 18 years old to 85 years old;

(iv) has a systolic blood pressure that is from about 100 mmHg to about 160 mmHg at the time of treating; and

(v) has a ventricular rate that is from about 80 BPM to about 155 BPM at the time of treating,

wherein the subject does not exhibit:

(a) abnormal left ventricular ejection fraction within 6 months prior to the treating;

(b) heart failure that is class 2 or greater as classified by New York Heart Association Functional Classification within 6 months prior to the treating;

(c) myocardial infarction or a history thereof;

(d) hemodynamic or cardiac instability at the time of treating; and

(e) an episode of atrial flutter within 6 months prior to the treating,

wherein the subject has not undergone cardiac surgery for any of the conditions of (a)-(e) within 6 months prior to the treating.

NUMBERED PARAGRAPHS

[1] A pharmaceutical composition, comprising: a therapeutically effective amount of a salt of flecainide, wherein said pharmaceutical composition is in the form of a liquid solution that has said salt of flecainide at a concentration above 60 mg/mL.

[2] The pharmaceutical composition of paragraph [1], further comprising a cyclodextrin.

[3] The pharmaceutical composition of paragraph [1] or [2], wherein a pH of said solution is above 5.5 at room temperature.

[4] The pharmaceutical composition of paragraph [1], wherein the pharmaceutical composition further comprises a cyclodextrin, and wherein a pH of said solution is above 5.5 at room temperature.

[5] The pharmaceutical composition of paragraph [2] or [4], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins.

[6] The pharmaceutical composition of paragraph [2] or [4], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins.

[7] The pharmaceutical composition of paragraph [2] or [4], wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

[8] The pharmaceutical composition of paragraph [2] or [4], wherein a concentration of said cyclodextrin in said pharmaceutical composition is about 1% (w/v) to about 80% (w/v) of said solution.

[9] The pharmaceutical composition of paragraph [2], [4], or [8], wherein said concentration of said cyclodextrin is from about 15% (w/v) to about 25% (w/v) of said solution.

[10] The pharmaceutical composition of paragraph [2], [4], or [8], wherein said concentration of said cyclodextrin is from about 10% (w/v) to about 30% (w/v) of said solution.

[11] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is at least about 5% (w/v) of said solution.

[12] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is at least about 10% (w/v) of said solution.

[13] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is about 20% (w/v) of said solution.

[14] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is at most about 20% (w/v) of said solution.

[15] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is about 25% (w/v) of said solution.

[16] The pharmaceutical composition of paragraph [8], wherein said concentration of said cyclodextrin is at most about 25% (w/v) of said solution.

[17] The pharmaceutical composition of any one of paragraphs [1]-[16], wherein said concentration of said salt of flecainide is at most about 200 mg/mL.

[18] The pharmaceutical composition of any one of paragraphs [1]-[17], wherein said concentration of said salt of flecainide is about 65 mg/mL to about 130 mg/mL.

[19] The pharmaceutical composition of any one of paragraphs [1]-[18], wherein said concentration of said salt of flecainide is about 65 mg/mL to about 95 mg/mL.

[20] The pharmaceutical composition of any one of paragraphs [1]-[19], wherein said concentration of said salt of flecainide is about 70 mg/mL to about 115 mg/mL.

[21] The pharmaceutical composition of any one of paragraphs [1]-[20], wherein said concentration of said salt of flecainide is about 100 mg/mL.

[22] The pharmaceutical composition of any one of paragraphs [1]-[21], wherein said concentration of said salt of flecainide is about 75 mg/mL.

[23] The pharmaceutical composition of any one of paragraphs [1]-[22], wherein said salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate.

[24] The pharmaceutical composition of any one of paragraphs [1]-[23], wherein said salt of flecainide comprises flecainide acetate.

[25] The pharmaceutical composition of any one of paragraphs [1]-[24], wherein said salt of flecainide comprises flecainide hydrochloride.

[26] The pharmaceutical composition of any one of paragraphs [1]-[25], further comprising an acid.

[27] The pharmaceutical composition of paragraph [26], wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[28] The pharmaceutical composition of paragraph [26], wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[29] The pharmaceutical composition of any one of paragraphs [26]-[28], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 200 mM.

[30] The pharmaceutical composition of any one of paragraphs [26]-[28], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 50 mM.

[31] The pharmaceutical composition of any one of paragraphs [26]-[28], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 10 mM.

[32] The pharmaceutical composition of paragraph [29], wherein said concentration of said acid is at most about 50 mM.

[33] The pharmaceutical composition of paragraph [29], wherein said concentration of said acid is about 20 mM.

[34] The pharmaceutical composition of paragraph [29], wherein said concentration of said acid is about 5 mM.

[35] The pharmaceutical composition of any one of paragraphs [29]-[32], wherein said acid comprises acetic acid.

[36] The pharmaceutical composition of paragraph [35], wherein said concentration of acetic acid is about 5 mM.

[37] The pharmaceutical composition of any one of paragraphs [29]-[32], wherein said acid comprises citric acid.

[38] The pharmaceutical composition of paragraph [37], wherein said concentration of citric acid is about 5 mM.

[39] The pharmaceutical composition of paragraph [26], wherein said acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[40] The pharmaceutical composition of paragraph [26], wherein said acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[41] The pharmaceutical composition of paragraph [26], wherein said acid comprises hydrochloric acid.

[42] The pharmaceutical composition of any one of paragraphs [26]-[36], wherein said salt of flecainide comprises flecainide acetate, and wherein said acid comprises acetic acid.

[43] The pharmaceutical composition of any one of paragraphs [3]-[42], wherein said pH of said solution is at most about 6.5.

[44] The pharmaceutical composition of any one of paragraphs [3]-[42], wherein said pH of said solution is from about 5.5 to about 6.5.

[45] The pharmaceutical composition of any one of paragraphs [3]-[42], wherein said pH of said solution is about 5.9.

[46] The pharmaceutical composition of any one of paragraphs [1]-[45], further comprising a sweetener.

[47] The pharmaceutical composition of paragraph [46], wherein said sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof.

[48] The pharmaceutical composition of paragraph [46], wherein said sweetener comprises saccharin.

[49] The pharmaceutical composition of paragraph [46], wherein said sweetener comprises a salt of saccharin.

[50] The pharmaceutical composition of paragraph [46], wherein said sweetener comprises saccharin sodium.

[51] The pharmaceutical composition of any one of paragraphs [46]-[50], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v).

[52] The pharmaceutical composition of any one of paragraphs [46]-[50], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v).

[53] The pharmaceutical composition of any one of paragraphs [46]-[50], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v).

[54] The pharmaceutical composition of any one of paragraphs [46]-[50], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

[55] The pharmaceutical composition of any one of paragraphs [1]-[54], wherein said pharmaceutical composition is formulated for administration via inhalation.

[56] The pharmaceutical composition of any one of paragraphs [1]-[55], wherein said pharmaceutical composition is a nebulized solution that comprises nebulized droplets having a mass median aerodynamic diameter of less than 10 μm.

[57] A unit dose of said pharmaceutical composition of any one of paragraphs [1]-[56], comprising about 50 mg to about 350 mg of said salt of flecainide.

[58] The unit dose of paragraph [57], comprising about 60 mg to about 150 mg of said salt of flecainide.

[59] The unit dose of paragraph [57], comprising about 75 mg to about 125 mg of said salt of flecainide.

[60] The unit dose of paragraph [57], comprising about 250 mg to about 350 mg of said salt of flecainide.

[61] The unit dose of paragraph [57], comprising about 100 mg to about 250 mg of said salt of flecainide.

[62] The unit dose of paragraph [57], comprising about 90 mg of said salt of flecainide.

[63] The unit dose of paragraph [57], comprising about 120 mg of said salt of flecainide.

[64] The unit dose of paragraph [57], comprising about 200 mg of said salt of flecainide.

[65] A kit, comprising: said pharmaceutical composition or said unit dose of any one of paragraphs [1]-[64], and instructions for use of said pharmaceutical composition for treatment of a heart condition.

[66] The kit of paragraph [65], wherein said heart condition comprises atrial fibrillation.

[67] The kit of paragraph [66], wherein said atrial fibrillation comprises tachycardia.

[68] The kit of paragraph [66], wherein said atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial

fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation.

[69] The kit of any one of paragraphs [65] to [68], further comprising a container containing said pharmaceutical composition.

[70] The kit of paragraph [69], wherein said container is selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.

[71] A kit, comprising:

(1) a pharmaceutical composition that comprises:

(a) a salt of flecainide,

(b) a cyclodextrin, and

(c) an acid;

(2) a receptacle containing said pharmaceutical composition; and

(3) instructions for use of a nebulizer to inhalationally administer a dose of said pharmaceutical composition in aerosol to a subject, wherein said dose contains from about 50 mg to about 250 mg of said salt of flecainide, and said aerosol of said pharmaceutical composition has droplets that have a mass median aerodynamic diameter of less than 10 μm; and

wherein said pharmaceutical composition is in the form of a liquid solution that has:

(i) said salt of flecainide at a concentration of from about 65 mg/mL to about 95 mg/mL,

(ii) said cyclodextrin at a concentration of from about 10% (w/v) to about 30% (w/v) of said solution; and

(iii) a pH of from about 5.5 to about 6.5 when said pH is measured at room temperature.

[72] The kit of paragraph [71], wherein said concentration of said salt of flecainide is from about 70 mg/mL to about 80 mg/mL.

[73] The kit of paragraph [71] or [72], wherein said concentration of said salt of flecainide is about 75 mg/mL.

[74] The kit of any one of paragraphs [71]-[73], wherein said salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate.

[75] The kit of any one of paragraphs [71]-[73], wherein said salt of flecainide comprises flecainide acetate.

[76] The kit of any one of paragraphs [71]-[75], wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, ascorbic acid, lactic acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[77] The kit of any one of paragraphs [71]-[75], wherein said acid comprises acetic acid.

[78] The kit of any one of paragraphs [71]-[75], wherein said acid comprises citric acid.

[79] The kit of any one of paragraphs [71]-[78], wherein a concentration of said acid in said pharmaceutical composition is from about 2 mM to about 10 mM.

[80] The kit of any one of paragraphs [71]-[78], wherein said concentration of said acid is about 5 mM.

[81] The kit of any one of paragraphs [71]-[80], wherein said pH of said solution is about 5.9 when measured at room temperature.

[82] The kit of any one of paragraphs [71]-[81], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins.

[83] The kit of any one of paragraphs [71]-[81], wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

[84] The kit of any one of paragraphs [71]-[83], wherein said concentration of said cyclodextrin is from about 15% (w/v) to about 25% (w/v) of said solution.

[85] The kit of any one of paragraphs [71]-[83], wherein said concentration of said cyclodextrin is about 20% (w/v) of said solution.

[86] The kit of any one of paragraphs [71]-[85], wherein said pharmaceutical composition further comprises an artificial sweetener.

[87] The kit of any one of paragraphs [71]-[86], wherein said dose contains from about 150 mg to about 250 mg of said salt of flecainide.

[88] The kit of any one of paragraphs [71]-[86], wherein said dose contains about 200 mg of said salt of flecainide.

[89] The kit of any one of paragraphs [71]-[88], further comprising a nebulizer selected from the group consisting of: a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer.

[90] The kit of any one of paragraphs [71]-[89], wherein said pharmaceutical composition is formulated for administration via a breath-actuated jet nebulizer, a vibrating mesh nebulizer, or a ultrasonic nebulizer.

[91] A system, comprising: said pharmaceutical composition of any one of paragraphs [1]-[70], and a nebulizer.

[92] The system of paragraph [91], wherein said pharmaceutical composition is formulated for administration via the nebulizer, wherein the nebulizer is selected from the group consisting of a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer.

[93] The system of paragraph [91], wherein said nebulizer selected from the group consisting of: a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer.

[94] The system of any one of paragraphs [91]-[93], further comprising instructions for use of said nebulizer and said pharmaceutical composition for treatment of a heart condition.

[95] The system of any one of paragraphs [91]-[93], further comprising instructions for use of said nebulizer and said pharmaceutical composition for treatment of atrial arrhythmia.

[96] The system of paragraph [95], wherein said atrial arrhythmia comprises tachycardia.

[97] The system of paragraph [95], wherein said atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation.

[98] The system of any one of paragraphs [91]-[97], wherein said nebulizer is configured to deliver said pharmaceutical composition as droplets having a mass median aerodynamic diameter of less than 10 μm.

[99] The system of any one of paragraphs [91]-[98], wherein said nebulizer is a breath-actuated nebulizer.

[100] The system of any one of paragraphs [91]-[98], wherein said nebulizer is a jet nebulizer.

[101] The system of any one of paragraphs [94]-[100], wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 60 mg to about 150 mg of said salt of flecainide.

[102] The system of any one of paragraphs [94]-[100], wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 75 mg to about 125 mg of said salt of flecainide.

[103] The system of any one of paragraphs [94]-[100], wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 90 mg of said salt of flecainide.

[104] The system of any one of paragraphs [94]-[100], wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 120 mg of said salt of flecainide.

[105] A system, comprising:

a pharmaceutical composition that comprises a salt of flecainide, a cyclodextrin, and an acid;

a nebulizer configured to deliver said pharmaceutical composition as droplets having a mass median aerodynamic diameter of less than 10 μm; and

instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains between about 50 mg and about 250 mg of said salt of flecainide,

wherein said pharmaceutical composition is in the form of a liquid solution that has (i) said salt of flecainide at a concentration of between 65 mg/mL and 100 mg/mL, (ii) said cyclodextrin at a concentration of between about 10% (w/v) and about 30% (w/v) of said solution; and (iii) a pH of between about 5.5 and about 6.5 at room temperature.

[106] A method of treating a subject suffering from a heart condition, comprising: administering to said subject via inhalation a pharmaceutical composition in the form of a liquid solution, wherein said pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein a concentration of said salt of flecainide in said pharmaceutical composition is above 60 mg/mL.

[107] The method of paragraph [106], wherein said pharmaceutical composition further comprises a cyclodextrin.

[108] The method of paragraph [106] or [107], wherein a pH of said solution is above 5.5 when said pH is measured at room temperature.

[109] A method of treating a human subject suffering from a heart condition, comprising administering to said subject via inhalation within about 10 min a pharmaceutical composition in the form of a liquid solution, wherein said pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein said administration results in a peak plasma concentration (Cmax) of said salt of flecainide in said subject that is at least 200 ng/mL.

[110] The method of paragraph [109], wherein a concentration of said salt of flecainide in said pharmaceutical composition is above 60 mg/mL of said solution.

[111] The method of paragraph [106], [109] or [110], wherein said pharmaceutical composition further comprises a cyclodextrin.

[112] The method of any one of paragraphs [106]-[108], or [111], wherein said administration of said pharmaceutical composition results in a peak plasma concentration (Cmax) of said salt of flecainide in said subject that is at least 200 ng/mL.

[113] The method of any one of paragraphs [106]-[112], wherein said administration of said pharmaceutical composition results in a peak plasma concentration (Cmax) of said salt of flecainide in said subject that is at least 250 ng/mL.

[114] The method of paragraph [113], wherein said Cmax is between about 250 ng/mL and about 1000 ng/mL.

[115] The method of paragraph [113], wherein said Cmax is between about 300 ng/mL and about 700 ng/mL.

[116] The method of paragraph [113], wherein said Cmax is between about 400 ng/mL and about 600 ng/mL.

[117] The method of any one of paragraphs [106]-[116], wherein said administration of said pharmaceutical composition is performed within about 10 min.

[118] The method of any one of paragraphs [106]-[116], wherein said administration of said pharmaceutical composition is performed within about 5 min.

[119] The method of any one of paragraphs [106]-[118], wherein said administration of said pharmaceutical composition is performed via one or two inhalations.

[120] The method of any one of paragraphs [106]-[118], wherein said administration of said pharmaceutical composition is performed via two inhalations that are separated by a break for from about 10 seconds to about 1 minute.

[121] The method of any one of paragraphs [106]-[120], wherein said administration is performed via a nebulizer.

[122] The method of paragraph [121], wherein said nebulizer is a breath-actuated nebulizer.

[123] The method of paragraph [121], wherein said nebulizer is a jet nebulizer.

[124] The method of paragraph [121], wherein said nebulizer is a vibrating mesh nebulizer.

[125] The method of paragraph [121], wherein said nebulizer is an ultrasonic nebulizer.

[126] The method of any one of paragraphs [106]-[123], wherein about 60 mg to about 150 mg of said salt of flecainide is administered to said subject via inhalation.

[127] The method of any one of paragraphs [106]-[123], wherein about 75 mg to about 125 mg of said salt of flecainide is administered to said subject via inhalation.

[128] The method of any one of paragraphs [106]-[125], wherein about 250 mg to about 350 mg of said salt of flecainide is administered to said subject via inhalation.

[129] The method of any one of paragraphs [106]-[125], wherein about 100 mg to about 250 mg of said salt of flecainide is administered to said subject via inhalation.

[130] The method of any one of paragraphs [106]-[123], wherein about 90 mg of said salt of flecainide is administered to said subject via inhalation.

[131] The method of any one of paragraphs [106]-[123], wherein about 120 mg of said salt of flecainide is administered to said subject via inhalation.

[132] The method of any one of paragraphs [106]-[125], wherein about 200 mg of said salt of flecainide is administered to said subject via inhalation.

[133] The method of any one of paragraphs [106]-[131], wherein said heart condition comprises atrial arrhythmia.

[134] The method of paragraph [133], wherein said atrial arrhythmia comprises tachycardia.

[135] The method of paragraph [133], wherein the atrial arrhythmia said atrial arrhythmia is selected from the group consisting of: supraventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, acute episodes in persistent and permanent atrial fibrillation, atrial flutter, paroxysmal atrial flutter, or lone atrial fibrillation.

[136] The method of any one of paragraphs [106]-[135], comprising aerosolizing said pharmaceutical composition by forming droplets having a mass median aerodynamic diameter of less than 10 μm.

[137] The method of any one of paragraphs [106]-[136], comprising acute treatment after detection of said atrial arrhythmia.

[138] The method of any one of paragraphs [106]-[137], wherein said subject has normal sinus rhythm within 10 minutes after said administering.

[139] The method of any one of paragraphs [106]-[137], wherein said subject has normal sinus rhythm within 8 minutes after said administering.

[140] The method of any one of paragraphs [106]-[137], wherein said subject has normal sinus rhythm within 5 minutes after said administering.

[141] The method of any one of paragraphs [107]-[140], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins.

[142] The method of any one of paragraphs [107]-[140], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether- β -cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether- β -cyclodextrins, and sulfoalkylether-γ-cyclodextrins.

[143] The method of any one of paragraphs [107]-[140], wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

[144] The method of any one of paragraphs [107]-[143], wherein a concentration of said cyclodextrin in said pharmaceutical composition is about 1% (w/v) to about 80% (w/v) of said solution.

[145] The method of any one of paragraphs [107]-[143], wherein said concentration of said cyclodextrin is from about 15% (w/v) to about 25% (w/v) of said solution.

[146] The method of any one of paragraphs [107]-[143], wherein said concentration of said cyclodextrin is from about 10% (w/v) to about 30% (w/v) of said solution.

[147] The method of paragraph [144], wherein said concentration of said cyclodextrin is at least about 5% (w/v) of said solution.

[148] The method of paragraph [144], wherein said concentration of said cyclodextrin is at least about 10% (w/v) of said solution.

[149] The method of paragraph [144], wherein said concentration of said cyclodextrin is about 20% (w/v) of said solution.

[150] The method of paragraph [144], wherein said concentration of said cyclodextrin is at most about 20% (w/v) of said solution.

[151] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is at most about 200 mg/mL.

[152] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is about 65 mg/mL to about 130 mg/mL.

[153] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is about 65 mg/mL to about 95 mg/mL.

[154] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is about 70 mg/mL to about 115 mg/mL.

[155] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is about 100 mg/mL.

[156] The method of any one of paragraphs [106]-[150], wherein said concentration of said salt of flecainide is about 75 mg/mL.

[157] The method of any one of paragraphs [106]-[156], wherein said salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate.

[158] The method of any one of paragraphs [106]-[156], wherein said salt of flecainide comprises flecainide acetate.

[159] The method of any one of paragraphs [106]-[156], wherein said salt of flecainide comprises flecainide hydrochloride.

[160] The method of any one of paragraphs [106]-[159], wherein said pharmaceutical composition further comprises an acid.

[161] The method of paragraph [160], wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[162] The method of paragraph [160], wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[163] The method of any one of paragraphs [160]-[162], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 200 mM.

[164] The method of any one of paragraphs [160]-[162], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 50 mM.

[165] The method of any one of paragraphs [160]-[162], wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 10 mM.

[166] The method of paragraph [163], wherein said concentration of said acid is at most about 50 mM.

[167] The method of paragraph [163], wherein said concentration of said acid is about 20 mM.

[168] The method of paragraph [163], wherein said concentration of said acid is about 5 mM.

[169] The method of paragraph [163], wherein said acid comprises acetic acid.

[170] The method of paragraph [169], wherein said concentration of acetic acid is about 5 mM.

[171] The method of paragraph [163], wherein said acid comprises citric acid.

[172] The method of paragraph [169], wherein said concentration of citric acid is about 5 mM.

[173] The method of paragraph [160], wherein said acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[174] The method of paragraph [160], wherein said acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[175] The method of paragraph [160], wherein said acid comprises hydrochloric acid.

[176] The method of any one of paragraphs [160]-[170], wherein said salt of flecainide comprises flecainide acetate, and wherein said acid comprises acetic acid.

[177] The method of any one of paragraphs [108]-[176], wherein said pH of said solution is at most about 6.5.

[178] The method of any one of paragraphs [108]-[176], wherein said pH of said solution is from about 5.5 to about 6.5.

[179] The method of any one of paragraphs [108]-[176], wherein said pH of said solution is about 5.9.

[180] The method of any one of paragraphs [106]-[179], wherein said salt of flecainide comprises flecainide acetate.

[181] The method of any one of paragraphs [106]-[180], wherein said pharmaceutical composition further comprises a sweetener.

[182] The method of paragraph [181], wherein said artificial sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof.

[183] The method of paragraph [181], wherein said sweetener comprises saccharin.

[184] The method of paragraph [181], wherein said sweetener comprises a salt of saccharin.

[185] The method of paragraph [181], wherein said sweetener comprises saccharin sodium.

[186] The method of any one of paragraphs [181]-[185], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v).

[187] The method of any one of paragraphs [181]-[185], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v).

[188] The method of any one of paragraphs [181]-[185], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

[189] A method of treating a human subject suffering from a heart condition, said method comprising: administering to said subject via inhalation a pharmaceutical composition according to any one of paragraphs 1-[56].

[190] A method of treating a human subject suffering from a heart condition, said method comprising: administering to said subject via inhalation a unit dose according to any one of paragraphs [57]-[64].

[191] The method of any one of paragraphs [106]-[190], wherein said heart condition comprises atrial fibrillation.

[192] The method of paragraph [191], wherein said atrial fibrillation is recurrent atrial fibrillation.

[193] The method of paragraph [191], wherein said atrial fibrillation is paroxysmal atrial fibrillation.

[194] The method of any one of paragraphs [106]-[193], wherein said subject has a systolic blood pressure that is greater than about 90 mmHg at the time of treating.

[195] The method of any one of paragraphs [106]-[193], wherein said subject has a systolic blood pressure that is from about 100 mmHg to about 160 mmHg at the time of treating.

[196] The method of any one of paragraphs [106]-[195], wherein said subject has a ventricular rate that is no more than 170 BPM at the time of treating.

[197] The method of any one of paragraphs [106]-[195], wherein said subject has a ventricular rate that is from about 80 BPM to about 155 BPM at the time of treating.

[198] The method of any one of paragraphs [106]-[197], wherein said subject is no more than 85 years old.

[199] The method of any one of paragraphs [106]-[197], wherein said subject is from 18 years old to 85 years old.

[200] The method of any one of paragraphs [106]-[199], wherein said subject has undergone cardiac ablation no less than 3 months prior to said administering.

[201] The method of any one of paragraphs [106]-[200], wherein said subject has an ongoing prescription for oral flecainide or a pharmaceutically acceptable salt thereof.

[202] The method of any one of paragraphs [106]-[201], wherein said atrial fibrillation has an onset that occurred no more than about 48 hours prior to said administering.

[203] The method of any one of paragraphs [106]-[201], wherein said atrial fibrillation has an onset that occurred from about 1 hour to about 48 hours prior to the treating prior to said administering.

[204] The method of any one of paragraphs [106]-[203], wherein said subject does not exhibit a pathology comprising abnormal left ventricular ejection fraction within 6 months prior to said administering.

[205] The method of any one of paragraphs [106]-[204], wherein said subject does not exhibit a pathology comprising heart failure that is class 2 or greater as classified by New York Heart Association Functional Classification within 6 months prior to said administering.

[206] The method of any one of paragraphs [106]-[205], wherein said subject does not exhibit a pathology comprising myocardial infarction or a history of myocardial infarction.

[207] The method of any one of paragraphs [106]-[206], wherein said subject does not exhibit a pathology comprising hemodynamic instability or cardiac instability.

[208] The method of any one of paragraphs [106]-[207], wherein said subject does not exhibit a pathology comprising an episode of atrial flutter within 6 months prior to said administering.

[209] The method of any one of paragraphs [106]-[208], wherein said subject has not undergone cardiac surgery for said pathology within 6 months prior to said administering.

[210] A method of preparing a liquid pharmaceutical composition, comprising combining:

(a) water;

(b) a pH adjusting agent;

(c) flecainide or a pharmaceutically acceptable salt thereof; and

(d) a cyclodextrin.

[211] The method of paragraph [210], wherein:

(i) a concentration of said flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in said pharmaceutical composition,

(ii) a concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and

(iii) a room-temperature pH in said pharmaceutical composition of from about 5.5 to about 6.5.

[212] The method of paragraphs [210] or paragraph [211], wherein said combining comprises:

(a) providing said water;

(b) contacting said portion of water with said flecainide or pharmaceutically acceptable salt thereof, said cyclodextrin, and said pH adjusting agent in a vessel; and

(c) adding a subsequent portion of said water to said vessel to provide said pharmaceutical composition, wherein:

(i) a concentration of said flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in said pharmaceutical composition,

(ii) a concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and

(iii) a room-temperature pH in said pharmaceutical composition of from about 5.5 to about 6.5.

[213] The method of any one of paragraphs [210]-[212], wherein said pH adjusting agent comprises an ion selected from the group consisting of: acetate, citrate, nitrate, chloride, sulfate, maleate, tartrate, phosphate, aconitate, adipate, ascorbate, benzoate, caprylate, cholate, formate, glutamate, lactate, propionate, sorbate, stearate, and succinate.

[214] The method of any one of paragraphs [210]-[213], wherein said pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

[215] The method of any one of paragraphs [210]-[214], wherein said pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[216] The method of any one of paragraphs [210]-[215], wherein said pH adjusting agent comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

[217] The method of any one of paragraphs [210]-[216], wherein a concentration of said pH adjusting agent in said pharmaceutical composition is about 2 mM to about 50 mM.

[218] The method of any one of paragraphs [210]-[217], wherein a concentration of said pH adjusting agent in said pharmaceutical composition is about 2 mM to about 10 mM.

[219] The method of paragraph [217] or paragraph [218], wherein said pH adjusting agent comprises acetic acid.

[220] The method of paragraph [219], wherein said concentration in said pharmaceutical composition of said acetic acid is about 5 mM.

[221] The method of paragraph [217] or paragraph [218], wherein said pH adjusting agent comprises citric acid.

[222] The method of paragraph [221], wherein said concentration in said pharmaceutical composition of said citric acid is about 5 mM.

[223] The method of any one of paragraphs [210]-[222], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, derivatized α -cyclodextrins, derivatized β-cyclodextrins, and derivatized γ-cyclodextrins.

[224] The method of any one of paragraphs [210]-[223], wherein said cyclodextrin is selected from the group consisting of: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin dimaltosyl-β-cyclodextrin, succinyl-β-cyclodextrin, 6A-amino-6A-deoxy-N-(3-hydroxypropyl)-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, sulfoalkylether-β-cyclodextrins, and sulfoalkylether-γ-cyclodextrins.

[225] The method of any one of paragraphs [210]-[224], wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

[226] The method of any one of paragraphs [211]-[225], wherein said concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v).

[227] The method of paragraph [210]-[226], further comprising adding a sweetener.

[228] The method of paragraph [227], wherein said sweetener is selected from the group consisting of: acesulfame potassium, aspartame, cyclamate, mogrosides, saccharin, stevia, sucralose, neotame, mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol, and pharmaceutically acceptable salts thereof.

[229] The method of paragraph [227], wherein said sweetener comprises saccharin.

[230] The method of paragraph [227], wherein said sweetener comprises a salt of saccharin.

[231] The method of paragraph [227], wherein said sweetener comprises saccharin sodium.

[232] The method of any one of paragraphs [227]-[231], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 1% (w/v).

[233] The method of any one of paragraphs [227]-[231], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.05% (w/v).

[234] The method of any one of paragraphs [227]-[231], wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

[235] The method of any one of paragraphs [210]-[234], wherein said pharmaceutically acceptable salt of flecainide is added.

[236] The method of paragraph [235], wherein said pharmaceutically acceptable salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate.

[237] The method of paragraph [235], wherein pharmaceutically acceptable said salt of flecainide comprises flecainide acetate.

[238] The method of paragraph [235], wherein pharmaceutically acceptable said salt of flecainide comprises flecainide hydrochloride.

[239] The method of any one of paragraphs [210]-[238], further comprising packaging said pharmaceutical composition in unit dose form.

[240] The method of any one of paragraphs [235]-[238], further comprising packaging said pharmaceutical composition in unit dose form, wherein said unit dose form comprises about 50 mg to about 350 mg of said pharmaceutically acceptable salt of flecainide.

[241] The method of paragraph [240], wherein said unit dose form comprises about 60 mg to about 150 mg of said pharmaceutically acceptable salt of flecainide.

[242] The method of paragraph [240], wherein said unit dose form comprises about 75 mg to about 125 mg of said pharmaceutically acceptable salt of flecainide.

[243] The method of paragraph [240], wherein said unit dose form comprises about 250 mg to about 350 mg of said pharmaceutically acceptable salt of flecainide.

[244] The method of paragraph [240], wherein said unit dose form comprises about 150 mg to about 250 mg of said pharmaceutically acceptable salt of flecainide.

[245] The method of paragraph [240], wherein said unit dose form comprises about 90 mg of said pharmaceutically acceptable salt of flecainide.

[246] The method of paragraph [240], wherein said unit dose form comprises about 120 mg of said pharmaceutically acceptable salt of flecainide.

[247] The method of paragraph [240], wherein said unit dose form comprises about 200 mg of said pharmaceutically acceptable salt of flecainide.

[248] The method of any one of paragraphs [239]-[247], wherein said unit dose form further comprises a container.

[249] The method of paragraph [248], wherein said container is selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.

EXAMPLES

[0251] The following examples are provided to further illustrate some embodiments of the present disclosure, but are not intended to limit the scope of the disclosure; it will be understood

by their exemplary nature that other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

EXAMPLE 1: Solubility of Flecainide Salts.

[0252] This example illustrates that flecainide acetate, among the different flecainide salts that were tested, had the highest solubility in water. This example also illustrates that sodium chloride, which is suggested to be desirable to be added to inhalation formulation to reduce the incidence of cough, can render precipitation of flecainide free base when added into flecainide solution.

[0253] In this example, the solubility of flecainide citrate, flecainide phosphate, flecainide hydrochloride, and flecainide nitrate were all compared with that of flecainide acetate. As shown in **TABLE 1**, the solubility of flecainide acetate in water was at least an order of magnitude higher than the other salts formed. Moreover, the addition of sodium chloride (e.g. saline) to the formulation results in precipitation and loss of solubility of flecainide acetate from solution. X-ray powder diffraction (XRPD) analysis confirmed that there is form conversion when sodium chloride was added into the solution.

TABLE 1. Solubility comparison of different flecainide salts

Media (0.1M)	**pH**	**Concentration (mg/mL)**		**Ksp**
		Freebase	**Anion**	
Acetic Acid	4.6	64.01	16.04	4.20E-02
Nitric Acid	4.0	12.63	0.18	8.53E-05
Sulfuric Acid	1.5	0.94	3.69	1.97E-07
Citric Acid	3.2	21.90	11.95	3.30E-03
Hydrochloric Acid	5.0	5.34	0.49	1.78E-04

[0254] It is of note that formulating at a pH under 5.2 can risk undesirable organoleptic properties and toxicity issues. This example suggests that acetate salt of flecainide is more suitable for pharmaceutical formulation than some other salts of flecainide.

EXAMPLE 2: Solubility of Flecainide Acetate in the Presence of Cyclodextrins.

[0255] This example demonstrates the change in the water solubility of flecainide acetate in the presence of different cyclodextrins.

[0256] In this example, the solubility of flecainide acetate in water was shown to increase with increased concentration of various cyclodextrins. **TABLE 2** summarizes the solubility of

flecainide acetate as a function of cyclodextrin concentration along with 100mM acetic acid buffer

TABLE 2. Solubility comparison of flecainide acetate in the presence of different cyclodextrins

Cyclodextrin	Concentration (%w/v)	pH	Solubility (mg/mL)
α-cyclodextrin	1	5.3	52.8
	2	5.4	52.8
	4	5.4	58.4
	8	5.4	71.5
β-cyclodextrin	1	5.3	55.0
	2	5.4	57.9
γ-cyclodextrin	1	5.4	56.2
	2	5.4	57.9
	4	5.4	61.1
	8	5.5	69.7
	10	5.5	71.1
	12	5.5	70.4
hydroxypropyl-β-cyclodextrin	1	5.3	56.0
	2	5.4	57.7
	4	5.4	60.4
	8	5.5	66.5
methyl-β-cyclodextrin	1	5.4	49.9
	2	5.4	53.0
	4	5.4	57.2
	8	5.5	61.4

[0257] Additionally, the solubility of flecainide acetate was measured in a constant cyclodextrin concentration (i.e. hydroxypropyl-β-cyclodextrin and β-cyclodextrin) with varying acetic acid buffer concentrations from 0 to 100mM and there was very little difference observed in their solubility.

[0258] The solubility of the flecainide freebase was compared to flecainide acetate using the same buffer and cyclodextrin concentrations. The flecainide acetate concentration was found to be nearly 6 times greater than that of the freebase form.

EXAMPLE 3: Solubility of Flecainide Acetate in the Presence of hydroxypropyl-β-cyclodextrin (HPβCD).

[0259] This example demonstrates that solubility of flecainide acetate in water is increased as the concentration of HPβCD in the solution increases.

[0260] In this example, the solubility of flecainide acetate in HPβCD (Trappsol® hydroxypropyl-β-cyclodextrin; purchased from CTD Inc.) solutions of different concentrations was tested. The average molecular weight and degree of substitution of the tested HPβCD are 1495 and 6.2, respectively.

[0261] Flecainide acetate (dosing concentration: 100~150 mg/mL) was suspended in HPβCD solutions of different concentrations (0% to 180% w/v). The suspension was then magnetic stirred (1000 r/min) at RT for 24 hrs or 48 hrs. The suspension was then subject to centrifugation at 10000 rpm (3 min) and filtration by 0.45 μm membrane to obtain supernatant for HPLC solubility test, and the residual solids were analyzed by X-ray powder diffraction (XRPD) assay.

[0262] As shown in **TABLE 3**, flecainide acetate solubility at 48 hrs increased linearly with the HPβCD concentration in the range of 0%~40% (w/v), which suggests that the complexation may have occurred (**FIGURE 1**). In one experiment, the solubility (48 hrs) of flecainide acetate in 40% (w/v) HPβCD solution reached 104.7 mg/mL (calculated as freebase). In another experiment, the solubility (48 hrs) of flecainide acetate in 40% (w/v) of HPβCD solution reached 108.6 mg/mL (calculated as freebase). It was also observed that flecainide acetate solubility in HPβCD solutions decreased from 60% to 140% (w/v) of HPβCD. The maximum solubility of 124.9 mg/mL (calculated as freebase) was observed in 180% (w/v) HPβCD solution at 24 hrs sampling time.

[0263] Within the range of 0%-40% (w/v) of HPβCD, the complexation stability constant ($K_{1:1}$) was determined as 5.75 by Phase Solubility Plot (Higuchi–Connors phase-solubility method).

TABLE 3. Solubility of flecainide acetate in HPβCD solution

HP-β-CD Concentration		**48 hrs Flecainide Acetate Solubility**	
% w/v	**mol/mL**	**mg/mL**	**mol/mL**
0	0	65.5	0.138
10	0.067	78.8	0.166
20	0.134	89.1	0.188
30	0.201	109.5	0.231
32	0.214	110.9	0.234
34	0.227	113.7	0.24
36	0.241	115.4	0.243
38	0.254	116.2	0.245
40	0.268	120.2	0.253

EXAMPLE 4: Viscosity of Flecainide Acetate-HPβCD Solution.

[0264] This example demonstrates the impact of HPβCD concentration on solution viscosity.

[0265] In this example and the following examples, the (HP)-β-cyclodextrin used is "Cavitron W7 HP7 PHARMA". The manufacturer (Ashland) specifies: <1.5% beta cyclodextrin (our batch had 1%) and molar substitution is between 0.86 and 1.14 (our batch had 1.05). From the manufacturer's brochure, the typical degree of substitution is 6.0 to 8.0 with an approximate average MW of 1520.

[0266] Higuchi-Connors phase-solubility experiments on solutions adjusted to a pH of 5.2 with NaOH confirmed that the complexation efficiency of HPβCD : flecainide acetate was 0.8, which means 80% of HPβCD molecules were complexed with flecainide acetate. As shown in **Table 4**, solution viscosity was increased with the addition of HPβCD. However, aerosol properties are not significantly affected up to at least about 22.5% HPβCD. Beyond this concentration, the aerosol output rate can diminish slightly.

TABLE 4. Viscosity of Flecainide Acetate HPβCD Solutions

Formulation	Viscosity
75 mg/mL FA (flecainide acetate), 90 mM AA (acetic acid), 10%w/v HPβCD, pH 5.2	1.8 cP
88 mg/mL FA, 90 mM AA, 20%w/v HPβCD, pH 5.9	2.9 cP
100 mg/mL FA, 90 mM AA, 30%w/v HPβCD, pH 5.9	4.9 cP

EXAMPLE 5: Pharmacokinetics and Pharmacodynamics Study in Pig Models.

[0267] This example demonstrates the bioequivalence and pharmacodynamic equivalence of exemplary cyclodextrin-containing flecainide acetate formulations as compared to original flecainide acetate formulation.

IV Infusion.

[0268] Experiments were carried out in pigs to determine the pharmacokinetics (PK) at the same dose of flecainide delivered via IV infusion.

[0269] In these example, there solutions (original and new cyclodextrin-containing formulations) were prepared and compared in pig models of atrial fibrillation: (1) 75 mg/mL flecainide acetate, 10% sulfobutylether-β-cyclodextrin, 90 mM acetic acid, pH 5.2; (2) 75 mg/mL flecainide acetate, 10% hydroxypropyl-β-cyclodextrin, 90 mM acetic acid, pH 5.2; and (3) 35 mg/mL flecainide acetate, 90 mM acetate buffer, pH 5.2.

[0270] Each pig was given the same dose of flecainide using the three solutions in a cross-over design experiment with an intervening wash-out period of 2 hours.

[0271] When adjusted for equivalent dose (1 mg/Kg body weight) and dose infusion rate (10 minutes), the three solutions appeared to result in near-equivalent PK profiles in the pig animal model, as shown in **FIGURE 2**.

[0272] It was also observed that the C_{max} attained with sulfobutylether-β-cyclodextrin was lower (about 20%) than that with hydroxypropyl-β-cyclodextrin and the original 35 mg/ml flecainide acetate formulations. The PK profile with hydroxypropyl-β-cyclodextrin was more similar to (7% higher in Cmax) that with the 35mg/mL acetate buffer formulation. The Cmax, distribution and elimination phases were all near-identical between HPβCD and the original 35 mg/ml flecainide acetate formulation. This suggests that complexation between flecainide acetate and the cyclodextrins is loose and flecainide dissociates quickly once it is delivered into the systemic bloodstream.

IT Instillation.

[0273] Experiments were carried out in pigs to determine the pharmacokinetics (PK) and pharmacodynamics (PD; duration of QRS interval and atrial depolarization, Pa) at the same dose of flecainide delivered via IV infusion and intratracheal instillation, using two formulations.

[0274] In these examples, there solutions (original and new cyclodextrin-containing formulations) were prepared and compared in pig models of atrial fibrillation: (1) 75 mg/mL flecainide acetate, 10% hydroxypropyl-β-cyclodextrin, 90 mM acetic acid, pH 5.2; and (2) 35 mg/mL flecainide acetate, 90 mM acetate buffer 35mg/mL, pH 5.2.

[0275] When adjusted for equivalent dose (0.75 mg Kg body weight and 1 mg/Kg body weight) and dose infusion rate (10 minutes), the two solutions appeared to result in near-equivalent PK and PD profiles in the pig animal model, as shown in **FIGURES 3A-3B** and **4A-4D**.

EXAMPLE 6: Safety Assessment of Inhalation Delivery of Flecainide Acetate Formulations.

[0276] Five Good Laboratory Practice (GLP) compliant 14-day repeat dose inhaled studies in rats and dogs were conducted to assess potential toxicology associated with FlecIH-101, FlecIH-102, and FlecIH-103 formulations (**TABLE 5**).

TABLE 5

Study	Formulation*	Study Type**	Species	Study Description	NOAEL (mg/kg/day)
1	FlecIH-101	14-Day with recovery and TK	Rat	14-Day nose only inhalation study with 14-day recovery	28.7

2	FlecIH-102	14-Day with recovery and TK	Rat	14-Day nose only inhalation study with 14-day recovery; neurobehavioral assessments	67.7
3	FlecIH-103	14-Day with recovery and TK	Rat	14-Day nose only inhalation study with 14-day recovery; neurobehavioral assessments	30
4	FlecIH-101	14-Day with recovery and TK	Dog	14-Day face mask inhalation study with 14-day recovery; respiratory and cardiovascular safety pharmacology	8.03
5	FlecIH-102	14-Day with recovery and TK	Dog	14-Day face mask inhalation study with 14-day recovery; respiratory and cardiovascular safety pharmacology	9.87

*See **TABLE 19** for composition of each formulation.

**TK: Toxicokinetic

***No Observed Adverse Effect Level

[0277] Results indicated that inhaled flecainide resulted in no new or unusual toxicology associated with inhalation of flecainide compared with the marketed IV and oral flecainide dosage forms. The No Observed Adverse Effect Levels (NOAELs) for the 14-day repeat dose rat and dog toxicology studies conducted with flecainide acetate in the acetic acid formulation (FlecIH-101) were 28.7 mg/kg/day (Study 1) and 8.03 mg/kg/day (Study 4), respectively; and the NOAELs for the 14-day repeat dose rat and dog toxicology studies conducted with flecainide acetate in the acetic acid formulation containing hydroxypropyl-β-cyclodextrin (Flec-IH-102) were 67.7 mg/kg/day (Study 2) and 9.87 mg/kg/day (Study 5), respectively. A bridging 14-day repeat dose rat study confirmed that 30 mg/kg/day flecainide acetate was the NOAEL in the acetic acid formulation containing hydroxypropyl-β-cyclodextrin and sodium saccharin (FlecIH-103, Study 3).

[0278] The critical effects identified were high dose respiratory tract findings in the rat inhalation toxicity study involving mild squamous cell metaplasia in the nose, minimal to mild squamous metaplasia in the larynx, and in the lung minimal to mild alveolar macrophage aggregates and neutrophilic infiltrates.

[0279] Overall, results indicate that nose-only exposure of rats to inhaled flecainide acetate at inhaled doses of 28.7 – 147.6 mg/kg resulted in few clinical signs, and no effects on body weight, neurobehavioral and clinical pathology parameters. Histopathological changes in the lungs, larynx and nasal turbinates during the dosing period were non-adverse changes at the lowest dose tested. Therefore, the NOAEL was 28.7 mg/kg flecainide by inhalation.

[0280] Inhalation toxicity studies were conducted in dogs. Overall, inhaled flecainide presented at doses up to 8.03 mg/kg in Study 4, and 9.87 mg/kg/day in Study 5 for 14 days (average for both genders) did not result in any adverse effects in clinical signs, body weights, clinical pathology parameters, pulmonary function parameters or histopathological changes. Electrocardiography showed changes of small magnitude in the PR intervals, QRS intervals, and HR. While possibly test-article related, these are non-adverse changes; therefore, the NOAEL was considered to be 9.87 mg/kg. Detailed study parameters and results for Study 5 are summarized below.

Study 5.

[0281] This example describes a 14-day repeated-dose toxicity study via face mask inhalation with 14 day recovery in dogs. The objective of this study was to evaluate the potential toxicity of aerosolized flecainide from the exemplary inhalation solution (75 mg/mL flecainide acetate / 10% w/v HPβCD / 90 mM acetic acid buffer formulation at pH 5.2) after face mask inhalation exposure for 14 consecutive days in Beagle dogs (4 dogs/sex/group), and to investigate whether the potential effects were reversible after a 14 day recovery period (2 dogs/sex/group); air and vehicle control groups were included. The study design is shown in **TABLE 6**.

TABLE 6. Study Design of Toxicity Assessment in Dogs

Exposure	Exposure Duration (min)	Dose (mg/kg/day)		Main Study		Recovery		TK Blood Collections	
		M	F	M	F	M	F		
Air	60	NA	NA	4	4	2	2	6	6
Vehicle	60	NA	NA	4	4	2	2	6	6
Low Dose	10	1.68	2.04	4	4	2	2	4	4
Mid Dose	30	4.59	5.52	4	4	2	2	4	4
High Dose	60	9.75	9.98	4	4	2	2	6	6

[0282] In addition to the aerosol drug concentration, the aerosol particle size distribution was also characterized. The particle size average MMAD and GSD for the Low-, Mid-, and High-dose groups were 2.38 (1.79), 2.03 (1.87) and 2.08 (1.79) microns, respectively, and 1.74 (1.88) microns for vehicle control group. Average presented flecainide acetate doses were 1.86, 5.08, and 9.88 mg/kg in Low-, Mid- and High-dose groups respectively. Chamber oxygen levels were monitored throughout the exposures. Main study animals were sacrificed on Day 15. Recovery animals were sacrificed on Day 29 following a 14-day recovery period. Endpoints included clinical observations, body weights, ophthalmology, clinical pathology, urinalysis, gross pathology, histopathology, and bioanalytical and toxicokinetic analyses.

[0283] All study dogs survived to the scheduled euthanasia without instance of morbidity or mortality. Body weights showed no treatment related differences. The most common clinical observation was soft stool and occurred with similar incidence across genders and study groups periodically for the duration of the study; none of the clinical observations appeared related to flecainide or vehicle exposures. The only observation associated with flecainide exposure was labored respiration during or immediately post exposure; this occurred in several Mid- or High-dose animals on Day 1 or Day 7. In post-study ophthalmology examinations, new cataracts (less than 5% of lens) were observed in 5 dogs in the air control (2), Low-dose (1) and Mid-dose (2) groups, but not in any vehicle control or High-dose animals. Due to the small size, they may have been present but undetected on the pre-study exam. Respiratory parameters indicated no significant effect of exposure at any dose level or any time point. All ECGs were considered normal with no rhythm or waveform abnormalities. Small changes in heart rate, PR intervals and QRS intervals were possibly test-article related but were not considered adverse findings.

[0284] Statistically significant clinical chemistry, hematology and coagulation changes generally did not occur with consistency across genders or dose during the treatment or recovery periods points and were generally of small magnitude. Tissues were generally unremarkable upon gross examination. Necropsy findings of lung and thymus discoloration were observed in several vehicle and flecainide animals during treatment and in the recovery period. Other sporadic incidental gross observations occurred that were within normal limits or background level, and were not test article related. Minor, sporadic incidental histologic findings, as expected, occurred in this study. Such findings included cysts and minor infiltrates of various cell types. These were sporadic and/or occurred with a prevalence, character and severity that were indistinguishable from controls. There were no histopathologic changes attributable to treatment with the test article.

[0285] Overall, inhaled flecainide administered at doses up to 9.88 mg/kg/day for 14 days (average for both genders) did not cause any adverse effects in clinical signs, body weights, clinical pathology parameters, pulmonary function parameters or histopathological changes. Electrocardiography showed changes of small magnitude in the PR intervals, QRS intervals, and HR. While possibly test-article related these are non-adverse changes; therefore, the NOAEL was considered to be 9.88 mg/kg.

[0286] In summary, inhaled flecainide from the exemplary inhalation solution (75 mg/mL flecainide acetate / 10% w/v HP-β-cyclodextrin / 90 mM acetic acid buffer formulation at pH 5.2) using a face mask for 14 consecutive days in male and female Beagle dogs showed comparable results to those from the study conducted with the original inhalation solution (35 mg/mL flecainide acetate / 90 mM acetic acid buffer formulation at pH 5.2).

EXAMPLE 7: Exemplary Formulations with Reduced Acetic Acid Strength.

[0287] This example demonstrates that in the presence of HPβCD, flecainide acetate solution can have less acetic acid buffer and can still maintain the solubility of flecainide acetate at concentrations higher than 125 mg/mL.

[0288] Although flecainide acetate shows high solubility at 0 mM acetic acid, freebase was observed to crash out in some instances. This was not observed at higher buffer strengths.

TABLE 7. Solubility of Flecainide Acetate at Different Acetic Acid Concentrations

Cyclodextrin	**Concentration (mM)**	**pH**	**Solubility (mg/mL)**
hydroxypropyl-β-cyclodextrin (40%w/v)	0	6.3	125
	25	5.5	131
	50	5.2	135
	75	5.1	135
	100	4.9	136

[0289] The acceptability of various formulations of flecainide inhalation solution was evaluated in terms of their organoleptic properties (specifically, the smell/odor, sensation in the mouth and throat and taste) upon oral inhalation of the solution (administered as liquid aerosol).

[0290] Inhalation solutions were prepared to identify whether additives (such as mannitol or ethanol), lowering of acetic acid content, or raising the pH can improve their acceptability compared to the 75 mg/mL flecainide acetate / 10% w/v HPβCD / 90 mM acetic acid buffer formulation at pH 5.2. The properties that the evaluation was based on were: sensation upon

inhalation (burning/stinging/ tingling or numbness); bitter taste/aftertaste in throat, cough, hoarseness of voice etc. Only 1 inhaled solution was tested per day per volunteer.

[0291] This evaluation was performed with in 3 consecutive iterations with different formulations to compare the various formulations in terms of their various concentrations of the active ingredient (flecainide acetate), pH of solution and other varying excipients.

[0292] Based on the observations made by the healthy volunteers, the most acceptable formulation as an inhalation solution in terms of the inhalation experience when compared to the control (75 mg/mL flecainide acetate / 10% w/v HPβCD / 90 mM acetic acid buffer formulation at pH 5.2) was the formulation with lower acetic acid concentration and higher pH (i.e. 75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v HPβCD in WFI, pH 5.99).

Experiment #1:

[0293] The set of solutions prepared for this experiment are shown in **TABLE 8**.

TABLE 8. Exemplary Formulations for Organoleptic Experiment #1

S. No.	Exemplary Formulations	Features / Comments
1.	75mg/mL Flecainide acetate, 90mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2, 5% Mannitol	Control + 5% mannitol
2.	75mg/mL Flecainide acetate, 25mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2	Control with lower (25 mM) acetic acid
3.	75mg/mL Flecainide acetate, 90mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH of 5.2	Control
4.	75mg/mL Flecainide acetate, 90mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH of 5.5	Control with higher pH (5.5)
5.	75mg/mL Flecainide acetate, 90mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH of 5.2, 10% Ethanol	Control + 10% ethanol

[0294] Inhalation device: the inhalation device used for testing was AeroEclipse® II BAN, a hand-held nebulizer. It was run with compressed air from a portable compressor pump, (INVACARE Mobilaire) at 30 psi.

[0295] Inhalation procedure: 3mL of the flecainide inhalation solution was placed in a newly opened package of the inhaler, for each solution tested (single use of inhaler). The subject was asked to relax, place the mouthpiece of the inhaler in the mouth and inhale the solution for about 2 seconds, hold their breath for 2 seconds and release the breath in about 4 seconds for a total time of not greater than 1 minute. This inhalation pattern was roughly followed by all volunteers.

[0296] Volunteers: 3 healthy male volunteers, 1 healthy female volunteer. Age of volunteers: 40-68 years.

[0297] Observations are summarized in **TABLE 9**.

TABLE 9. Summary of observations from all 4 volunteers (experiment #1)

S. No.	Exemplary Formulations	Cough	Burning/Stinging Of throat	Numbness/Tingling Of throat or lips	Bitter taste/ aftertaste	Voice turning hoarse	Comments
1.	75 mg/mL Flecainide acetate, 90 mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2, 5% Mannitol	high	Moderate	----	low	moderate	
2.	75 mg/mL Flecainide acetate, 25 mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2	low	low	----	low	low	
3.	75 mg/mL Flecainide acetate, 90 mM acetic acid, 10% w/v hydroxypropyl-	moderate	moderate	moderate	moderate	Moderate - high	Tightness in throat

	b-cyclodextrin in WFI, pH of 5.2						
4.	75 mg/mL Flecainide acetate, 90 mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH of 5.5	moderate	moderate	moderate	moderate	high	
5.	75 mg/mL Flecainide acetate, 90 mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH of 5.2, 10% Ethanol	high	high	---	moderate	high	Headache, lightheadedness for several hours

[0298] Conclusions**:** Based on the observations made by the volunteers in the testing above, the most acceptable formulation as an inhalation solution in terms of the inhalation experience when compared to the control was the formulation with lower acetic acid concentration **(i.e.** 75mg/mL Flecainide acetate, **25 mM acetic acid**, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2**).**

Experiment #2:

[0299] The set of solutions prepared for this experiment are shown in **TABLE 10**.

TABLE 10. Exemplary Formulations for Organoleptic Experiment #2

S. No.	**Exemplary Formulations**	**Comments**
1.	**75mg/mL Flecainide acetate**, 90mM acetic acid, **10% w/v hydroxypropyl-b-cyclodextrin** in WFI, pH of 5.2	**Control**
2.	75mg/mL Flecainide acetate, **5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin** in WFI, **pH 5.99**	Lower acetic acid, higher cyclodextrin, higher pH

S. No.	Exemplary Formulations	Comments
3.	75mg/mL Flecainide acetate, **5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin** in WFI, **pH 5.99** (+ 2 drops of liquid Sweet N Low* to 3mL of IH solution)	**Formulation 2 + 2 drops of liquid sweetener**

*Other sweeteners that tried were liquid **stevia**, sweet n low powder, stevia powder, xylitol containing sprays and lozenges

[0300] The inhalation device and procedure remained the same as for experiment #1. Number of volunteers was 3 (2 male volunteers + 1 female volunteer). The solutions were tested for the same organoleptic properties as for experiment #1.

[0301] Observations from all 3 volunteers are summarized in **TABLE 11.**

TABLE 11. Summary of observations from all 3 volunteers (experiment #2)

S. No.	Exemplary Formulations	Cough	Burning/ Stinging Of throat	Numbness /Tingling Of throat or lips	Bitter taste/ aftertaste	Voice turning hoarse	Comments
1.	**75mg/mL Flecainide acetate**, 90mM acetic acid, **10% w/v hydroxypropyl-b-cyclodextrin** in WFI, pH of 5.2	moderate	moderate	moderate	moderate	Moderate - high	Tightness in throat
2.	75mg/mL Flecainide acetate, **5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin** in WFI, **pH 5.99**	v. low	low	----	low	low	
3.	75mg/mL Flecainide acetate, **5mM acetic acid,**	v. low	v. low	----	v. low	low	Much smoother; easier to

	20% w/v hydroxypropyl-b-cyclodextrin in WFI, **pH 5.99** (+ 2 drops of liquid Sweet N Low* to 3mL of IH solution)						inhale; less stinging or burning sensation; almost no cough

[0302] Conclusions**:** Based on the observations made by the volunteers in the testing above, the most acceptable formulation as an inhalation solution in terms of the inhalation experience when compared to the control (1in table above) was the formulation with lower acetic acid concentration and higher pH **(i.e.** 75mg/mL Flecainide acetate, **5mM acetic acid**, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.99**).**

[0303] Adding 2 drops of liquid Stevia or liquid sweet n low (saccharin) to the solution were found to highly improve the inhalation experience. Liquid Sweet n Low (containing saccharin; concentration unknown) was found to be most effective.

[0304] IH flecainide solutions containing varying amounts of saccharin were prepared for testing as a next step.

Experiment #3:

[0305] The set of solutions containing saccharin prepared for this experiment are shown in **TABLE 12**.

TABLE 12. Exemplary Formulations for Organoleptic Experiment #3

S. No.	**Composition of solution**	**Comments**
1.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.99	Lower acetic acid, higher cyclodextrin, higher pH 0 μM sodium saccharin
2.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 250 μM sodium saccharin, pH 5.99	250 μM sodium saccharin
3.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 500 μM sodium saccharin, pH 5.99	500 μM sodium saccharin

4.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 750 μM sodium saccharin, pH 5.99	750 μM sodium saccharin
5.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 1000 μM sodium saccharin, pH 5.99	1000 μM sodium saccharin
6.	75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 1250 μM sodium saccharin, pH 5.99	1250 μM sodium saccharin

[0306] The inhalation device and procedure remained the same as for experiment #2. Number of volunteers was 3 (2 male volunteers + 1 female volunteer). The solutions were tested for the same organoleptic properties as for experiments #1 and 2.

[0307] Observations from all 3 volunteers are summarized in **TABLE 13.**

TABLE 13. Summary of observations from all 3 volunteers (experiment #3)

S. No.	**Composition of solution**	**Cough**	**Burning/ Stinging Of throat**	**Numbness/ Tingling Of throat or lips**	**Bitter taste/ aftertaste**	**Voice turning hoarse**	**Comments**
1.	75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.99	v. low	low	----	low	low	Voice turned hoarse

2.	75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 250 µM sodium saccharin, pH 5.99	Very low	Low	low	low	v. low	Localized burning in the throat
3.	75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 500 µM sodium saccharin, pH 5.99	v. low	low	----	low	low	Burning or stinging at the back of throat
4.	75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 750 µM sodium saccharin, pH 5.99	v. low	v. low	none	v. low	none	Delayed and minor burning sensation of throat; minor cough reflex; overall the best inhalation experience of all solutions in this set. Easy to inhale.
5.	75 mg/mL Flecainide	low	low	low	----	low	

	acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 1000 µM sodium saccharin, pH 5.99						
6.	75 mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 1250 µM sodium saccharin, pH 5.99	low	low	----	Low to moderate	Low to moderate	More burning of throat compared to 750 µM; lingering sensation in throat

[0308] Conclusions: Based on the observations made by the volunteers in the testing above, the most acceptable formulation as an inhalation solution in terms of the inhalation experience when compared to the control (1in table above) was the formulation the one containing 750 µM saccharin (i.e. 75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 750 µM sodium saccharin, pH 5.99).

EXAMPLE 8. Further Improvement in Organoleptic Properties by Saccharin.

[0309] This example demonstrates that organoleptic properties of the inhalation formulation can be further improved by addition of saccharin.

[0310] In this example, various products were tested to be used either prior to the inhalation procedure (prophylactic) or immediately following (treat) it with the goal to lessen the unpleasant sensory characteristics of the inhalation solution and thereby, improve the overall inhalation experience. A list of sweeteners that were tested is shown in **TABLE 14**.

[0311] Adding 2 drops of liquid Stevia or liquid Sweet-n-Low (saccharin) to the solution were found to highly improve the inhalation experience. Liquid Sweet-n-Low (containing saccharin; concentration unknown) was found to be most effective.

[0312] Various sugars (in powdered and liquid form) were used as additives to the flecainide acetate inhalation solution to improve the organoleptic properties, starting with the following Flec IH solution: 75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.9.

[0313] If the sugar was in a powder form, a few grains of it were added to ~ 3mL of Flec IH inhalation solution and stirred to dissolve. For solutions containing sugars (liquid form), 2 drops of each (exact/precise concentration unknown) were added to ~ 3mL of Flec IH inhalation solution. In both cases, the solution was "homogenized" by gently swirling the nebulizer while held upright, on the benchtop. Liquids were found to be easier/more convenient to work with than the powdered forms of sugars listed.

TABLE 14. List of Sweeteners Tested for Organoleptic Properties

S. No.	Product	Country of origin	Results
1.	Sweet n' low powder sweetener (saccharin)	USA	Lessens the bitter taste in mouth during and after inhalation; less stinging/burning of throat
2.	Truvia powder sweetener	USA	Lessens bitter taste in mouth during and after inhalation
3.	Equal (aspartame)	USA	Lessens the bitter taste in mouth during and after inhalation
4.	Stevia powder sachet	USA	Lessens the bitter taste in mouth during and after inhalation, less stinging/burning of throat
5.	Aspen Naturals liquid stevia	USA	Much smoother mouthfeel; easier to inhale; less stinging or burning sensation; almost no cough
6.	Now Better Stevia liquid sweetener	USA	Less bitter taste during/after inhalation; smoother mouthfeel

S. No.	Product	Country of origin	Results
7.	Sweet N' Low liquid sweetener (contains saccharin)	USA	**Much smoother mouthfeel; easier to inhale; less stinging or burning sensation; almost no cough**
8.	Quick Sweet: Neotame liquid sweetener	China	Less bitter taste. More intensely sweet than saccharin or stevia solution.
9.	Splenda powder sachet	USA	Lessens the bitter taste in mouth during and after inhalation

[0314] Inhalation flecainide solutions containing varying amounts of saccharin were prepared for testing as a next step. Based on the observations made by healthy volunteers, the most acceptable formulation in terms of the inhalation experience contained 75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, 750 μM sodium saccharin, pH 5.99.

EXAMPLE 9. Cardioversion of Atrial Fibrillation Induced by An Exemplary Formulations in Pigs.

[0315] This example illustrates the therapeutic effect of an exemplary HPβCD-flecainide acetate formulation via pulmonary delivery (intratracheal instillation).

METHODS.

Reagents and chemical analysis.

[0316] Flecainide HPβCD (the exemplary HPβCD-flecainide acetate formulation being tested in this example) dosing solutions of 0.5 and 1.0 mg/kg for intratracheal instillation were prepared to have 75 mg/mL flecainide acetate, 10% (w/v) HPβCD, 90 mM acetic acid, and pH 5.2. Plasma samples were analyzed using a high-performance liquid chromatography tandem mass spectrometric assay at Climax Laboratories, Inc. (San Jose CA, USA).

Experimental preparation.

[0317] Male Yorkshire pigs (n=10) weighing 35±0.7 kg (mean ± standard error of the mean) were studied. The pigs were preanesthetized with telazol (4.7 mg/kg, intramuscularly) and subsequently further anesthetized using alpha-chloralose (80 mg/kg, IV bolus, followed by 24 mg/kg/h continuous IV infusion). The pigs were intubated, and the lungs were ventilated at a

constant rate of 12 breaths/min and a tidal volume of 400 mL per stroke. All catheters were positioned under fluoroscopic guidance. Two catheters were positioned in the left ventricle, a decapolar catheter to obtain ventricular electrograms and a pigtail catheter to monitor left ventricular blood pressure continuously. Mean arterial pressure (MAP) was continuously monitored from a femoral arterial sheath. A catheter was positioned in the pericardial space through the right atrial appendage for delivery of intrapericardial acetylcholine. An Orbiter electrode catheter (Boston Scientific, Boston, MA) with close bipolar electrodes was placed in the right atrium for recording atrial depolarization (P_a) duration and for pacing. Electrograms were recorded from atrial and ventricular sites using a Prucka CardioLab workstation (GE Medical Systems, Milwaukee WI). Dominant frequency of AF was analyzed at 2 minutes after initiation of AF using the intracardiac electrograms from the right atrium. The data files were downloaded from the CardioLab workstation at 977 samples/s and imported into MATLAB (The MathWorks, Inc., Natick, MA). The dominant frequency was determined by fast Fourier transform analysis of 4096 spectra from 4-second segments of electrocardiographic data and was defined as the frequency with the highest power. For intratracheal instillation of flecainide HPβCD solution, a 5Fr angiography catheter was introduced into the trachea via the endotracheal tube, extending ~1 cm past the tube, and its tip was positioned under fluoroscopy at the level of the tracheal carina.

Study protocols.

[0318] The experiments were carried out according to two protocols. In the dose-response protocol (N=4), intratracheal instillation of flecainide HPβCD (2 mL of 0.5-, 0.75-, or 1.0-mg/kg doses followed by 3 mL of air in a 5 mL syringe) was administered in a single "push" via the modified angiography catheter positioned in the endotracheal tube at the beginning of the inspiration phase. A washout period of 60 min was allowed between doses. Electrocardiographic measurements of the QRS complex, PR interval, atrial depolarization (P_a) duration, and mean arterial pressure (MAP) were performed at various times and intervals throughout the experiment.

[0319] For the AF induction protocol (N=6) (**FIGURE 5**), 1 mL of 10.3 mM solution of acetylcholine bolus was injected into the intrapericardial catheter, followed by 2 mL of saline flush. At 1 minute after intrapericardial administration of acetylcholine, burst pacing was performed at cycle length of 150 ms to induce AF. After sustained AF was induced, a lavage with 20 mL of saline was performed to prevent further acetylcholine action. Flecainide HPβCD (2 mL of 0.5- or 1.0-mg/kg doses followed by 3 mL of air in a 5 mL syringe) was instilled intratracheally at 2 min after confirming the stability of AF in a single "push" via the modified

angiography catheter positioned in the endotracheal tube at the beginning of the inspiration phase. Sterile water (2 mL followed by 3 mL of air in a 5 mL syringe) was given as the placebo. AF duration was determined starting at the time of drug or placebo delivery until normal sinus rhythm was restored. A washout period of 60 min was allowed between doses. The effects on AF duration, mean arterial pressure (MAP), ventricular rate during AF, and dominant frequency were determined.

Plasma samples.

[0320] Blood samples were drawn from a 7 Fr sheath placed in the jugular vein into sodium heparin tubes at the time when AF terminated and at 0, 2, 5, 10, 15, 30, 45, 60 min after bolus intratracheal flecainide HPβCD administration in the 60-min analysis protocol. All the samples were centrifuged and frozen at −80 °C.

Statistical analysis.

[0321] Data are reported as means ± SEM. Statistical analyses were performed using paired 2-tailed t tests. Statistical significance was assumed at $p<0.05$. Analysis of variance (ANOVA) with a post hoc Dunnett's test was performed when multiple comparisons were made.

RESULTS.

Time course of plasma levels following intratracheal administration of Flecainide HPβCD.

[0322] Plasma levels of flecainide at both 0.5- and 1.0 mg/kg intratracheal doses exhibited a classical pharmacokinetic bio-exponential profile with peak levels (C_{max}) achieved at 2.0 or 2.8 minutes (T_{max}), respectively, after administration of the drug, and followed first by a rapid (distribution phase) and then later by a progressive decline (elimination phase) in plasma concentration of the drug (**FIGURE 6**).

Effects on atrial fibrillation duration.

[0323] AF was successfully induced in all animals. Intratracheal instillation of flecainide HPβCD (0.5 mg/kg) decreased AF duration by 47% or 4.9 min in comparison to sterile water placebo (from 10.4±0.05 to 5.5±0.01 min, p=0.014). The intratracheal dose of 1.0 mg/kg flecainide HPβCD shortened the AF duration by 72% or 7.5 min (from 10.4±0.05 to 2.9±0.02 min, p=0.008) compared to sterile water placebo. The reduction in AF duration by the higher dose was 1.5-fold that of the lower dose (p=0.03). The summary data on AF duration and electrocardiograms from an illustrative example of conversion of AF are presented in **FIGURES 7** and **8**, respectively. Specifically, compared to placebo, the exemplary HPβCD-flecainide acetate formulation caused a dose-dependent shortening of AF duration by 48% (p=0.008) and 72% (p=0.03) for the 0.5- and 1.0-mg/kg doses, respectively (**FIGURE 7**). Note in the ECG

recordings the smooth transition to normal sinus rhythm. In the presence of the drug, there was one case of a brief 15-sec atrial flutter episode with a ventricular rate of 134±0.5 bpm.

Effects on dominant frequency during AF.

[0324] Intratracheal delivery of flecainide HPβCD at both doses resulted in a significant reduction in dominant frequency during AF (**FIGURE 9**), which can be an important measure associated with the organization of AF and of rotor dynamics, factors that can be responsible for initiation and maintenance of the arrhythmia. Compared to sterile water, the 0.5 mg/kg flecainide HPβCD reduced AF dominant frequency by 11% (from 7.3±0.8 to 6.5±1.0 Hz, $p<0.04$) and the 1.0 mg/kg dose reduced dominant frequency by 26% (from 7.3±0.8 to 5.4±1.0 Hz, $p<0.01$). The reduction in AF dominant frequency was associated with shortening of AF duration in a dose-response manner.

Effects on ventricular rate during AF.

[0325] At both doses, flecainide HPβCD lowered ventricular rate during AF (**FIGURE 10**). The lower dose reduced ventricular rate by 16% or 46 beats/min (from 286±10.7 to 240±15.5 beats/min, $p=0.002$) and the higher dose reduced ventricular rate by 27% or 77 beats/min (from 286±10.7 to 209±18.8 beats/min, $p=0.005$), both compared to intratracheal delivery of sterile water placebo. After conversion, the ventricular rate for the placebo, 0.5 mg/kg and 1.0mg/kg dose of flecainide HPβCD were 131±10.9, 99.6±3.5 and 103±4.9 bpm, respectively.

Effects on Atrial Depolarization (P_a) and PR Interval.

[0326] Administration of flecainide HPβCD at both the 0.5- and 1.0-mg/kg intratracheal doses was accompanied by an increase in both atrial depolarization (P_a) and PR interval duration, which followed the plasma concentration profile. The increases in P_a and PR interval duration were statistically significant at 2 and 5 min after drug administration. The increases in PR interval duration are indicative of a slowing of AV conduction, which is likely to be responsible for the observed decrease in ventricular rate during AF.

[0327] At 2 minutes after administration of intratracheal flecainide, P_a duration was increased by 12% (from 43±1.6 to 48±2.2 ms; $p=0.02$) for the 0.5-mg/kg dose and by 17% (from 41±1.0 to 48±2.0 ms; $p=0.009$) for the 1.0-mg/kg dose, compared to pre-drug baseline. At 5 minutes, P_a duration was increased by 12% (from 43±1.6 to 48±2.2 ms; $p=0.007$) and 20% (from 41±1.0 to 49±1.7 ms; $p=0.005$) for the lower and higher doses, respectively.

[0328] The 1.0-mg/kg intratracheal flecainide HPβCD dose significantly increased PR interval at both 2 ($p=0.03$) and 5 minutes ($p=0.01$) compared to pre-drug baseline (from 171±3.1 ms baseline to 186±6.7 ms and to 189±6.7 ms, increasing by 9% and 11%, respectively). The 0.5-

mg/kg dose did not cause a significant change in PR interval at 2 minutes but provoked a significant 5% increase at 5 min (from 167±4.7 to 175±5.6 ms; p=0.007).

Effects on heart rate and mean arterial pressure.

[0329] The responses of heart rate and mean arterial pressure (MAP) to the induction and conversion of AF by intratracheal instillation of flecainide HPβCD doses of either 0.5 or 1.0 mg/kg are shown in **FIGURE 11**. Induction of AF resulted in a marked increase in ventricular rate when compared to baseline pre-drug sinus rate ($p<0.002$ for both doses) and a corresponding reduction in MAP. With either dose, when AF was successfully terminated, both heart rate and MAP returned toward baseline levels within 2 minutes after conversion.

[0330] The multimodal actions of intratracheal delivery of the exemplary HPβCD-flecainide acetate formulation are likely to relate to the fact that this formulation inhibits both peak and late sodium currents. Inhibition of the fast sodium channel can contribute to an increase in atrial action potential duration reflected in the observed increase in P_a duration and can also slow intra-atrial conduction, which is evident in the prolonged PR interval. In turn, the net effect of slowing atrial conduction can account for the demonstrated reduction in ventricular rate during AF. The inhibition of late I_{Na} by the exemplary formulation has been found to suppress early and delayed afterdepolarizations in atrial and pulmonary veins, with a corresponding decrease in atrial ectopy. The net effect is likely to have contributed to a decrease in the firing rate of pulmonary vein foci during AF, which can lead to a decrease in AF dominant frequency, as found in the current study.

EXAMPLE 10. Comparison of Cardioversions of Atrial Fibrillation Induced by Two Exemplary Formulations in Pigs.

[0331] This example compares the therapeutic effects of two exemplary HPβCD-flecainide acetate formulations via pulmonary delivery (intratracheal instillation).

[0332] In this example, two formulations were tested: (a) 75mg/mL Flecainide acetate, 90mM acetic acid, 10% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.2 (the "High Acetate" formulation; the same exemplary formulation tested in Example 9); and (b) 75mg/mL Flecainide acetate, 5mM acetic acid, 20% w/v hydroxypropyl-b-cyclodextrin in WFI, pH 5.9 (the "Low Acetate" formulation). Experiments with "High Acetate" formulation are the same as the experiments described in Example 9, while experiments with "Low Acetate" formulation were conducted similarly to what is described in Example 9 except for the use of "Low Acetate" formulation instead of the "High Acetate" formulation. Briefly, Yorkshire pigs were administered with an intrapericardial injection of acetylcholine and burst pacing to induce AFIB

(atrial fibrillation). They were then dosed by intratracheal instillation with a cyclodextrin-based formulation (HPβCD) 2 min after AFIB initiation. After AFIB conversion, AFIB reinduction was attempted 30 minutes after dosing and 60 minutes after dosing, and the duration of AFIB was measured.

[0333] The following observations were made:

[0334] (1) The "Low Acetate" and "High Acetate" HPβCD formulations had equivalent efficacy in accelerating conversion of AFIB to normal sinus rhythm, as demonstrated in **FIGURES 12** and **16**.

[0335] (2) As shown in **FIGURES 13** and **16**, the "Low Acetate" solution appeared to have a persistent effect on both prolonging atrial depolarization (Pa) and suppressing AFIB re-induction. AFIB durations after re-induction in the "Low Acetate" group were approximate half of that in the placebo group, even an hour after dosing.

[0336] (3) The hemodynamic effects on heart rate, arterial blood pressure, and left ventricular contractility were comparable between the two solutions (**FIGURES 17-19**).

[0337] (4) As shown in **FIGURE 20**, the "Low Acetate" solution resulted in a greater increase in C_{max} than the "High Acetate" solution. Without wishing to be bound by a particular theory, there could be greater tissue penetration of the "Low Acetate" solution in the alveoli, and enhanced tissue penetration by the "Low Acetate" solution can help explain the persistent effect on atrial depolarization (Pa) duration and suppression of AFIB.

[0338] In addition to the above, it was also observed "High Acetate" formulations produced a "gag response" in the pigs (a contraction of the back of the throat triggered by the delivery of the formulation.) In contrast, the "Low Acetate" solution appeared to induce minimal or no gag response in the pigs to IT administration.

EXAMPLE 11. Exemplary Mixed Acid Flecainide Formulations.

[0339] This example demonstrates several exemplary formulations of flecainide in which flecainide acetate is dissolved in a mixture of different acids. This example also demonstrates that by mixing with a variety of acids, the solubility of flecainide acetate can be increased.

[0340] In this example, solubility of flecainide acetate was measured in total 38 different acid mixture (binary/ternary/quaternary-mixtureofaceticacid/nitricacid/sulfuricacid/citricacid), as listed in **TABLES 15-17**. In this example, flecainide acetate (dosing concentration: ~90 mg/mL) were suspended in the corresponding medium with different binary, ternary, or quaternary acid systems. The suspensions were magnetic stirred (1000 r/min) at 25 °C for 24 hrs and 48 hrs. Centrifugation of the suspension solutions was performed at 10000 rpm (3 min) and then

filtration conducted with 0.45 μm membrane to obtain supernatant for HPLC solubility test and pH test, and residual solids for XRPD test. The max solubility of flecainide acetate (82.4mg/mL) was observed, which was in a mixture of 50 mM acetic acid, 0.5 mM nitric acid, and 0.00375 mM sulfuric acid, with no form conversion.

TABLE 15. Solubility of Flecainide Acetate in Binary Acid Mixture

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
18-A1	50 mM HOAc + 0.5 mM HNO3	64.0	69.5	73.3	79.6	4.6	4.7	N	N
18-A2	50 mM HOAc + 0.25 mM HNO3	64.7	66.7	74.1	76.4	4.5	4.8	N	N
18-A3	50 mM HOAc + 0.0075 mM H2SO4	67.1	67.1	76.8	76.9	4.6	5.0	N	N
18-A4	50 mM HOAc + 0.00375 mM H2SO4	65.8	65.4	75.4	74.9	5.1	4.9	N	N
31-A25	50 mM HOAc + 6 mM Citric acid	65.8	68.2	75.3	78.1	4.7	4.9	Y	Y
31-A26	50 mM HOAc + 3 mM Citric acid	68.6	71.4	78.6	81.4	4.7	4.9	N	N
18-A7	25 mM HOAc + 0.5 mM HNO3	66.0	63.6	75.5	72.9	5.6	5.6	N	N
18-A8	25 mM HOAc + 0.25 mM HNO3	65.5	64.4	75.0	73.7	5.7	5.3	N	N
18-A9	25 mM HOAc + 0.0075 mM H2SO4	64.2	63.5	73.5	72.7	5.5	5.4	N	N
18-A10	25 mM HOAc + 0.00375 mM H2SO4	65.1	65.1	74.6	74.5	5.2	5.4	N	N

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
31-A27	25 mM HOAc + 6 mM Citric acid	65.8	64.1	75.4	73.4	4.9	5.0	Y	Y
31-A28	25 mM HOAc + 3 mM Citric acid	64.6	67.1	73.9	76.8	5.0	5.2	Y	Y

TABLE 16. Solubility of Flecainide Acetate in Ternary Acid Mixture

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
31-A1	50 mM HAc + 0.5 mM HNO3 + 0.0075 mM H2SO4	68.2	66.4	78.1	76.0	4.9	5.0	N	N
31-A2	50 mM HAc + 0.5 mM HNO3 + 0.00375 mM H2SO4	67.4	72.0	77.2	82.4	4.9	5.0	N	N
31-A3	50 mM HAc + 0.5 mM HNO3 + 6 mM Citric acid	63.9	65.3	73.1	74.7	4.8	5.0	Y	Y
31-A4	50 mM HAc + 0.5 mM HNO3 + 3 mM Citric acid	65.9	68.9	75.5	78.9	4.9	5.0	N	N
31-A5	50 mM HAc + 0.25 mM HNO3 + 0.0075 mM H2SO4	65.9	67.0	75.5	76.7	5.0	5.1	N	N
31-A6	50 mM HAc + 0.25 mM HNO3 + 0.00375 mM H2SO4	65.4	67.7	74.9	77.6	5.0	5.2	N	N

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
31-A7	50 mM HAc + 0.25 mM HNO3 + 6 mM Citric acid	62.2	66.1	71.3	75.7	4.8	5.0	Y	Y
31-A8	50 mM HAc + 0.25 mM HNO3 + 3 mM Citric acid	64.2	71.3	73.5	81.6	4.9	5.1	Y	Y
31-A9	50 mM HAc + 0.0075 mM H_2SO4 + 6 mM Citric acid	62.6	69.6	71.7	79.7	4.8	5.0	Y	Y
31-A10	50 mM HAc + 0.0075 mM H2SO4 + 3 mM Citric acid	64.5	66.3	73.9	75.9	4.9	5.0	Y	Y
31-A11	50 mM HAc + 0.00375 mM H2SO4 + 6 mM Citric acid	62.6	63.7	71.7	73.0	4.8	5.0	Y	Y
31-A12	50 mM HAc + 0.00375 mM H2SO4 + 3 mM Citric acid	63.4	64.5	72.5	73.8	4.9	5.2	Y	Y
31-A13	25 mM HAc + 0.5 mM HNO3 + 0.0075 mM H2SO4	64.1	64.6	73.3	73.9	5.3	5.6	N	N
31-A14	25 mM HAc + 0.5 mM HNO3 + 0.00375 mM H2SO4	64.0	67.5	73.3	77.2	5.3	5.6	N	N

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
31-A15	25 mM HAc + 0.5 mM HNO3 + 6 mM Citric acid	62.3	63.0	71.4	72.1	5.0	5.3	Y	Y
31-A16	25 mM HAc + 0.5 mM HNO3 + 3 mM Citric acid	62.5	66.6	71.6	76.3	5.1	5.1	Y	Y
31-A17	25 mM HAc + 0.25 mM HNO3 + 0.0075 mM	62.7	69.0	71.8	79.0	5.3	5.3	N	N
31-A18	25 mM HAc + 0.25 mM HNO3 + 0.00375 mM H2SO4	64.5	66.5	73.8	76.2	5.3	5.3	N	N
31-A19	25 mM HAc + 0.25 mM HNO3 + 6 mM Citric	61.8	64.4	70.8	73.7	5.0	5.0	Y	Y
31-A20	25 mM HAc + 0.25 mM HNO3 + 3 mM Citric	61.8	63.1	70.8	72.3	5.2	5.2	Y	Y
31-A21	25 mM HAc + 0.0075 mM H2SO4 + 6 mM	61.6	63.6	70.5	72.8	5.0	5.1	Y	Y
31-A22	25 mM HAc + 0.0075 mM H2SO4 + 3 mM	62.4	64.6	71.4	74.0	5.1	5.2	Y	Y
31-A23	25 mM HAc + 0.00375 mM H2SO4 + 6 mM Citric acid	62.1	62.5	71.1	71.6	5.0	5.2	Y	Y
31-A24	25 mM HAc + 0.00375 mM H2SO4 + 3 mM Citric acid	62.8	63.8	71.9	73.1	5.1	5.4	Y	Y

TABLE 17. Solubility of Flecainide Acetate in Quaternary Acid Mixture

No.	Medium in Exemplary Formulation	Solubility (mg/mL)				pH		Form Conversion	
		Freebase		Acetate base					
		24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
A29	50 mM HAc + 0.5 mM HNO_3 + 0.0075 mM H2SO4 + 6 mM Citric acid	70.9	71.4	81.1	81.7	4.4	4.5	N	N
A30	25 mM HAc + 0.25 mM HNO_3 + 0.00375 mM H_2SO_4 + 3 mM Citric acid	67.4	69.0	77.2	78.9	4.7	4.8	N	N

EXAMPLE 12. Clinical Performance of Exemplary Flecainide Formulations.

[0341] This example describes an ongoing Phase 2 clinical study conducted with exemplary flecainide formulations as described herein. The FLE-002 (INSTANT) study is a Phase 2, prospective, multi-center study of flecainide acetate oral inhalation solution ("IH Flec") for acute cardioversion to sinus rhythm (SR) in patients with recent onset of symptomatic paroxysmal atrial fibrillation (AF).

[0342] *Patient eligibility*. Patient eligibility for this study is generally consistent with eligibility for IV flecainide. 18 years and older, both male and female sexes are eligible for this study. Inclusion and exclusion criteria are summarized in **TABLE 18A** and **TABLE 18B**, respectively.

TABLE 18A. Patient Inclusion Criteria for Clinical Study

Inclusion	Phase 2a	Phase 2b/3
Clinical Presentation	• Recent-onset, symptomatic AF >1 or <48 hours	• Same
Pre-Study Inclusion	• Current PIP users, post-3 months ablation, recurrent AF	• Same

TABLE 18B. Patient Exclusion Criteria for Clinical Study

Exclusion	Phase 2a	Phase 2b/3
Clinical Presentation	• <**18 years** of age	• <18 **or >85 years of age**

Hemodynamic Criteria	• **Hemodynamic Instability** • **SBP < 90mmHg** • **Ventricular HR <70 or 170 bpm** • History of acute decompensated HF • **Any history** or HF with reduced Ejection Fraction • Other relevant structural heart disease (**prior MI**, signs/symptoms of myocardial ischemia, stenosis, cardiomyopathy)	• Hemodynamic **and/or cardiac** instability • **SBP <100 or > 160 mmHg** • Ventricular HR **<80 or >155 upon screening** • Same • **Abnormal LVEF or Class 2+ HF (NYHA) within 6 months prior to screening** • Prior MI **OR Signs of <u>prior</u> MI**
Arrhythmia Criteria	• Persistent AF • **Atrial flutter at presentation** • History of rhythm abnormalities: LQTS, conduction disease, sick sinus, Brugada, Torsades de pointes • ECG-related features: QTc interval >480ms, QRS duration ≥ 120ms or history of wide QRS, predominately paced heart rhythm, sustained or non-sustained VT, excessive PVC's.	• **One or more episodes of atrial flutter within 6 months prior to screening**
Treatment	• Current AF episode treated with Class 1 or 3 AAD, or ECV • Previous non-responder to flecainide	• **Cardiac Surgery for any exclusionary conditions within 6 months prior to screening**

[0343] *Study Design.* The study consists of 2 parts: Part A and Part B. Part A (dose finding) evaluates the feasibility of administration of IH Flec. Part B will confirm the dose and will include a pilot sub-study to simulate a patient led scenario with medical supervision.

[0344] Part A study. Dosing regimen includes: 30, 60, 90 and 120 mg of IH Flec (inhaled flecainide, *e.g.*, eTLD) and the concentration of flecainide in the inhalation solutions tested includes 35, 45 and 75 mg/mL. IH Flec formulations tested in this study include the ones listed in **TABLE 19** (*, "CD" denotes a cyclodextrin-based formulation including 10% (w/v) hydroxypropyl β-cyclodextrin, 90 mM acetic acid buffer, and having a pH of 5.2; **, "iCD-SAC" denotes a cyclodextrin-based formulation including 20% (w/v) hydroxypropyl β-cyclodextrin, 5 mM acetic acid, and 750 μM saccharin, and having a pH of 5.9.).

Table 19. Exemplary flecainide formulations tested in the clinical study

Formulation / Inhalation solution [concentration (mg/mL)]	**30 [35]**	**60 [35]**	**90 [45]**	**120 [75]**	
	Flec IH-101			**CD* (Flec IH-102)**	**iCD-SAC** (Flec IH-103)**

Flecainide Dose (eTLD)	30 mg	60 mg	90 mg	120 mg	
Concentration of flecainide acetate (mg/mL)	35	35	45	75	
Other components:					
Acetic acid buffer	90 mM			90 mM	5 mM
Hydroxypropyl β-cyclodextrin (w/v)	0			10%	20%
pH*	5.2			5.2	5.9
Estimated Duration of Inhalation Regimen (min)	4.5	10	10	8	
Dosing pattern[a]	A	B	B	C	
Approximate Rate of Dose Delivery (mg/min)	6.7	6.0	9.0	15.0	
Inhalation Regimen	Dose/inhale to completion			Dose/inhale to conversion	

[a]A: 4.5 minutes inhalation (no breaks); B: 4.5 minutes inhalation, followed by 1 minute break, followed by 4.5 minutes inhalation; C: 3 minutes inhalation, followed by 1 minute break, followed by 3 minutes inhalation
- 'Dose/inhale to completion' = inhale until the full dose is administered
- 'Dose/inhale to conversion' = Inhale until the time of conversion of AF to SR, or continue to inhale until the full dose is administered, whichever occurs first
*NaOH is added as necessary to achieve specified pH

[0345] In this study, for inhalation delivery of flecainide, the estimated total lung doses (eTLDs) were calculated to account for losses of flecainide in the inhalation device and losses of flecainide in subjects' mouth and throat. eTLD was thereby used to denote the dose that actually reached the lungs of the subjects. By design, in all nebulizers there can be a residual volume or mass of drug solution that stays in the nebulizer, and there can also be a percentage of the aerosol caught by subject's throat and mouth. For instance, in this study, it was estimated that 30% of the aerosol was lost in subject's throat and mouth. Therefore the eTLD would be:

[0346] eTLD = (100-30)% * amount of aerosolized drug that left nebulizer = 70% * (amount of drug placed in nebulizer – amount of drug staying in nebulizer).

[0347] Part B study. The effective dose in Part A will be confirmed in Part B study. Part B is an open-label, multicenter study in the same patient population as Part A (i.e., recent onset, symptomatic PAF, without known structural heart disease) to confirm the safety (including tolerability) and efficacy of the optimal inhaled flecainide dose determined in Part A. A total of up to 85 patients will be enrolled to evaluate safety and tolerability of the 120 mg eTLD, and to

more accurately determine the AF conversion rate for the 120 mg dose. Part B also includes optional sub-studies that are open to consenting patients: 1) to evaluate the feasibility of using a hand-held echocardiograph device during screening, and 2) to evaluate independent self-administration of inhaled flecainide in the hospital setting for a recurrent episode of recent-onset AF, but only for patients whose recent-onset AF was converted to SR with inhaled flecainide with the initial treatment.

Data Collection

[0348] In both parts of the study, after written informed consent has been obtained, the patient is connected to cardiac telemetry monitoring and study ECG devices to evaluate the stability of AF during the next hour. Vital signs, triplicate 12-lead ECGs, and blood samples for PK analysis are collected at multiple serial time points just before, during, and after the inhalation regimen, and at the time of conversion to SR. Ambulatory ECG (12-lead Holter) data are collected from the time of informed consent until 90 minutes postdose in order to identify the time of conversion to SR and to monitor safety. Discharge is at the discretion of the treating physician but may not be scheduled prior to 90 minutes postdose. If conversion to SR does not occur within a certain time period postdose, the Investigator may offer another appropriate therapy, as per the clinical site's standard-of-care, except for IV ibutilide or sotalol which are not allowed. All patients have a Day 2 and a Day 5 (± 1 day) telephone assessment.

Nebulizer configuration.

[0349] The AeroEclipse®II BAN inhaler was used for nebulization and inhalation of the exemplary flecainide formulations. It is available as an approved device in several countries across the world including European countries, USA, and Canada. The inhaler is a hand-held, breath actuated, jet nebulizer which operates through a source of compressed air available as medical air in the hospital ER. The AeroEclipse®BAN delivers a high respirable dose and an optimal particle size to reach the deeper lung regions to enable faster drug absorption. Flecainide acetate inhalation solution or placebo inhalation solution is transferred from the vial into the reservoir of the AeroEclipse®II BAN at a volume corresponding to the required dose to the lung (**TABLE 20**), in accordance with the specific instructions provided for each study protocol.

TABLE 20

Study Drug	Nominal Dose Level (eTLD) (mg)	Nominal Volume per Dose (mL)	Number of Nebulizers Required	Total Volume Filled into each Nebulizer (mL)*
FlecIH-101	30	2.7	1	2.7†
	60	5.4	2	2.7†
	90	6.6	2	3.3‡
FlecIH-102	120	4.2	1	4.2‡
	90	3.5	1	3.5‡
FlecIH-103	120	4.2	1	4.2‡
	90	3.5	1	3.5‡

* The total volume to be filled in each dosing cup are based on the following calculations:

1. † Assumes a 70% lung deposition;
   ‡ Assumes a 70% lung deposition and in addition, 12.5 % loss due to fugitive aerosol based on in-vitro experiments.
2. Accounts for device retention of approximately 1.5 mL.

Inhalation guidelines.

[0350] Participants in the study were administered the study medications according to the following guidelines:

- Subject self-administers inhalation using the AeroEclipse® II BAN
- Subject is seated upright in a comfortable chair or adjustable bed with table that has adjustable height in front (e.g. overbed table on casters) where the subject can rest his/her arms (e.g. overbed table on casters) from approximately 30 minutes prior to the start of inhalation up to at least 15 minutes after the last inhalation is completed. The setting at the site allows for subject to remain in this upright sitting position while linked to cardiac monitoring systems, while blood samples are being collected and while self-administering the inhalation solution which is linked to compressed air.
- The subject receives clear instructions from trained study personnel on how to self-administer the treatment in accordance with the instructions for use.
- A topical oral anesthetic spray (e.g., containing lidocaine [e.g., Medica] or phenol [e.g., Chloraseptic]) or lozenge [e.g., Trachitol or Cepacol] may be applied to the back of the subject's throat prophylactically if not contraindicated, to improve the tolerability of the inhalation procedure.

- A sugar-containing spray or lozenge (e.g., for dry mouth) may be applied or used prophylactically if not contraindicated, to improve the tolerability of the inhalation procedure.
- The subject may practice the inhalation procedure (without flecainide and for approximately 1 minute, for example) prior to study drug administration.
- Once the inhalation pattern is established, the subject should not remove inhaler device from the mouth for the required inhalation time. If the subject removes the nebulizer for any reason (e.g., cough, excessive saliva, etc.) for > 30 seconds, then the inhalation time for that inhalation should be extended by the length of the interruption. Subjects can elect to terminate inhalation of study medication at any time, for any reason.

Part A: Study Enrollment, Demographics, and Medical History by Inhaled Flecainide Dose Cohort

[0351] Enrollment status for completed Part A of the study is shown in **TABLE 21**.

TABLE 21. Number of Patients Enrolled in the Study

Flecainide Dose (eTLD)	**30 mg**	**60 mg**	**90 mg**	**120 mg**		**Total (N)**
Inhalation Solution & Formulation	**35 mg/mL FlecIH-101 (N)**		**45 mg/mL FlecIH-101 (N)**	**75 mg/mL FlecIH-102 (N)**	**75 mg/mL FlecIH-103 (N)**	
Enrolled & Completed	10	22	21	19	29	101
Efficacy Evaluable	10	20[a]	21	17[b]	27[c]	95

Abbreviations: N = number of patients in a given group
[a]2 patients were not in AF at the time of inhaled flecainide administration
[b]2 patients: 1 was not in AF at the time of inhaled flecainide administration and 1 did not complete the inhalation (dosing was interrupted)
[c]2 patients: 1 was not in AF at the time

[0352] Selected demographic and medical history information of the patients enrolled in Part A is provided in **TABLE 22**.

TABLE 22. Demographic and Medical History of Enrolled Patients

Characteristic	**30 mg (N=10)**	**60 mg (N=22)**	**90 mg (N=21)**	**120 mg**	
				FlecIH-102 (N=19)	**FlecIH-103 (N=27)**
Age					
mean ± SD	59.3±6.5	62.0±13.4	58.9±9.3	63.4±8.6	62.9±12.8
median	60.0	63.0	59.0	62.0	61.0
Min-Max	48.0 – 66.0	33.0 – 89.0	39.0 – 76.0	53.0 – 82.0	39.0 – 84.0
Gender: Male	90.0%	77.3%	66.7%	42.1%	70.4%

Duration of presenting AF period					
≥ 1 h up to ≤ 24 h	60.0%	63.6%	85.7%	94.7%	88.9%
> 24 h up to ≤ 48 h	40.0%	36.4%	14.3%	5.3%	11.1%
Body Mass Index					
mean ± SD	26.9±3.9	26.3±3.1	27.3±3.9	28.2±5.4	26.6±3.8
median	25.75	26.05	26.40	26.60	26.30
Min-Max	23.1 – 36.3	21.5 – 31.6	20.6 – 34.1	20.9 – 38.8	29.6 – 36.2
CHA2DS2VASc score					
mean ± SD	1.1±0.9	1.6±1.5	1.3±1.3	1.7±1.4	1.5±1.5
median	1.00	1.50	1.00	1.00	1.00
Min-Max	0.0 – 2.0	0.0 – 6.0	0.0 – 4.0	0.0 – 4.0	0.0 – 4.0
NYHA Class					
No heart failure	90.0%	100.0%	100.0%	100.0%	92.6%
Class I	10.0%	0.0%	0.0%	0.0%	7.4%
AF Episode is:					
First AF episode	60.0%	50.0%	38.1%	47.4%	40.7%
Recurrent episode of PAF	40.0%	40.0%	47.6%	47.4%	55.6%
Episode post-cardiac ablation for PAF	0.0%	10.0%	14.3%	5.3%	3.7%

Abbreviations: N = number of patients in a given group; PAF = paroxysmal atrial fibrillation; SD = standard deviation; h = hour
Source: February 2020 DSMB Report, 17 February 2020

Part A: Pharmacodynamic (QRS Interval) Results

[0353] The 12-lead ECG recordings for the patients enrolled in Part A of the study have been analyzed to summarize the maximal QRS interval and change from baseline QRS (L QRS) interval durations following inhaled flecainide (**TABLE 23**). The QRS interval was found to transiently increase soon after the end of dose inhalation and quickly return toward pre-dose levels. The mean maximal QRS interval durations following inhaled flecainide at the 30, 60, 90 and 120 mg eTLDs were similar (93 to 99 msec). The mean L QRSmax increases above baseline (i.e., prior to dosing) for the 30, 60, 90 and 120 mg (FlecIH-102 and FlecIH-103) eTLD cohorts were 1.6, 4.2, 4.1, 9.0 and 9.5 msec, respectively.

TABLE 23. Summary of Maximal QRS Intervals

Parameter	**30 mg (N=9)**	**60 mg (N=20)**	**90 mg (N=20)**	**120 mg**	
				FlecIH-102 (N=15)	**FlecIH-103 (N=21)**
QRSmax					
mean ± SD	99.1 ± 20.0	95.9 ± 7.6	92.7 ± 9.4	94.7 ± 12	98.5 ± 6.5
Min-Max	79.1 – 109.1	83 – 115.5	83.3 - 113	86.3 – 136	91 – 106.3
ΔQRSmax					
mean ± SD	1.6 ± 1.7	4.2 ± 4.6	4.1 ± 3.2	9.0 ± 7.5	9.5 ± 4.1
Min-Max	0 – 5.3	-3.0 – 13.1	0.3 – 9.7	0.3 – 30.5	5.8 – 20.3

[0354] The magnitude of the prolongations of the QRS interval duration (Δ QRSmax) for the individual patients in Part A of the study (60, 90 and 120 mg eTLDs) are graphically presented in **FIGURE 21**. There was only one patient who had a Δ QRS of ≥ 30 msec following inhaled flecainide; this patient (120 mg FlecIH-102) with a baseline pre-dose QRS interval duration of 106 msec had a maximum QRS duration of 136 msec (Δ QRSmax of 30.5 msec). The ECG was consistent with left anterior fascicular block, and no treatment was required.

Part A: Adverse Events

[0355] Adverse event data for 99 patients dosed at the different dose levels with inhaled flecainide is summarized in **TABLE 24**. Treatment-emergent adverse events (TEAEs) were reported by 80/99 patients (81%) and were considered related to study drug in 74/99 (75%) patients. Treatment-emergent serious adverse events (TESAEs) were reported by 7 patients. Three patients in the 60 mg group experienced an SAE that was considered to be unrelated to study drug. SAEs considered study drug-related were reported for 1/21 patients in the 90 mg group (5%) and 3/46 patients (6.5%) in the 120 mg group. All study drug-related SAEs were transient and resolved without treatment or clinical sequelae. No deaths have been reported in patients enrolled in the study.

TABLE 24. Summary of Number of Adverse Events

	Flecainide Dose (eTLD)					
	30 mg	**60 mg**	**90 mg**	**120 mg**		**Total**
	FlecIH-101			**FlecIH-102**	**FlecIH-103**	
	(N=10) n (%)	**(N=22) n (%)**	**(N=21) n (%)**	**(N=19) n (%)**	**(N=27) n (%)**	**(N=99) n (%)**
Patients with at least one:						
TEAE	9 (90)	16 (73)	18 (86)	16 (84)	21 (78)	80 (81)
Study-drug Related[a,b]	8 (80)	14 (64)	17 (81)	16 (84)	19 (70)	74 (75)
Moderate or Severe[c]	1 (10)	6 (27)	6 (29)	11 (58)	11 (41)	35 (35)
Severe[c]	0	1 (5)	0	0	1 (4)	2 (2)
TESAE[d]	0	3 (14)	1 (5)	1 (5)	2 (7)	7 (7)
Study-drug Related[a,b]	0	0	1 (5)	1 (5)	2 (7)	4 (4)
Moderate or Severe[c]	0	2 (9)	1 (5)	1 (5)	2 (7)	6 (6)
Severe[c]	0	1 (5)	0	0	1 (4)	2 (2)

Abbreviations: N = number of patients in a given group; n = number of patients with a given event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] Study-drug related = Investigator assessment of probably or possibly related to Study Drug

[b] Patients reporting more than one event were counted only once using the strongest study-drug relationship category

[c] Patients reporting more than one event were counted only once using the highest severity grade

[d] TESAE tally based on manual review of SAEs reported

[0356] The most commonly reported (≥ 5 patients [5%] overall) TEAEs in decreasing order of frequency were (**TABLE 25**): cough (52%), oropharyngeal pain (14%), throat irritation (12%), dysphagia (9%), salivary hypersecretion (8%), hypotension (7%), dyspnea (6%) and dizziness (5%). In general, the incidence of AEs by preferred term did not increase with an increase in dose. The incidence of AEs associated with the inhalation (e.g., cough, throat irritation, etc.) appeared to be less in patients treated at the 120 mg eTLD with the FlecIH-103 inhalation solution. The majority of patients had events that were considered mild (64/99; 65%); 33/99 (33%) patients had events that were moderate in intensity. Only 2 (2%) patients had severe TEAEs, and in both cases, it was a worsening of a pre-existing condition; both events were considered SAEs. In general, the incidence of TEAEs that were considered related to study drug did not an increase with an increase in dose.

TABLE 25. Summary of Adverse Events

	Flecainide Dose Group (eTLD)					
	30 mg	**60 mg**	**90 mg**	**120 mg**		**Total**
	FlecIH-101			**FlecIH-102**	**FlecIH-103**	
System Organ Class, Preferred Term[a]	**(N = 10) n (%)**	**(N = 22) n (%)**	**(N = 21) n (%)**	**(N = 19) n (%)**	**(N = 27) n (%)**	**(N = 99) n (%)**
Gastrointestinal disorders	0	5 (23)	8 (38)	3 (16)	7 (26)	23 (23)
Dysphagia	0	2 (9)	3 (14)	2 (11)	2 (7)	9 (9)
Salivary hypersecretion	0	1 (5)	4 (19)	1 (5)	2 (7)	8 (8)
Nervous system disorders	2 (20)	2 (9)	0	1 (5)	2 (7)	7 (7)
Dizziness	2 (20)	1 (5)	0	0	2 (7)	5 (5)
Respiratory, thoracic and mediastinal disorders	8 (80)	14 (64)	12 (57)	14 (74)	12 (44)	60 (61)
Cough	8 (80)	9 (41)	11 (52)	13 (68)	10 (37)	51 (52)
Oropharyngeal pain	0	3 (14)	4 (19)	4 (21)	3 (11)	14 (14)
Dyspnea	0	1 (5)	1 (5)	3 (16)	1 (4)	6 (6)
Throat irritation	1 (10)	6 (27)	1 (5)	3 (16)	1 (4)	12 (12)
Vascular disorders	1 (30)	2 (9)	1 (5)	2 (11)	3 (11)	10 (10)

Hypotension	1 (10)	1 (5)	1 (5)	2 (11)	2 (7)	7 (7)

Abbreviations: N = number of patients in a given group; n = number of patients with a given event; TEAE = treatment-emergent adverse events

Note: If a patient had more than one event coded to the same MedDRA term, the patient was counted only once

[a] 8 patients had their AF terminated on the study day (either by study drug or other means [or they did not have AF at presentation]), and had a recurrence of AF in the days following the study day; these events of AF ('atrial fibrillation') were categorized as TEAEs, and none were considered related to study drug.

[0357] Adverse events of special interest (AESIs) for the study include the following:

1. AEs related to the AeroEclipse® BAN inhalation device
2. Elevation of liver enzyme laboratory findings (combined elevations of aminotransferases and bilirubin) considered to signal possible liver injury
3. Pregnancy in a female study participant or in a female partner of a study participant while participating in the study
4. Cardiac AEs known to be related to other formulations of flecainide (i.e., IV and oral): hypotension, ventricular tachycardia, bradycardia, sinus pauses post conversion of AF to SR, and atrial flutter with 1:1 conduction with fast ventricular response (ventricular heart rate $\geq$ 200 bpm).

These events are closely monitored in the trial in order to rapidly detect any trends indicative of a safety concern. The cardiac AESIs are monitored by frequent review of AEs, vital sign and ECG listings.

[0358] No AESIs related to the inhalation device, liver enzymes or pregnancies have been reported. Cardiac AESIs have been reported as follows:

- Hypotension: 7 patients (3 mild and 1 moderate, related; 3 moderate, not related). All hypotension cases were transient, none were considered to be serious, and none required treatment with vasopressors or positive chronotropic/inotropic agents.
- Bradycardia: 4 patients (2 mild, 1 related [post-conversion to SR] and 1 not related; 1 moderate, related [post-conversion to SR]; 1 SAE, related. All bradycardia events resolved without treatment.
- Sinus pause post-conversion of AF to SR: 2 patients (2 SAEs, related. Both sinus pause events resolved quickly without treatment.
- Atrial flutter with 1:1 conduction and rapid ventricular response: 1 patient (1 SAE, related. Event resolved quickly without treatment.

[0359] 4 patients experienced SAEs (**TABLE 26)** that were considered study-drug related: sinus pause/ventricular asystole associated with conversion to SR (2 patients), bradycardia (1 patient), and atrial flutter with 1:1 conduction and a fast ventricular response (1 patient).

TABLE 26. Summary of Adverse Events of Special Interest

Patient ID	**Dose Cohort (mg eTLD)**	**SAE**	**C_{max} (ng/mL)**
NL020-1013	90	Sinus Pause post conversion	833.8
NL033-1008	120	Sinus Pause post conversion	430.8
NL030-1008	120	Severe Bradycardia	332.4
NL038-1001	120	Atrial flutter rapid VR	204.6

[0360] Three additional patients (60 mg dose cohort) had SAEs reported, none of which were considered to be related to study-drug treatment.

Part A; Pharmacokinetics and Conversion Rate

[0361] Plasma levels of flecainide are used to monitor drug delivery of flecainide into the systemic circulation following oral inhalation of the drug. Peak plasma levels (C_{max}) of flecainide achieved following the inhalation have been shown to occur within 3 minutes of completion of the inhalation. The C_{max} values for the 30, 60, 90 and 120 mg dose cohorts are provided in **TABLE 27**, along with the rate of AF conversion to SR (within 60 minutes of dosing) for each dose cohort. There was a dose-related increase in mean C_{max} values.

TABLE 27.

Parameter	**Flecainide Dose (eTLD)**				
	30 mg	**60 mg**	**90 mg**	**120 mg**	
				FlecIH-102	**FlecIH-103**
Number of patients treated	10	20	21	19	27
Number of evaluable patients (by PK)	10	20	21	17	27
C_{max} (mean ± SD, ng/mL) Range (ng/mL)	127 ± 99.5 5.8 – 369 78%	199 ± 222 6.6 – 817 111%	248 ± 207 17 – 834 83%	400 ± 269 3.6 – 854 67%	385 ± 209 (n=26) 131 – 871
Conversion Rate (AF to SR)	1/10 (10%)	7/20 (35%)	7/21 (33%)	6/17 (35%)	12/27 (44%)
ΔQRS_{max} (msec, (SEM)) (number of patients)	5.5±13.1 (4.1) (10)	4.2 ± 4.6 (1.0) (20)	4.1 ± 3.2 (0.7) (20)	9.0 ± 7.5 (1.9) (15)	9.5 ± 4.1 (0.9) (21)

Note: Evaluable patients include those who were in AF at the time of treatment and completed inhalation of the flecainide dose

[0362] The rate of conversion of AF to SR by dose level is depicted in the bar graph in **FIGURE 23A**; although the conversion rate increased from 10 to 35% between the 30 and 60 mg eTLD cohorts, the conversion rate remained in the mid-30% range for the 90 and 120 mg (FlecIH-102) eTLDs. With implementation of the FlecIH-103 inhalation solution, the conversion rate for the 120 mg (FlecIH-103) cohort increased to 44%. The therapeutic plasma range for oral and IV flecainide is generally considered to be 200-1000 ng/mL (Conard et al., 1984a and 1984b; Flecainide Acetate Tablets US Prescribing Information, 2017). For patients in AF who were treated with inhaled flecainide doses of 60, 90 or 120 mg dose, a categorical analysis was performed using a C_{max} cut-off of 250 ng/mL; patients achieving a Cmax higher than 250 ng/mL had a conversion rate of 45%, whereas patients with C_{max} less than 250 ng/mL had a conversion rate of ~30% (**FIGURE 23D**). As would be expected, these data suggest that the probability of conversion of AF to SR is greater in patients who reach a plasma concentration in the therapeutic range following inhalation of flecainide.

[0363] For the 32 patients across all dose groups (30, 60, 90 and 120 mg) whose AF converted to SR within 60 minutes of completing the inhalation, the median time to conversion was very rapid, that is, 3.5 minutes from the end of the inhalation (**FIGURE 24**), with the time of conversion ranging from -7 to 40 minutes from the end of the inhalation. The time to conversion was $\leq$ 3 minutes for 50% of those who converted and was $\leq$ 4 minutes for 56% of those who converted to SR.

[0364] Eligibility for enrollment in Part A of the study included a requirement that the baseline ventricular rate be $\geq$ 70 bpm and $\leq$ 170 bpm. In a post-doc analysis, it was observed that patients having a slow ventricular rate (< 80 bpm) responded less favorably to conversion of their AF to SR by inhaled flecainide. The conversion rate for the pooled dose groups of patients (eTLDs of 60, 90 and 120 mg) with a baseline ventricular rate < 80 bpm was 15%, whereas those having a baseline ventricular rate of $\geq$ 80 bpm and $\leq$ 155 bpm had a higher conversion rate of 42% (**FIGURE 25**). For the 120 mg cohort (FlecIH-103), the conversion rate for patients with a baseline ventricular rate $\geq$ 80 bpm and $\leq$ 155 bpm was 58% (11/19), whereas for those with a baseline rate < 80 bpm, it was only 17% (1/6).

[0365] Patients in AF with slower ventricular rates can still have a very rapid atrial rate due to AF. The slower ventricular rate in patients with AF can be indicative of high vagal tone. The high vagal tone can lead to slower AV nodal conduction and shorter atrial refractory period. The slower AV nodal conduction can be the cause of the slower ventricular rate and the shorter atrial

refractory period can render flecainide less effective to convert AF to SR. Without wishing to be bound by aby particular theory, the latter is a plausible explanation to for the lower effectiveness of flecainide to convert AF to SR when the heart rate is <80 bpm.

Part A: Summary

[0366] 101 patients have been treated with inhaled flecainide (30 mg, n=10; 60 mg, n=22; 90 mg, n=21; 120 mg [FlecIH-102], n=19; and 120 mg [FlecIH-103], n=29) in the INSTANT (FLE-002) Study. Inhaled flecainide in this dose range has been shown to be safe. Dose-related increases in C_{max} were observed (127, 199, 248, 400 and 385 ng/mL, respectively) with conversion rates of AF to SR (10%, 35%, 33%, 35% and 44%, respectively). In patients whose AF converted to SR with inhaled flecainide, the median time to conversion was 3.5 minutes after completion of the inhalation. Conversion of AF to SR was shown to be greater in patients who achieved C_{max} in the therapeutic range for flecainide (> 250 ng/mL), and in patients with a ventricular rate > 80 bpm while in AF.

[0367] Prolongation of the QRS interval in patients receiving inhaled flecainide was in a range considered to be safe. There was only one patient (120 mg eTLD) who had a ΔQRSmax of ≥ 30 msec following inhaled flecainide; the patient had a transient increase in QRS duration to 136 msec from a baseline of 106 msec (ΔQRSmax of 30.5 msec). The ECG was consistent with left anterior fascicular block, and no treatment was required.

[0368] The majority of patients had AEs that were mild in severity and the most commonly reported AEs were associated with the inhalation route of administration, e.g., cough and throat irritation. Among all patients treated in Part A, 4 patients experienced SAEs considered related to inhaled flecainide that are consistent with the known effects of IV flecainide used for the same indication: sinus pause/arrest post-conversion of AF to SR (2 patients), bradycardia (1 patient), and atrial flutter with 1:1 conduction and rapid ventricular response (1 patient). All SAEs resolved rapidly without treatment.

[0369] Patients treated with the FlecIH-103 inhalation solution with improved organoleptic properties appeared to have a lower incidence of AEs related to the inhalation and a higher conversion rate.

EXAMPLE 13. Sensory Property Evaluation of Exemplary Formulations.

[0370] This example describes sensory property evaluations of some exemplary formulations according to the present disclosure.

[0371] One example formulation that was tested contains 75 mg/mL flecainide acetate in 20% HPβCD, 5 mM ascorbic acid, and 0.75 mM saccharin. The pH of the solution is 5.9. This

formulation has less odor as compared to acetic acid-based formulations. Subjects inhaling this formulation did not cough and reported it caused stinging feeling in the throat, but such feeling went away in minutes. Its overall sensory property is much improved as compared to Flec IH-103 formulation (75 mg/mL flecainide acetate in 20% HPβCD, 5 mM acetic acid, 0.75 mM saccharin).

[0372] Another example formulation contains 75 mg/mL flecainide acetate in 20% HPβCD, 5 mM DL-lactic acid, 0.75 mM saccharin. The pH of the solution is 5.9. This formulation also has less odor as compared to acetic acid-based formulations. Subjects inhaling this formulation reported there was no stinging feeling in the throat and its overall feeling was even better as compared to the above ascorbic acid-based formulation.

A third example formulation contains 75 mg/mL flecainide acetate in 20% HPβCD, 5 mM citric acid, 0.75 mM saccharin. The pH of the solution is 5.7. This formulation also has no vinegary odor. Subjects inhaling this formulation reported there was minimal throat discomfort or the discomfort would disappear in minutes. No cough was observed.

EXAMPLE 14. Solubility of Flecainide in D/L-Lactic Acid Media

[0373] The solubility of flecainide was measured in both D-lactic acid and L-lactic acid aqueous solutions after resting for 24 hours and 48 hours.

[0374] Flecainide freebase was suspended in pure water or 20% w/v HPβCD at 100 mg flecainide per milliliter of solution. D-lactic acid, L-lactic acid, or DL-lactic acid was slowly added portionwise to the suspension while stirring. The system was left to equilibrate for 30 minutes, and the pH was determined. The pH was then adjusted to 5.2-6 with NaOH if necessary. After addition of NaOH, the system was again left to equilibrate for 30 minutes before pH was measured. After the desired pH was achieved, the suspension was stirred (1000 rpm) at ambient temperature for 48 hours. At 24 hours and 48 hours of stirring, samples of each solution were centrifuged at 10000 rpm for 2 minutes and filtered with a 0.45 μm membrane to obtain supernatant for pH determination and HPLC analysis. Solids from each sample were also characterized by X-ray powder diffraction (XRPD) analysis. The results are summarized in **TABLE 28**.

TABLE 28

Media		Solubility (mg/mL)		pH			Form Change	
Excipient	**Acid**	**24 h**	**48 h**	**initial**	**24 h**	**48 h**	**24 h**	**48 h**
none	DL-lactic acid	76.3	73.4	5.3	6.1	6	Y	Y

	D-lactic acid	90.1	91	5.2	5.1	5.4	*	*
	L-lactic acid	96.6	97.8	5.3	5.6	5.1	*	*
20% w/v HPβCD	DL-lactic acid	72.4	71.3	5.3	6.5	6.4	Y	Y
	D-lactic acid	84.8	88.4	5.2	5.8	5.5	*	*
	L-lactic acid	87.6	89.3	5.7	6.3	6	*	*

*No XPRD characterization was performed because residual solid was observed other than slight cloudiness after 24 h and 48 h.

EXAMPLE 15. Pulmonary Delivery of Flecainide Can Reduce Atrial Fibrillation Conversion Dose and Minimize Negative Inotropic Burden

[0375] This example examines the negative inotropic burden created by pulmonary delivery or intravenous delivery of flecainide in a porcine model of atrial fibrillation.

[0376] In an intact porcine model of AF, the effects of pulmonary and intravenous (IV) administration of flecainide on left ventricular (LV) contractility (LV dP/dt max) were examined at doses that are effective in converting AF to sinus rhythm. The magnitude of the decrease in LV dP/dt max and time that it remained below baseline, measured by the area under the curve (AUC), is referred to as the negative inotropic burden.

[0377] Flecainide was delivered via intratracheal administration at 1.5 mg/kg bolus and compared to IV infusion at 1.0 mg/kg over 2 min (lower-dose, rapid) and 2.0 mg/kg over 10 min (higher-dose, slow; ESC guideline) in 11 closed-chest, anesthetized Yorkshire pigs. These doses of flecainide have been shown effective in converting AF to sinus rhythm. Catheters were fluoroscopically positioned in the right atrium for pacing at 140 beats/min and in the LV to measure QRS complex duration and contractility (LV dP/dt). Intratracheal flecainide was delivered via a catheter positioned at the bifurcation of the main bronchi.

[0378] Peak plasma levels (C_{max} values) were similar among three groups. But the AUC of plasma concentrations over time was greater for the higher-dose, slow IV infusion of flecainide than for either intratracheal instillation (by 32%) or lower-dose, rapid IV infusion (by 88%).

[0379] FIGURE 26A is a summary of the negative inotropic burden observed in the animals. Based on AUC of LV dP/dt max, the negative inotropic burden is 3.1- to 3.8-fold greater for the higher IV (1006% • min) than for lower IV (323% • min) or intratracheal doses (263% • min).

[0380] Further, there was a corresponding inverse increase in QRS complex prolongation. The decrease in LV dP/dt max (Δ %) was correlated with the prolongation of the QRS complex (Δ ms) ($y = -1.43x - 3.67$, $r^2 = 0.69$, $p<0.0001$) (FIGURE 26B).

[0381] These data suggest that rapid delivery of pulmonary or IV flecainide can reduce the dose of drug required to achieve C_{max} levels associated with conversion of AF, and the attendant decrease across time in exposure of the ventricles to flecainide can reduce QRS complex prolongation and the accompanying negative inotropic burden.

[0382] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the present disclosure may be employed in practicing the present disclosure. It is intended that the following claims define the scope of the present disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. A pharmaceutical composition, comprising: a therapeutically effective amount of a salt of flecainide, wherein said pharmaceutical composition is in the form of a liquid solution that has said salt of flecainide at a concentration above 60 mg/mL.

2. The pharmaceutical composition of claim 1, further comprising a cyclodextrin.

3. The pharmaceutical composition of claim 1 or 2, wherein a pH of said solution is above 5.5 at room temperature.

4. The pharmaceutical composition of claim 2, wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

5. The pharmaceutical composition of claim 2, wherein said concentration of said cyclodextrin is from about 15% (w/v) to about 25% (w/v) of said solution.

6. The pharmaceutical composition of claim 2, wherein said concentration of said cyclodextrin is at least about 10% (w/v) of said solution.

7. The pharmaceutical composition of claim 2, wherein said concentration of said cyclodextrin is about 20% (w/v) of said solution.

8. The pharmaceutical composition of claim 1, wherein said concentration of said salt of flecainide is about 65 mg/mL to about 130 mg/mL.

9. The pharmaceutical composition of claim 1, wherein said concentration of said salt of flecainide is about 75 mg/mL.

10. The pharmaceutical composition of claim 1, wherein said salt of flecainide is selected from the group consisting of: flecainide acetate, flecainide hydrochloride, flecainide citrate, flecainide phosphate, and flecainide nitrate.

11. The pharmaceutical composition of any prior claim, wherein said salt of flecainide comprises flecainide acetate.

12. The pharmaceutical composition of claim 1, further comprising an acid.

13. The pharmaceutical composition of claim 12, wherein said acid is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

14. The pharmaceutical composition of claim 12, wherein a concentration of said acid in said pharmaceutical composition is about 2 mM to about 50 mM.

15. The pharmaceutical composition of claim 12, wherein said concentration of said acid is about 20 mM.

16. The pharmaceutical composition of claim 12, wherein said concentration of said acid is about 5 mM.

17. The pharmaceutical composition of claim 12, wherein said acid comprises acetic acid.

18. The pharmaceutical composition of claim 17, wherein a concentration of acetic acid is about 5 mM.

19. The pharmaceutical composition of claim 12, wherein said acid comprises citric acid.

20. The pharmaceutical composition of claim 19, wherein a concentration of citric acid is about 5 mM.

21. The pharmaceutical composition of claim 12, wherein said acid comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

22. The pharmaceutical composition of claim 3, wherein said pH of said solution is from about 5.5 to about 6.5.

23. The pharmaceutical composition of claim 3, wherein said pH of said solution is about 5.9.

24. The pharmaceutical composition of claim 1, further comprising a sweetener.

25. The pharmaceutical composition of claim 24, wherein said sweetener comprises saccharin.

26. The pharmaceutical composition of claim 24, wherein said sweetener comprises saccharin sodium.

27. The pharmaceutical composition of any prior claim, wherein said pharmaceutical composition is formulated for administration via inhalation.

28. The pharmaceutical composition of any prior claim, wherein said pharmaceutical composition is a nebulized solution that comprises nebulized droplets having a mass median aerodynamic diameter of less than 10 μm.

29. A unit dose of said pharmaceutical composition of any prior claim, comprising about 50 mg to about 350 mg of said salt of flecainide.

30. The unit dose of claim 29, comprising about 60 mg to about 150 mg of said salt of flecainide.

31. The unit dose of claim 29, comprising about 100 mg to about 250 mg of said salt of flecainide.

32. The unit dose of claim 29, comprising about 90 mg of said salt of flecainide.

33. The unit dose of claim 29, comprising about 120 mg of said salt of flecainide.

34. The unit dose of claim 29, comprising about 200 mg of said salt of flecainide.

35. A kit, comprising: said pharmaceutical composition or said unit dose of any prior claim and instructions for use of said pharmaceutical composition for treatment of a heart condition.

36. The kit of claim 35, further comprising a container containing said pharmaceutical composition.

37. The kit of claim 36, wherein said container is selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.

38. A kit, comprising:

(1) a pharmaceutical composition that comprises:

(a) a salt of flecainide,

(b) a cyclodextrin, and

(c) an acid;

(2) a receptacle containing said pharmaceutical composition; and

(3) instructions for use of a nebulizer to inhalationally administer a dose of said pharmaceutical composition in aerosol to a subject, wherein said dose contains from about 50 mg to about 250 mg of said salt of flecainide, and said aerosol of said pharmaceutical composition has droplets that have a mass median aerodynamic diameter of less than 10 μm; and

wherein said pharmaceutical composition is in the form of a liquid solution that has:

(i) said salt of flecainide at a concentration of from about 65 mg/mL to about 95 mg/mL,

(ii) said cyclodextrin at a concentration of from about 10% (w/v) to about 30% (w/v) of said solution; and

(iii) a pH of from about 5.5 to about 6.5 when said pH is measured at room temperature.

39. A system, comprising: said pharmaceutical composition of any prior claim and a nebulizer.

40. The system of claim 39, wherein said pharmaceutical composition is formulated for administration via the nebulizer, wherein the nebulizer is selected from the group consisting of a breath-actuated jet nebulizer, a vibrating mesh nebulizer, and a ultrasonic nebulizer.

41. The system of claim 39, further comprising instructions for use of said nebulizer and said pharmaceutical composition for treatment of a heart condition.

42. The system of claim 39, further comprising instructions for use of said nebulizer and said pharmaceutical composition for treatment of atrial arrhythmia.

43. The system of claim 39, wherein said nebulizer is configured to deliver said pharmaceutical composition as droplets having a mass median aerodynamic diameter of less than 10 μm.

44. The system of claim 39, wherein said nebulizer is a breath-actuated nebulizer.

45. The system of claim 39, wherein said nebulizer is a jet nebulizer.

46. The system of claim 39, wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 60 mg to about 150 mg of said salt of flecainide.

47. The system of claim 39, wherein said instructions contain instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains about 75 mg to about 125 mg of said salt of flecainide.

48. A system, comprising:

a pharmaceutical composition that comprises a salt of flecainide, a cyclodextrin, and an acid;

a nebulizer configured to deliver said pharmaceutical composition as droplets having a mass median aerodynamic diameter of less than 10 μm; and

instructions for use of said nebulizer to deliver said pharmaceutical composition in a unit dose that contains between about 50 mg and about 250 mg of said salt of flecainide,

wherein said pharmaceutical composition is in the form of a liquid solution that has (i) said salt of flecainide at a concentration of between 65 mg/mL and 100 mg/mL, (ii) said cyclodextrin at a concentration of between about 10% (w/v) and about 30% (w/v) of said solution; and (iii) a pH of between about 5.5 and about 6.5 at room temperature..

49. A method of treating a subject suffering from a heart condition, comprising: administering to said subject via inhalation a pharmaceutical composition in the form of a liquid solution, wherein said pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein a concentration of said salt of flecainide in said pharmaceutical composition is above 60 mg/mL.

50. The method of claim 49, wherein said pharmaceutical composition further comprises a cyclodextrin.

51. The method of claim 49 or 50, wherein a pH of said solution is above 5.5 when said pH is measured at room temperature.

52. A method of treating a human subject suffering from a heart condition, comprising administering to said subject via inhalation within about 10 min a pharmaceutical composition in the form of a liquid solution, wherein said pharmaceutical composition comprises a therapeutically effective amount of a salt of flecainide, and wherein said administration results in a peak plasma concentration (Cmax) of said salt of flecainide in said subject that is at least 200 ng/mL.

53. The method of claim 52, wherein a concentration of said salt of flecainide in said pharmaceutical composition is above 60 mg/mL of said solution.

54. The method of claim 49, 52 or 53, wherein said pharmaceutical composition further comprises a cyclodextrin.

55. The method of claim 52, wherein said Cmax is between about 250 ng/mL and about 1000 ng/mL.

56. The method of claim 52, wherein said Cmax is between about 300 ng/mL and about 700 ng/mL.

57. The method of claim 49 or 52, wherein said administration of said pharmaceutical composition is performed within about 10 min.

58. The method of claim 49 or 52, wherein said administration of said pharmaceutical composition is performed via one or two inhalations.

59. The method of claim 49 or 52, wherein said administration of said pharmaceutical composition is performed via two inhalations that are separated by a break for from about 10 seconds to about 1 minute.

60. The method of claim 49 or 52, wherein said administration of said pharmaceutical composition is performed within about 5 min.

61. The method of claim 49 or 52, wherein said administration is performed via a nebulizer.

62. The method of claim 61, wherein said nebulizer is a breath-actuated nebulizer.

63. The method of claim 61, wherein said nebulizer is a jet nebulizer.

64. The method of claim 61, wherein said nebulizer is a vibrating mesh nebulizer.

65. The method of claim 49 or 52, wherein about 100 mg to about 250 mg of said salt of flecainide is administered to said subject via inhalation.

66. The method of claim 49 or 52, wherein about 90 mg of said salt of flecainide is administered to said subject via inhalation.

67. The method of claim 49 or 52, wherein about 120 mg of said salt of flecainide is administered to said subject via inhalation.

68. The method of claim 49 or 52, wherein about 200 mg of said salt of flecainide is administered to said subject via inhalation.

69. The method of claim 49 or 52, wherein said heart condition comprises atrial arrhythmia.

70. The method of claim 49 or 52, wherein said atrial arrhythmia comprises tachycardia.

71. The method of claim 49 or 52, comprising acute treatment after detection of said atrial arrhythmia.

72. The method of claim 49 or 52, wherein said heart condition comprises atrial fibrillation.

73. The method of claim 72, wherein said atrial fibrillation is recurrent atrial fibrillation.

74. The method of claim 72, wherein said atrial fibrillation is paroxysmal atrial fibrillation.

75. The method of claim 49 or 52, wherein said subject has a systolic blood pressure that is greater than about 90 mmHg at the time of treating.

76. The method of claim 49 or 52, wherein said subject has a systolic blood pressure that is from about 100 mmHg to about 160 mmHg at the time of treating.

77. The method of claim 49 or 52, wherein said subject has a ventricular rate that is no more than 170 BPM at the time of treating.

78. The method of claim 49 or 52, wherein said subject has a ventricular rate that is from about 80 BPM to about 155 BPM at the time of treating.

79. A method of preparing a liquid pharmaceutical composition, comprising combining:
    (a) water;
    (b) a pH adjusting agent;
    (c) flecainide or a pharmaceutically acceptable salt thereof; and
    (d) a cyclodextrin.

80. The method of claim 79, wherein:

(i) a concentration of said flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in said pharmaceutical composition,

(ii) a concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and

(iii) a room-temperature pH in said pharmaceutical composition of from about 5.5 to about 6.5.

81. The method of claims 79 or 80, wherein said combining comprises:

(a) providing said water;

(b) contacting said portion of water with said flecainide or pharmaceutically acceptable salt thereof, said cyclodextrin, and said pH adjusting agent in a vessel; and

(c) adding a subsequent portion of said water to said vessel to provide said pharmaceutical composition, wherein:

(i) a concentration of said flecainide or a pharmaceutically acceptable salt thereof is from about 65 mg/mL to about 95 mg/mL in said pharmaceutical composition,

(ii) a concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v); and

(iii) a room-temperature pH in said pharmaceutical composition of from about 5.5 to about 6.5.

82. The method of claim 79, wherein said pH adjusting agent comprises an ion selected from the group consisting of: acetate, citrate, nitrate, chloride, sulfate, maleate, tartrate, phosphate, aconitate, adipate, ascorbate, benzoate, caprylate, cholate, formate, glutamate, lactate, propionate, sorbate, stearate, and succinate.

83. The method of claim 79, wherein said pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, sulfuric acid, maleic acid, tartaric acid, phosphoric acid, aconitic acid, adipic acid, ascorbic acid, benzoic acid, caprylic acid, cholic acid, formic acid, glutamic acid, lactic acid, propionic acid, sorbic acid, stearic acid, and succinic acid.

84. The method of claim 79, wherein said pH adjusting agent is selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

85. The method of claim 79, wherein said pH adjusting agent comprises a mixture of acids selected from the group consisting of: acetic acid, citric acid, nitric acid, hydrochloric acid, and sulfuric acid.

86. The method of claim 79, wherein a concentration of said pH adjusting agent in said pharmaceutical composition is about 2 mM to about 10 mM.

87. The method of claim 79, wherein said pH adjusting agent comprises acetic acid.

88. The method of claim 87, wherein said concentration in said pharmaceutical composition of said acetic acid is about 5 mM.

89. The method of claim 79, wherein said pH adjusting agent comprises citric acid.

90. The method of claim 89, wherein said concentration in said pharmaceutical composition of said citric acid is about 5 mM.

91. The method of claim 79, wherein said cyclodextrin comprises hydroxypropyl-β-cyclodextrin.

92. The method of claim 79, wherein said concentration of said cyclodextrin in said pharmaceutical composition is from about 10% (w/v) to about 30% (w/v).

93. The method of claim 79-92, further comprising adding a sweetener.

94. The method of claim 93, wherein said sweetener comprises saccharin.

95. The method of claim 93, wherein said sweetener comprises saccharin sodium.

96. The method of claim 93, wherein a concentration of said sweetener in said pharmaceutical composition is from about 0.001% (w/v) to about 0.01% (w/v).

97. The method of claim 79, wherein said pharmaceutically acceptable salt of flecainide is added.

98. The method of claim 97, wherein pharmaceutically acceptable said salt of flecainide comprises flecainide acetate.

99. The method of claim 79, further comprising packaging said pharmaceutical composition in unit dose form.

100. The method of claim 99, wherein said unit dose form further comprises a container selected from the group consisting of: a vial, a syringe, a capsule, a blow fill seal, a blister, a cartridge, and an ampoule.