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(71) Applicant: **SONIEVIE LTD.** [IL/IL]; 26 Shabazi Street, 4802126 Rosh HaAyin (IL).

(72) Inventors: **SHABTAY, Or**; 2011000 Kibbutz Farod (IL). **SHAV, Dalit**; 1/51 Prof. Israel Uman Street, 7608654 Rehovot (IL).

(74) Agent: **EHRLICH, Gal** et al.; G. E. Ehrlich (1995) LTD., 11 Menachem Begin Road, 5268104 Ramat Gan (IL).

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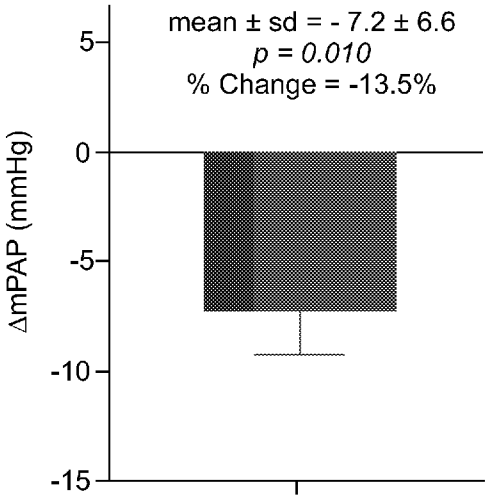


FIG. 5A

(57) Abstract: Disclosed herein is a therapeutically active agent usable in the treatment of pulmonary arterial hypertension (PAH), for use in the treatment of pulmonary arterial hypertension, as well as methods of treating PAH, said treatment and methods comprising administering such an active agent and effecting pulmonary artery denervation in the subject. In some aspects, a sub- therapeutically effective amount of the active agent is administered. In some aspects, the method is devoid of administering such an active agent for at least one month subsequent to the denervation. Further disclosed is a method of treating PAH comprising determining a responsiveness of the subject to at least one therapeutically active agent usable in treating PAH; and effecting pulmonary artery denervation in a subject responsive to the active agent(s).

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PULMONARY HYPERTENSION TREATMENT

RELATED APPLICATIONS

This application claims the benefit of priority under 35 USC §119(e) of U.S. Provisional Patent Application No. 62/473,532 filed 20 March 2017, Provisional Patent Application No. 62/473,545 filed 20 March 2017 and Provisional Patent Application No. 62/473,512 filed 20 March 2017, the contents of which are incorporated herein by reference in their entirety.

This application is related to a PCT Application entitled "PULMONARY HYPERTENSION TREATMENT METHOD AND/OR SYSTEM" of the same applicant, filed on the same filing date as this application.

This application is also related to PCT Application No. PCT/IL2018/050316 of the same applicant, filed on the same filing date as this application.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to therapy, and more particularly, but not exclusively, to a treatment of pulmonary arterial hypertension.

Pulmonary arterial hypertension (PAH) generally involves the narrowing of blood vessels connected to and within the lungs, which may result in fibrosis of the blood vessels over time. As with other forms of pulmonary hypertension, the increased workload of the heart causes hypertrophy of the right ventricle, and ultimately right heart failure.

The following forms of PAH have been internationally recognized: idiopathic PAH; heritable PAH (associated with a BMPR2 mutation, with an ALK1 or endoglin mutation, or with an unknown cause); drug-induced and toxin-induced PAH; PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis or chronic hemolytic anemia; persistent pulmonary hypertension of the newborn; and pulmonary veno-occlusive disease (POVD) and/or pulmonary capillary hemangiomatosis (PCH) [Simonneau et al., *J Am Coll Cardiol* 2009, 54:S43-S54].

Current therapies in pulmonary arterial hypertension (PAH) target three separate signaling pathways: the prostaglandin pathway, endothelin pathway, and nitric oxide/guanylate cyclase pathway [Sitbon & Gaine, *Eur Respir Rev* 2016, 25:408-417; Galie et al., *Eur Heart J* 2016, 37:67-119].

Prostacyclin (prostaglandin I_2) is a potent vasodilator which induces relaxation of vascular smooth muscle, as well as being a potent inhibitor of platelet aggregation. Dysregulation of the prostacyclin metabolic pathway has been reported in patients with PAH.

Prostanoids (synthetic prostacyclin analogues) used in treatment of PAH include epoprostenol (synthetic prostacyclin) for intravenous administration; iloprost, for administration by inhalation or intravenous administration; beraprost, for oral administration; and treprostinil, for administration by inhalation, or oral, subcutaneous or intravenous administration.

Selexipag is an additional orally available drug for use in treating PAH. Selexipag and its active metabolite are selective prostacyclin receptor (IP) agonists. Although the mode of action of selexipag is similar to those of prostanoids, selexipag is chemically distinct from prostanoids and characterized by different pharmacology.

The endothelin (ET) system has an important role in the pathogenesis of PAH. Activation of the endothelin system has been reported in both plasma and lung tissue of PAH patients. Endothelin receptor antagonists used in treatment of PAH (especially mild to moderate PAH) include bosentan, ambrisentan, and macitentan. Ambrisentan is a selective inhibitor of type A endothelin receptor (ET_A), and bosentan and macitentan inhibit both type A (ET_A) and type B (ET_B) endothelin receptor.

Nitric oxide (NO) promotes vasodilation by activating soluble guanylate cyclase (sGC), an enzyme which synthesizes cyclic GMP (cGMP), a mediator of vasodilation.

Phosphodiesterase type-5 (PDE-5) inhibitors inhibit the breakdown of cyclic GMP (by PDE-5), thereby augmenting signaling downstream of nitric oxide, resulting in pulmonary vasodilation and anti-proliferation. PDE-5 inhibitors used for treatment of PAH include sildenafil, tadalafil and vardenafil.

Riociguat is a soluble guanylate-cyclase stimulator (sGCS), which increases sGC activity, thereby promoting vasodilation and inhibiting smooth muscle proliferation, leukocyte recruitment, platelet aggregation, and vascular remodeling. Riociguat is used to treat PAH and chronic thromboembolic pulmonary hypertension.

Sitbon & Gaine [*Eur Respir Rev* 2016, 25:408-417] and the 2015 European Society of Cardiology (ESC) / European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension [Galie et al., *Eur Heart J* 2016, 37:67-119] describe various combination therapies which target two or three of the abovementioned pathways, and which are recommended therein for treating PAH.

Chen et al. [*J Am Coll Cardiol* 2013, 62:1092-1100] report the use of pulmonary artery denervation using an ablation catheter to treat idiopathic PAH in human subjects. All subjects had received a diuretic and beraprost, with either sildenafil, bosentan or digoxin, and were identified as not responding optimally to therapy prior to denervation.

International Patent Application Publication WO 2016/084081 describes devices and methods for treating pulmonary hypertension, using a catheter device introduced to the pulmonary artery lumen to selectively modify nerve activity by emitting ultrasound energy.

Additional background art includes Galie & Manes [*J Am Coll Cardiol* 2013, 62:1101-1102], and U.S. Patent Application Publication No. 2013/0204068.

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the invention, there is provided a therapeutically active agent usable in the treatment of pulmonary arterial hypertension, for use in the treatment of pulmonary arterial hypertension in a subject in need thereof, wherein the treatment comprises administering the active agent to the subject and effecting pulmonary artery denervation in the subject.

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising:

a) determining a responsiveness of the subject to at least one therapeutically active agent usable in treating pulmonary arterial hypertension; and

b) effecting pulmonary artery denervation in a subject responsive to the at least one therapeutically active agent,

thereby treating the pulmonary arterial hypertension.

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising:

a) effecting pulmonary artery denervation in the subject; and

b) administering to the subject at least one therapeutically active agent usable in treating pulmonary arterial hypertension,

wherein the administering is at a sub-therapeutically effective amount,

thereby treating the pulmonary arterial hypertension.

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising effecting pulmonary artery denervation in the subject,

the method being devoid of administering to the subject a therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one month subsequent to the denervation,

thereby treating the pulmonary arterial hypertension.

According to some of any of the embodiments of the invention, the at least one therapeutically active agent is selected from the group consisting of an anticoagulant, a prostacyclin receptor agonist, an endothelin inhibitor, and a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention, the therapeutically active agent comprises a prostacyclin receptor agonist.

According to some of any of the embodiments of the invention relating to a therapeutically active agent which comprises prostacyclin receptor agonist, the at least one therapeutically active agent further comprises an endothelin inhibitor.

According to some of any of the embodiments of the invention relating to a therapeutically active agent which prostacyclin receptor agonist, the at least one therapeutically active agent further comprises a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention relating to a treatment involving a prostacyclin receptor agonist, the treatment further comprises administering an endothelin inhibitor.

According to some of any of the embodiments of the invention relating to a treatment involving a prostacyclin receptor agonist, the treatment further comprises administering a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention, the therapeutically active agent comprises an endothelin inhibitor.

According to some of any of the embodiments of the invention relating to a therapeutically active agent which comprises an endothelin inhibitor, the at least one therapeutically active agent further comprises a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention relating to a treatment involving an endothelin inhibitor, the treatment further comprises administering a prostacyclin receptor agonist.

According to some of any of the embodiments of the invention relating to a treatment involving an endothelin inhibitor, the treatment further comprises administering a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention, the therapeutically active agent comprises a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention relating to a therapeutically active agent which comprises a guanylate cyclase activity enhancer, the at least one therapeutically active agent further comprises a prostacyclin receptor agonist.

According to some of any of the embodiments of the invention relating to a treatment involving a guanylate cyclase activity enhancer, the treatment further comprises administering a prostacyclin receptor agonist.

According to some of any of the embodiments of the invention relating to a treatment involving a guanylate cyclase activity enhancer, the treatment further comprises administering an endothelin inhibitor.

According to some of any of the embodiments of the invention, the therapeutically active agent comprises an anticoagulant.

According to some of any of the embodiments of the invention relating to a therapeutically active agent which comprises an anticoagulant, the at least one therapeutically active agent further comprises at least one therapeutically active agent selected from the group consisting of a prostacyclin receptor agonist, an endothelin inhibitor, and a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention relating to a treatment involving an anticoagulant, the treatment further comprises administering at least one therapeutically active agent selected from the group consisting of a prostacyclin receptor agonist, an endothelin inhibitor, and a guanylate cyclase activity enhancer.

According to some of any of the embodiments of the invention, the anticoagulant is selected from the group consisting of warfarin, acenocoumarol, dicoumarol, ethylbiscoumacetate, phenprocoumon, tecarfarin, anisindione, fluindione, phenindione, atromentin, a heparin, fondaparinux, idraparinux, idrabiotaparinux, apixaban, betrixaban, darexaban, edoxaban, eribaxaban, letaxaban, otamixaban, rivaroxaban, hirudin, lepirudin, bivalirudin, desirudin, argatroban, inogatran, dabigatran, melagatran, ximelagatran, antithrombin, batroxobin, hementin, and vitamin E.

According to some of any of the embodiments of the invention, the prostacyclin receptor agonist is selected from the group consisting of prostacyclin (epoprostenol), iloprost, beraprost, treprostinil and selexipag.

According to some of any of the embodiments of the invention, the endothelin inhibitor comprises a selective ET_A receptor antagonist, optionally ambrisentan.

According to some of any of the embodiments of the invention, the endothelin inhibitor comprises a dual ET_A/ET_B receptor antagonist, optionally bosentan and/or macitentan.

According to some of any of the embodiments of the invention, the guanylate cyclase activity enhancer is selected from the group consisting of sildenafil, tadalafil, vardenafil and riociguat.

According to some of any of the embodiments of the invention relating to a treatment, the treatment comprises administering the active agent prior to and/or subsequent to the denervation.

According to some of any of the embodiments of the invention, the administering is of a therapeutically effective amount of the therapeutically active agent.

According to some of any of the embodiments of the invention relating to a treatment, the treatment comprises administering a sub-therapeutically effective amount of the therapeutically active agent subsequent to the denervation.

According to some of any of the embodiments of the invention relating to a treatment, the treatment comprises administering the active agent prior to the denervation, the treatment being devoid of administering the active agent for a time period of at least one month subsequent to the denervation.

According to some of any of the embodiments of the invention, the method or treatment described herein is devoid of administering to the subject the therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one year subsequent to the denervation.

According to some of any of the embodiments of the invention relating to a sub-therapeutically effective amount, administering the sub-therapeutically effective amount comprises administering, subsequently to the denervation, a dosage of at least one therapeutically active agent which is lower than a dosage of the agent administered to the subject prior to the denervation.

According to some of any of the embodiments of the invention relating to a sub-therapeutically effective amount, administering the sub-therapeutically effective amount comprises administering, subsequently to the denervation, fewer therapeutically active agents than are administered to the subject prior to the denervation, wherein at least two therapeutically active agent usable in treating pulmonary arterial hypertension are administered to the subject prior to the denervation.

According to some of any of the embodiments of the invention, effecting the pulmonary artery denervation comprises thermally damaging nerve tissue associated with a main pulmonary artery.

According to some of any of the embodiments of the invention, thermally damaging nerve tissue comprises selectively damaging nerves that are not coated by myelin, by emitting energy at a frequency, intensity and duration sufficient to damage only nerves that are not coated by myelin, by producing a predetermined temperature profile in the treated tissue, the temperature profile ranging between 47-57 °C.

According to some of any of the embodiments of the invention, thermally damaging nerve tissue is effected by cryotherapy and/or by emitting energy from at least one energy-emitting device introduced into the body.

According to some of any of the embodiments of the invention, the energy is selected from the group consisting of ultrasound energy and monopolar or bipolar radiofrequency energy.

According to some of any of the embodiments of the invention, the energy comprises unfocused ultrasound energy.

According to some of any of the embodiments of the invention, effecting the pulmonary artery denervation comprises introducing a catheter device comprising the at least one energy-emitting device into a main pulmonary artery lumen.

According to some of any of the embodiments of the invention, the energy-emitting device is a transceiver, and effecting the pulmonary artery denervation further comprises:

receiving, using the at least one energy-emitting transceiver, echo signals reflected from non-targeted tissue following emission of energy by the at least one transceiver;

analyzing the received echo signals to identify at least one of a type and location of the non-targeted tissue relative to the at least one transceiver; and

emitting energy from the at least one transceiver in accordance with the analyzing, to modify nerve activity without substantially damaging the identified non-targeted tissue.

According to some of any of the embodiments of the invention, effecting the pulmonary artery denervation further comprises:

positioning the at least one energy-emitting device within the left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk at a location which is in between the first bifurcation of the left pulmonary artery and the first bifurcation of the right pulmonary artery,

wherein thermally damaging nerve tissue comprises emitting energy having parameters selected to damage nerves only within a distance window of between 0.2 mm and 10 mm from the intimal aspect of the pulmonary artery wall when the at least one device is positioned at the aforementioned location.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a table showing a protocol of a study for determining an effect of denervation in combination with drug therapy, according to some embodiments of the invention.

FIG. 2 is a flow chart for a protocol of a study for determining an effect of denervation in combination with drug therapy, according to some embodiments of the invention.

FIG. 3 is a table showing a protocol of a study for determining an effect of denervation in combination with drug therapy, according to some embodiments of the invention.

FIG. 4 is a flow chart for a protocol of a study for determining an effect of denervation in combination with drug therapy, according to some embodiments of the invention.

FIGs. 5A-5D present column charts showing changes in mean pulmonary arterial pressure (mPAP) (FIG. 5A), cardiac index (FIG. 5B), pulmonary vascular resistance (PVR) (FIG. 5C), and right arterial pressure (RAP) (FIG. 5D), 4 months after denervation treatment according to some embodiments of the invention, in comparison with baseline levels.

FIG. 6 is a column chart showing changes in 6-minute walking distance (6MWD) 4 months after denervation treatment according to some embodiments of the invention, in comparison with baseline levels.

FIG. 7 is a column chart showing changes in activity, as determined by the number of steps detected by actigraphy, 4 months after denervation treatment according to some embodiments of the invention, in comparison with baseline levels.

FIG. 8 is a column chart showing changes in quality of life, as determined by an emPHasis-10 questionnaire score 4 months after denervation treatment according to some embodiments of the invention, in comparison with baseline levels (lower score is associated with higher quality of life).

FIG. 9 is a column chart showing changes in pulmonary vascular resistance (PVR) in comparison with baseline levels 4 months after denervation treatment, in a group of patients receiving an anti-coagulation medication and in a group of patients that did not receive the anti-coagulation medication, according to some embodiments of the invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to therapy, and more particularly, but not exclusively, to a treatment of pulmonary arterial hypertension.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

While investigating the effects of pulmonary artery denervation on pulmonary arterial hypertension, the present inventors have uncovered drug treatments which are particularly effective in combination with denervation.

The present inventors have further uncovered novel regimens for providing improved treatment of pulmonary arterial hypertension and/or for identifying subject populations with enhanced responsiveness to denervation.

While reducing the present invention to practice, the inventors have shown that denervation is effective in providing a considerable additional therapeutic effect in treating pulmonary arterial hypertension in subjects already undergoing drug therapy.

Without being bound by any particular theory, it is believed that drug treatment are particularly useful at targeting small distal pulmonary artery vessels, whereas denervation procedures are particularly useful at improving proximal pulmonary artery compliance, such that the drug administration and denervation procedures complement one another. It is further believed that the drug treatment influences vasodilation and remodeling processes, and the denervation reduces right ventricular afterload.

The inventors have further shown that subjects being treated (for pulmonary arterial hypertension) with anticoagulants are particularly responsive to denervation.

According to an aspect of some embodiments of the invention, there is provided a therapeutically active agent usable in the treatment of pulmonary arterial hypertension (PAH) (e.g., an agent according to any of the respective embodiments described herein), for use in the treatment of PAH in a subject in need thereof, wherein the treatment comprises administering the active agent to the subject and effecting pulmonary artery denervation (e.g., according to any of the respective embodiments described herein) in the subject.

According to an aspect of some embodiments of the invention, there is provided a use of a therapeutically active agent usable in the treatment of pulmonary arterial hypertension (PAH) (e.g., an agent according to any of the respective embodiments described herein) in the manufacture of a medicament for use in the treatment of PAH in a subject in need thereof,

wherein the treatment comprises administering the active agent to the subject and effecting pulmonary artery denervation (e.g., according to any of the respective embodiments described herein) in the subject.

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension (PAH) in a subject in need thereof. The method comprises: a) effecting pulmonary artery denervation in the subject (e.g., according to any of the respective embodiments described herein); and b) administering to the subject at least one therapeutically active agent usable in the treatment of PAH (e.g., according to any of the respective embodiments described herein).

According to an aspect of some embodiments of the invention, there is provided a use of a device configured for effecting pulmonary artery denervation (e.g., according to any of the respective embodiments described herein) in the treatment of pulmonary arterial hypertension (PAH) in a subject in need thereof, wherein the treatment comprises administering at least one therapeutically active agent usable in the treatment of PAH (e.g., according to any of the respective embodiments described herein) and effecting pulmonary artery denervation in the subject.

Therapeutically active agent(s):

Examples of therapeutically active agents usable in the treatment of PAH (according to any one of the embodiments described herein) include, without limitation, anticoagulants, prostacyclin receptor agonists, endothelin inhibitors, and guanylate cyclase activity enhancers (as these terms are defined herein).

In some embodiments of any of the respective embodiments described herein, the therapeutically active agent comprises an anticoagulant. In some embodiments, denervation (e.g., according to any of the respective embodiments described herein) acts in synergy with an anticoagulant in treating pulmonary arterial hypertension.

In some embodiments of any of the respective embodiments described herein, the only therapeutically active agent utilized (according to any one of the embodiments described herein) is an anticoagulant.

In some embodiments of any of the respective embodiments described herein, an anticoagulant is utilized (according to any one of the embodiments described herein) in combination with an active agent other than an anticoagulant, for example, a prostacyclin receptor agonist, an endothelin inhibitor and/or a guanylate cyclase activity enhancer (e.g., according to any of the respective embodiments described herein).

Anticoagulants include, without limitation, vitamin K antagonists (e.g., coumarin derivatives and/or 1,3-inandione derivatives), heparin (optionally low molecular weight heparin) and derived substances, direct Xa inhibitors, direct thrombin inhibitors, antithrombin, batroxobin, hementin and vitamin E. In some embodiments of any of the embodiments described herein relating to an anticoagulant, the anticoagulant is a vitamin K antagonist, heparin or derived substance, direct Xa inhibitor, and/or direct thrombin inhibitor.

Examples of vitamin K antagonists include, without limitation, 4-hydroxycoumarin derivatives such as warfarin, acenocoumarol, dicoumarol, ethylbiscoumacetate, phenprocoumon and tecarfarin; 1,3-inandione derivatives such as anisindione, fluindione and phenindione; and atromentin. Warfarin, acenocoumarol and phenprocoumon are examples of relatively common vitamin K antagonists. Warfarin is an exemplary vitamin K antagonist.

Examples of heparins and derived substances include, for example, low molecular weight heparins such as bemiparin, nadroparin, reviparin, enoxaparin, parnaparin, certoparin, dalteparin and tinzeparin; and oligosaccharides such as fondaparinux, idraparinux and idrabiotaparinux. Enoxaparin and fondaparinux are exemplary anticoagulants which are a low molecular weight heparin or heparin-derived substance.

Examples of direct Xa inhibitors (which act directly on Factor X) include, without limitation, rivaroxaban, apixaban, betrixaban, darexaban, edoxaban, eribaxaban, letaxaban, and otamixaban. Rivaroxaban, apixaban, edoxaban and betrixaban are examples of relatively common direct Xa inhibitors. Rivaroxaban, apixaban and edoxaban are exemplary direct Xa inhibitors.

Examples of direct thrombin inhibitors (which directly inhibit thrombin) include, without limitation, bivalent direct thrombin inhibitors such as hirudin, bivalirudin, lepirudin and desirudin; and univalent direct thrombin inhibitors such as argatroban, inogatran, melagatran and dabigatran. Bivalirudin, lepirudin, desirudin, argatroban, and dabigatran are examples of relatively common direct thrombin inhibitors. Dabigatran is an exemplary direct thrombin inhibitor.

In some embodiments of any of the respective embodiments described herein, the anticoagulant is orally administrable. Examples of orally administrable anticoagulants include, without limitation, rivaroxaban, apixaban, edoxaban, betrixaban, dabigatran, and vitamin K antagonists which are 4-hydroxycoumarin or 1,3-inandione derivatives (according to any of the respective embodiments described herein).

In some embodiments of any of the respective embodiments described herein, the anticoagulant is intravenously and/or subcutaneously administrable, for example, administrable

by IV (intravenous) pump and/or subcutaneous (SC) pump. Examples of intravenously and/or subcutaneously administrable prostacyclin receptor agonists include, without limitation, hirudin, bivalirudin, lepirudin, desirudin, batroxobin, and heparin and derived substances, according to any of the respective embodiments described herein.

In some embodiments of any of the respective embodiments described herein, a dosage of anticoagulant is sufficient to maintain an ACT (activated clotting time) higher than 270 seconds, for example, before, during and/or after a denervation treatment. In some embodiments, the ACT is higher than 275 seconds or higher than 280 seconds or any intermediate, smaller or larger value, for example, before, during and/or after a denervation treatment.

In some embodiments of any of the respective embodiments described herein, the therapeutically active agent comprises a prostacyclin receptor agonist. In some embodiments, denervation (e.g., according to any of the respective embodiments described herein) acts in synergy with a prostacyclin receptor agonist in treating pulmonary arterial hypertension.

In some embodiments of any of the respective embodiments described herein, the only therapeutically active agent utilized (according to any one of the embodiments described herein) is a prostacyclin receptor agonist.

In some embodiments of any of the respective embodiments described herein, a prostacyclin receptor agonist is utilized (according to any one of the embodiments described herein) in combination with an active agent other than a prostacyclin receptor agonist, for example, an anticoagulant, an endothelin inhibitor and/or a guanylate cyclase activity enhancer (e.g., according to any of the respective embodiments described herein).

Prostacyclin receptor agonists include prostacyclin (including epoprostenol) and prostacyclin analogues (also referred to as "prostanoids"), as well as agonists which are structurally unrelated to prostacyclin.

Examples of prostanoids include, without limitation, prostacyclin, AFP-07 (5Z-[(3aR,4R,5R,6aS)-3,3-difluorohexahydro-5-hydroxy-4-[(1E,3S,4S)-3-hydroxy-4-methyl-1-nonen-6-ynyl]-2H-cyclopenta[b]furan-2-ylidene]-pentanoic acid), alprostadil, beraprost, carbacyclin, cicaprost, iloprost, isocarbacyclin, taprostene, and treprostinil. Prostacyclin, iloprost, beraprost and treprostinil are examples of relatively common prostanoids.

Selexipag, ralinepag, ACT-333679 (a metabolite of selexipag), BMY-45778 ([3-(4,5-diphenyl[2,4'-bioxazol]-5'-yl)phenoxy]acetic acid) and TRA-418 ({4-[2-(1,1-diphenylethylsulfanyl)-ethyl]-3,4-dihydro-2H-benzo[1,4]oxazin-8-yloxy}-acetic acid) are non-limiting examples of a prostacyclin receptor agonist which is not a prostanoid. Selexipag is an example of a relatively common prostacyclin receptor agonist.

In some embodiments of any of the respective embodiments described herein, the prostacyclin receptor agonist is orally administrable. Examples of orally administrable prostacyclin receptor agonists include, without limitation, beraprost, treprostinil and selexipag.

In some embodiments of any of the respective embodiments described herein, the prostacyclin receptor agonist is administrable by inhalation. Examples of prostacyclin receptor agonists administrable by inhalation include, without limitation, treprostinil and iloprost.

In some embodiments of any of the respective embodiments described herein, the prostacyclin receptor agonist is intravenously administrable, for example, administrable by IV (intravenous) pump. Examples of intravenously administrable prostacyclin receptor agonists include, without limitation, prostacyclin, treprostinil, and iloprost.

In some embodiments of any of the respective embodiments described herein, the prostacyclin receptor agonist is subcutaneously administrable, for example, administrable by subcutaneous (SC) pump. Treprostinil is a non-limiting example of a subcutaneously administrable prostacyclin receptor agonist.

In some embodiments of any of the respective embodiments described herein, the therapeutically active agent comprises an endothelin inhibitor. In some embodiments, denervation (e.g., according to any of the respective embodiments described herein) acts in synergy with an endothelin inhibitor in treating pulmonary arterial hypertension.

In some embodiments of any of the respective embodiments described herein, the only therapeutically active agent utilized (according to any one of the embodiments described herein) is an endothelin inhibitor.

In some embodiments of any of the respective embodiments described herein, an endothelin inhibitor is utilized (according to any one of the embodiments described herein) in combination with an active agent other than an endothelin inhibitor, for example, an anticoagulant, a prostacyclin receptor agonist and/or a guanylate cyclase activity enhancer (e.g., according to any of the respective embodiments described herein).

Herein, the term "endothelin inhibitor" refers to an agent which inhibits a biological activity of an endothelin (e.g., endothelin-1, endothelin-2 and/or endothelin-3); for example, by interacting with an endothelin receptor (e.g., endothelin receptor antagonists) and/or by interacting with endothelin (e.g., by binding to endothelin) and/or by inhibiting endothelin secretion, as well as prodrugs of agents which exhibit such interactions.

In some embodiments of any of the respective embodiments described herein, the endothelin inhibitor is an endothelin receptor antagonist; optionally an antagonist of endothelin receptor type A (ET_A), endothelin receptor type B (ET_B) or both ET_A and ET_B (dual antagonists).

Examples of ET_A receptor antagonists (e.g., selective antagonists) include, without limitation, ambrisentan, atrasentan, BQ-123, sitaxentan, and zibotentan. Ambrisentan is an example of an ET_A antagonist particularly suitable for treating PAH, according to some embodiments.

Examples of dual antagonists of ET_A/ET_B receptor include, without limitation, bosentan, macitentan and tezosentan. Bosentan and macitentan are examples of dual antagonists particularly suitable for treating PAH, according to some embodiments.

In some embodiments of any of the respective embodiments described herein, the therapeutically active agent comprises a guanylate cyclase activity enhancer. In some embodiments, denervation (e.g., according to any of the respective embodiments described herein) acts in synergy with a guanylate cyclase activity enhancer in treating pulmonary arterial hypertension.

In some embodiments of any of the respective embodiments described herein, the only therapeutically active agent utilized (according to any one of the embodiments described herein) is a guanylate cyclase activity enhancer.

In some embodiments of any of the respective embodiments described herein, a guanylate cyclase activity enhancer is utilized (according to any one of the embodiments described herein) in combination with an active agent other than a guanylate cyclase activity enhancer, for example, an anticoagulant, a prostacyclin receptor agonist and/or an endothelin inhibitor (e.g., according to any of the respective embodiments described herein).

Herein, the term "guanylate cyclase activity enhancer" refers to an agent which enhances a biological activity of guanylate cyclase; for example, by increasing a concentration of cyclic GMP (a compound formed by guanylate cyclase) by interacting with guanylate cyclase so as to increase cyclic GMP production (e.g., guanylate cyclase activators and/or stimulators) and/or by inhibiting breakdown of cyclic GMP (e.g., phosphodiesterase inhibitors), as well as prodrugs of agents which exhibit such interactions.

In some embodiments of any of the respective embodiments described herein, the guanylate cyclase activity enhancer is an inhibitor of phosphodiesterase 5 (a cyclic GMP-specific phosphodiesterase).

Examples of phosphodiesterase 5 (PDE5) inhibitors include, without limitation, avanafil, benzamidenafil, dasantafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil, udenafil, and zaprinast. Sildenafil, tadalafil and vardenafil are examples of PDE5 inhibitors particularly suitable for treating PAH, according to some embodiments.

In some embodiments of any of the respective embodiments described herein, the guanylate cyclase activity enhancer is an activator and/or stimulator of guanylate cyclase.

Examples of guanylate cyclase activators and/or stimulators include, without limitation, riociguat and cinaciguat. Riociguat is an example of a guanylate cyclase activity stimulator particularly suitable for treating PAH, according to some embodiments.

Regimen and/or patient population:

In some embodiments of any of the embodiments described herein relating to a treatment and/or method, the treatment and/or method comprises administering the active agent(s) (according to any of the respective embodiments described herein) prior to and/or subsequent to denervation (according to any of the respective embodiments described herein).

In some embodiments of any of the embodiments described herein relating to a treatment and/or method, the treatment and/or method comprises administering a therapeutically effective amount (as defined herein) of the therapeutically active agent (according to any of the respective embodiments described herein).

In some embodiments of any of the embodiments described herein relating to a treatment and/or method, the treatment and/or method comprises administering a sub-therapeutically effective amount (as defined herein) of the therapeutically active agent (according to any of the respective embodiments described herein), for example, subsequently to denervation (according to any of the respective embodiments described herein).

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising: a) effecting pulmonary artery denervation; and b) administering to the subject at least one therapeutically active agent usable in treating pulmonary arterial hypertension, wherein the administering is at a sub-therapeutically effective amount (of the therapeutically active agent) and/or for a time period shorter than otherwise.

According to an aspect of some embodiments of the invention, there is provided a use of a device configured for effecting pulmonary artery denervation (e.g., according to any of the respective embodiments described herein) in the treatment of pulmonary arterial hypertension (PAH) in a subject in need thereof, wherein the treatment comprises administering to the subject at least one therapeutically active agent usable in the treatment of PAH (e.g., according to any of the respective embodiments described herein) at a sub-therapeutically effective amount and/or for a time period shorter than otherwise, and effecting pulmonary artery denervation in the subject.

Herein, the phrase "sub-therapeutically effective amount" refers to a dosage which is lower than a dosage (or dosage range) which is a therapeutically effective amount (as defined herein) in the absence of treatment by denervation.

The term "therapeutically effective amount" denotes a dosage of an active agent or a composition comprising the active agent that will provide the therapeutic effect for which the active agent is indicated, herein, treating pulmonary arterial hypertension (e.g., extending a life expectancy of subjects afflicted by pulmonary arterial hypertension).

In some embodiments of any of the embodiments described herein, according to any of the aspects described herein, a treatment and/or method comprises administering a sub-therapeutically effective amount (as defined herein) of an active agent subsequently to denervation, and administering a therapeutically effective amount (as defined herein) of the active agent prior to denervation (optionally only prior to denervation).

In some embodiments of any of the respective embodiments described herein, a sub-therapeutically effective amount is at least 25 % lower than a therapeutically effective amount (e.g., the lower bound of a range of therapeutically effective amounts). In some such embodiments, the sub-therapeutically effective amount is at least 50 % lower than a therapeutically effective amount.

Herein, the phrase "time period shorter than otherwise" refers to a duration of administration of an active agent which is shorter than a duration of administration of the active agent in the absence of treatment by denervation. Such a "shorter" time period may relate, for example, to cessation of administration (in a subject treated by denervation) at a time point during which administration would be continued in a subject not treated by denervation.

In some embodiments of any of the respective embodiments described herein, the subject is treated with at least two therapeutically active agents (according to any of the respective embodiments described herein), and the method comprises ceasing administration of at least one therapeutically active agent (such that administration of such an agent is for a time period shorter than otherwise) and continuing administration of at least one other therapeutically active agent (at a therapeutically effective amount and/or a sub-therapeutically effective amount, according to any of the respective embodiments described herein). In some such embodiments, ceasing administration of at least one therapeutically active agent is effected subsequent to denervation; optionally immediately subsequent to denervation (i.e., wherein the agent is not administered after denervation).

In some embodiments of any of the embodiments described herein relating to a treatment and/or method, the treatment and/or method comprises administering the active agent(s)

(according to any of the respective embodiments described herein) prior to denervation (according to any of the respective embodiments described herein), and is devoid of administering the active agent for a time period of at least one month subsequent to the denervation (no agent is administered until after at least one month has elapsed from denervation). In some embodiments, the treatment and/or method is devoid of administering the active agent for a time period of at least three months subsequent to the denervation. In some embodiments, the treatment and/or method is devoid of administering the active agent for a time period of at least six months subsequent to the denervation. In some embodiments, the treatment and/or method is devoid of administering the active agent for a time period of at least one year subsequent to the denervation.

According to an aspect of some embodiments of the invention, there is provided a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising effecting pulmonary artery denervation (according to any of the respective embodiments described herein) in the subject, the method being devoid of administering to the subject a therapeutically active agent usable in the treatment of PAH (according to any of the respective embodiments described herein) for a time period of at least one month subsequent to the denervation (no agent is administered until after at least one month has elapsed from denervation). In some embodiments, the method is devoid of administering the active agent for a time period of at least three months subsequent to the denervation. In some embodiments, the method is devoid of administering the active agent for a time period of at least six months subsequent to the denervation. In some embodiments, the method is devoid of administering the active agent for a time period of at least one year subsequent to the denervation.

Denervation may optionally be effected in a selected population of subjects, for example, based on observed correlations between responsiveness to active agents and responsiveness to denervation.

In some embodiments of any of the respective embodiments described herein, denervation is effected in a subject selected as being responsive to one or more therapeutically active agent.

In some embodiments of any of the respective embodiments described herein, the treatment comprises determining a responsiveness of the subject to one or more therapeutically active agent (according to any of the respective embodiments described herein).

In some embodiments of any of the respective embodiments described herein, the treatment comprises administering to a subject one or more therapeutically active agent (according to any of the respective embodiments described herein) during a first time period;

determining a responsiveness of the subject to one or more therapeutically active agent (according to any of the respective embodiments described herein) administered during the first time period; and effecting denervation in a subject determined as being responsive to one or more therapeutically active agent administered during the first time period. In some such embodiments, the treatment is further characterized in that during a second time period subsequent to denervation, the treatment further comprises administering a sub-therapeutically effective amount of a therapeutically active agent (according to any of the embodiments described herein relating to a sub-therapeutically effective amount) and/or the treatment is devoid of administering a therapeutically active agent. In some embodiments, the second time period is at least one month (optionally at least one year) subsequent to the denervation (according to any of the respective embodiments described herein.

According to an aspect of some embodiments of the invention, there is provided a method of treating PAH in a subject in need thereof, the method comprising determining a responsiveness of the subject to one or more therapeutically active agent usable in treating PAH (according to any of the respective embodiments described herein). The method further comprises effecting pulmonary artery denervation (e.g., according to any of the embodiments described herein) in a subject responsive to the therapeutically active agent(s).

Responsiveness of a subject to a therapeutically active agent may be determined according to any suitable technique and/or criterion known in the art, for example, as described in the 2015 European Society of Cardiology (ESC) / European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension [Galie et al., *Eur Heart J* 2016, 37:67-119], the contents of which are incorporated herein by reference, especially contents regarding determining responsiveness (or lack thereof) of a treatment for PAH.

In some embodiments of any of the respective embodiments described herein, according to any of the aspects described herein, a subject responsive to a therapeutically active agent (e.g., as determined according to any of the respective embodiments described herein) achieves and/or maintains, upon treatment with the therapeutically active agent, at least one of the following features:

WHO functional class I or II (as defined in the art);

absence of progression of symptoms and clinical signs of right heart failure;

absence of syncope;

a six-minute walking distance (as defined and determined in the art) of over 440 meters;

a peak VO_2 - a.k.a. maximal oxygen consumption - (as determined by cardiopulmonary exercise testing) of over 15 ml per minute per kg and/or over 65 % of the predicted peak VO_2 (e.g., according to sex, weight and/or height);

a VE/VCO_2 (ventilatory equivalents for CO_2) slope of less than 36;

BNP (brain natriuretic peptide) plasma levels of less than 50 ng/liter;

NT-proBNP (N-terminal prohormone of BNP) plasma levels of less than 300 ng/liter;

A right atrium (RA) area of less than 18 cm^2 with no pericardial effusion (as determined by echocardiography and/or cardiac magnetic resonance imaging);

a right atrial pressure (RAP) of less than 8 mmHg;

a cardiac index (CI) (as defined in the art) of at least 2.5 liters per minute per $meter^2$; and/or

a mixed venous oxygen saturation (SvO_2) of over 65 %.

Denervation:

Pulmonary artery denervation in the context of any of the embodiments described herein may optionally be effected according to any suitable denervation technique known in the art.

Herein and in the art, the term "denervation" refers to deprivation of an organ or body (e.g., an artery) from at least a portion of nerve supply, for example, by damaging and/or killing nerve cells.

Herein throughout, the phrase "pulmonary artery denervation" refers to denervation (as defined herein) of any one or more arteries in the pulmonary circulation system, including large arteries (e.g., the main pulmonary artery, including the right and left pulmonary arteries), small arteries, and arterioles.

In some embodiments of any of the embodiments described herein, pulmonary artery denervation comprises reducing nerve supply to pulmonary small arteries and/or arterioles.

In some embodiments of any of the embodiments described herein, pulmonary artery denervation comprises reducing sympathetic nerve supply to at least one artery in the pulmonary circulation system, for example, by damaging and/or killing sympathetic nerve cells innervating the artery. In some embodiments, pulmonary artery denervation comprises reducing sympathetic nerve supply to pulmonary small arteries and/or arterioles, for example, by damaging and/or killing sympathetic nerve cells innervating the small arteries and/or arterioles.

In some embodiments of any of the embodiments described herein, denervation comprises damaging nerve tissue (optionally killing nerve cells therein) in proximity to a main pulmonary artery. In some such embodiments, denervation is effected using a device (e.g., a

catheter device) introduced into the main pulmonary artery (e.g., according to any of the respective embodiments described herein).

Herein, the phrase "main pulmonary artery" encompasses the pulmonary artery trunk, the right pulmonary artery (i.e., the right branch of the main pulmonary artery), and/or the left pulmonary artery (i.e., the left branch of the main pulmonary artery), including the bifurcation area of the pulmonary artery trunk.

It is to be appreciated that an artery deprived of nerve supply upon denervation is not necessarily an artery in proximity to nerve tissue damaged upon denervation. For example, damage to nerve tissue in proximity to a pulmonary artery trunk, right pulmonary artery, and/or left pulmonary artery may effect denervation of one or more small arteries and/or arterioles of the pulmonary circulation, which receive nerve supply from nerve cells which pass through a region in proximity to the pulmonary artery trunk, right pulmonary artery, and/or left pulmonary artery.

Denervation according to any one of the embodiments described herein may optionally be effected according to a technique described in International Patent Application Publication WO2016/084081, in Chen et al. [*J Am Coll Cardiol* 2013, 62:1092-1100], and/or in U.S. Patent Application Publication No. 2013/0204068; the contents of each of which are incorporated herein by reference in their entirety, and especially contents describing techniques for effecting denervation, and more especially contents describing denervation by emitting energy (e.g., ultrasound and/or electromagnetic radiation), for example, in accordance with any of the embodiments specifically described herein.

In some embodiments of any of the embodiments described herein, effecting denervation comprises thermally damaging nerve tissue surrounding the main pulmonary artery. Thermally damaging nerve tissue may optionally be effected by emitting energy (e.g., thereby heating the nerve tissue to a high temperature associated with tissue damage) and/or by cryotherapy (e.g., thereby cooling the nerve tissue to a low temperature associated with tissue damage).

In some embodiments of any of the embodiments described herein, effecting denervation by cryotherapy comprises introducing a catheter device into a main pulmonary artery lumen, wherein the catheter is configured to contain a low-temperature object.

In some embodiments of any of the embodiments described herein, effecting denervation comprises emitting energy from at least one energy-emitting device introduced into the body, for example, by introducing a catheter device comprising the energy-emitting device(s) into a main pulmonary artery lumen. The energy-emitting device(s) may optionally comprise a transmitter

and/or a transceiver (e.g., an ultrasound transmitter and/or transceiver, and/or a radiofrequency transmitter and/or transceiver).

Emitted energy utilized for denervation (e.g., by thermally damaging nerve tissue) according to any of the respective embodiments described herein may optionally be ultrasound energy and/or electromagnetic radiation. Unfocused ultrasound energy is a non-limiting example of a suitable form of emitted ultrasound energy. Examples of suitable forms of emitted electromagnetic radiation include, without limitation, radiofrequency (RF) energy (monopolar or bipolar); microwave radiation; and ultraviolet, visible and/or infrared radiation (including, for example, phototherapy).

Additionally or alternatively, other forms of energy suitable to thermally damage nerve tissue are applied, such as plasma, mechanical manipulation, kinetic, nuclear, magnetic, electrical, potential, elastic mechanical, chemical and hydrodynamic energy.

In some embodiments, energy having parameters (e.g., intensity, frequency, beam shape, duration and/or other parameters) suitable to thermally damage nerve tissue is emitted. In some embodiments, parameters of the applied energy are selected in accordance with the anatomical treatment location, based on the type(s) and/or quantity and/or distribution of tissue that exist within the targeted volume. Optionally, selective treatment is performed, in which only a part of the tissue and/or a certain type of tissue within the target volume such as nerve tissue is affected by the emitted energy, while other tissue remains substantially unharmed. In an example, the applied energy parameters are selected to produce a temperature profile in the target tissue which thermally damages nerve tissue, but does not have a substantial effect (e.g., necrosis, denaturation) on non-targeted tissue within the target volume.

In some embodiments of any of the embodiments described herein, denervation of nerve tissue is effected within a predefined distance window from the main pulmonary artery wall. In some embodiments, the distance ranges between, for example, from 0.2 to 20 mm, 0.2 to 10 mm, 4 to 9 mm, 1 to 6 mm, or any intermediate, larger or smaller distance ranges relative to the intimal aspect of the artery wall. In some embodiments, a position of an energy-emitting devices (e.g., transceiver) and/or a catheter (according to any of the respective embodiments described herein) along the artery, and suitable energy parameters, are selected together in order to target nerve tissue within the predefined distance window. In some embodiments, one or more energy-emitting devices (e.g., transceivers), optionally of a catheter according to any of the respective embodiments described herein, are positioned within the main pulmonary artery (left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk) within a limited area, in which the first bifurcation of the right pulmonary artery sets a border line and a first bifurcation of the left

pulmonary artery sets a second border line. In some embodiments, an angiogram and/or CT and/MRI images acquired before and/or during treatment are used for determining border line locations.

In some embodiments, the energy-emitting device(s) (e.g., transceiver(s)) are positioned such that a tissue volume covered by the beam of emitted energy encompasses mostly nerves innervating one or more arteries of the pulmonary circulation. Optionally, the volume is selected such that nerves innervating other organs are avoided or their presence is insignificant. Optionally, at least 25%, at least 50 %, at least 60 %, at least 70 %, at least 80 % by volume of nerve tissue within the tissue volume covered by the beam includes sympathetic nerves, or intermediate, higher or lower volume of nerve tissue.

In some embodiments, energy parameters are selected using a computational model that takes into account one or more of metabolic heat generation in tissue, heat absorption characteristics of the tissue, heat conductivity, metabolic flow in the tissue, tissue density, acoustic absorption, volumetric blood perfusion in the tissue, cell sensitivity to heat, cell sensitivity to mechanical or acoustical damage and/or other tissue parameters. In some embodiments, the model is constructed according to a finite element analysis which assists in determining a temperature distribution profile in the tissue, in space and/or time. Optionally, the finite element analysis takes into account a solution of the bioheat equation under selected conditions.

In some embodiments, the energy parameters are selected so that energy deposited in the tissue outside the artery is sufficient to thermally damage nerves within the distance window. In some embodiments, the emitted beam is selective in the sense that nerve tissue within the beam coverage is thermally damaged, while other, non-target tissue within the beam coverage (such as adipose tissue, lymph and/or other non-target tissue) remains substantially undamaged. In some embodiments, the tissue specific damage has a higher affinity to nerve tissue surrounded by fatty tissue, due to the low heat conductivity of the fatty tissue. Optionally, due to acoustic absorption and/or thermal sensitivity properties that are higher than acoustic absorption and/or thermal sensitivity properties of other tissue, such as lymph tissue, fibrous tissue, or connective tissue, the acoustic energy affects the nerve tissue most.

In some embodiments, cooling as a result of blood flow through the main pulmonary artery and/or cooling as a result of perfusion in the tissue reduces or prevents thermal damage to the intima and media layers of the artery wall, so that a significant thermal effect starts only at a distance away from the wall.

In some embodiments of any of the respective embodiments described herein, denervation comprises reducing thermal damage to the main pulmonary artery wall by taking advantage of a streaming effect produced in response to emission of ultrasound. In some embodiments, ultrasound emitted at a frequency of 8-13 MHz, 5-10 MHz, 10-20 MHz or intermediate, higher or lower frequency ranges and an intensity of from 20-100 W/cm^2, 30-70 W/cm^2, 35-65 W/cm^2, or intermediate, higher or lower intensity ranges produces fluid circulation in which fluid is caused to flow from the energy-emitting device surface towards the artery wall, thereby dissipating heat away from the ultrasound-emitting device (e.g., transceiver) and, in turn, from the artery wall. In some embodiments, even if fluid (e.g. blood) in the artery is static or the flow is reduced (e.g. due to pulsation, such as during diastole) the acoustic streaming effect produced by emission of ultrasound energy sufficiently cools the artery wall, preventing at least the intima and media of the artery wall from thermal damage. In some embodiments, cooling provided by the streaming effect is sufficient to dissipate at least 10 %, at least 20 %, at least 40 % or intermediate, higher or lower percentage of the power of the emitted energy. In some embodiments, cooling provided by the streaming effect is sufficient to reduce a temperature of the intima to a temperature of 42 °C or lower.

In some embodiments of any of the embodiments described herein, denervation is performed at a plurality of locations situated along a long axis of the main pulmonary artery (left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk), for example, from 2 to 8 locations within each of the left, right and main artery. According to some exemplary embodiments, denervation is performed at from 6 to 16 treatment locations, for example 6, 7, 8, 10, 12, 14 or any smaller or larger number of treatment locations within the pulmonary arteries. In some embodiments, the number of treatment locations within the pulmonary arteries is selected based on the anatomy of one or more of the pulmonary arteries and/or the distance from a selected nerve. In some embodiments, the number of treatment locations is selected based on the size of the "working frame", as described herein.

Optionally, a distance between adjacent treatment locations ranges from 0.1 to 2 cm, from 0.5 to 1 cm, from 1 to 2 cm, or intermediate, longer or shorter distances. In some embodiments, energy is emitted at plurality of locations to damage a nerve (or a bundle of nerves) at a plurality of sections along the length of the nerve. For example, a nerve may be damaged at an initial section of the axon and at a distal section of the axon (e.g., at or near the synapse), impairing also an intermediate section of the axon as a result. In some embodiments, the extent of thermal damage is high enough to prevent the nerve from reconnecting and/or regenerating for at least a time period following treatment (for example at least 1 month, 3

months, 6 months, 1 year following treatment). In some embodiments, nerve portions that transport, store and/or produce neurotransmitters are damaged.

In some embodiments, the catheter used for delivering the denervation has a length in a range of 80-200 cm, for example 80 cm, 100 cm, 120 cm or any intermediate, smaller or larger value.

According to some embodiments, denervation is effected for a duration in a range of 10-40 minutes, for example 15 minutes, 20 minutes, 25 minutes, 30 minutes or any intermediate, smaller or larger time duration. In some embodiments, the treatment duration is determined based on the number of selected treatment sites. Alternatively or additionally, the treatment duration is determined based on the distance between the treated nerve and the one or more treatment locations within the pulmonary arteries. Optionally, the treatment duration is determined based on the treatment protocol or parameters thereof.

In some embodiments of any of the respective embodiments described herein, thermal damage is manifested as coagulation, vacuolation and/or nuclei pyknosis of the targeted nerve. In some embodiments, the thermal damage results in tissue fibrosis and optionally in formation of remodeled scar tissue.

In some embodiments, a temperature distribution profile of the thermal damage produced depends on tissue homogeneity. Optionally, in homogenous tissue, a cross section profile of thermal damage takes the form of a teardrop.

In some embodiments of any of the respective embodiments described herein, denervation comprises thermally damaging nerve tissue (e.g., by emitting energy according to any of the respective embodiments described herein) without causing substantial damage to the artery wall. Optionally, damage to the wall is reduced by keeping the energy-emitting device(s) (e.g., ultrasound-emitting device(s)) according to any of the respective embodiments described herein away from the wall, for example by using a distancing device. In some embodiments, denervation comprises treating from an artery in which a wall disorder such as thrombus or atheroma exist, while reducing a risk of breakage of the thrombus or atheroma, which may result in emboli and possibly occlude the artery.

In some embodiments of any of the respective embodiments described herein, denervation comprises activating one or more energy-emitting devices (e.g., ultrasound-emitting devices) according to any of the respective embodiments described herein to emit energy towards a selected direction, and/or deactivating one or more energy-emitting devices (e.g., ultrasound-emitting devices) according to any of the respective embodiments described herein to reduce or prevent emission in one or more other directions.

In some embodiments of any of the respective embodiments described herein, thermally damaging nerve tissue associated with a pulmonary artery (e.g., a main pulmonary artery) comprises selectively damaging nerves that are not coated by myelin, for example, by subjecting the nerve tissue to a temperature at which nerves that are not coated by myelin are selectively damaged, optionally a temperature in a range of from 47 °C to 57 °C. In some embodiments, selective damage of nerve tissue is effected by emitting energy (e.g., according to any of the embodiments described herein) at a frequency, intensity and/or duration sufficient to produce a suitable predetermined temperature profile in the tissue, for example, in a range of from 47 °C to 57 °C. Optionally, upon increasing the temperature, for example, to a range of from 58 °C to 70 °C, both non-coated nerves and myelin coated nerves are thermally damaged.

In some embodiments of any of the respective embodiments described herein, denervation comprises utilizing a transceiver, optionally an ultrasonic transceiver, as an energy-emitting device (according to any of the respective embodiments described herein), for example, to facilitate selective treatment of nerve tissue (e.g., causing damage to selected nerves without causing substantial damage to non-targeted tissue, such as surrounding organs and/or other nerve tissue). In some embodiments, denervation comprises using the same transceiver to characterize tissue and to emit energy for treating targeted tissue. In some embodiments, characterizing tissue comprises identifying one or more organs such as the lungs, trachea, lymph, bronchi or others. In some embodiments, organs are identified based on their echo signal reflection. Optionally, the reflected signals are received by the one or more ultrasonic transceivers (e.g., of a catheter device, according to any of the respective embodiments described herein), and are analyzed to determine the organ type and/or the relative distance of the organ from the lumen from which treatment is applied, such as the main pulmonary artery lumen. In some embodiments, the transceivers (e.g., ultrasonic transceivers) are activated at a first energy profile to identify and/or characterize tissue, and at a second energy profile to treat tissue. Optionally, non-targeted tissue is identified. Additionally or alternatively, targeted tissue is identified.

In some embodiments of any of the respective embodiments described herein, denervation comprises feedback-based treatment of the pulmonary vasculature. In some embodiments, treatment is continued and/or modified based on one or more measurements of physiological control parameters, including local parameters such as, for example, pulmonary artery diameter, bronchi diameter, and/or systemic parameters, which may be a byproduct of denervation, including, for example, heart rate, respiratory volume, and/or other physiological parameters. In some embodiments, the physiological parameters are measured internally to the body. Additionally or alternatively, the physiological parameters are measured externally to the

body. In some embodiments, a catheter (e.g., ultrasonic catheter) according to any of the respective embodiments described herein is configured to acquire the one or more physiological parameters. In an example, a physiological parameter such as a diameter of the pulmonary artery is estimated by analyzing echo signals (e.g., ultrasound echo signals) reflected by the artery walls and received by the one or more transceivers (e.g., of a catheter device) according to any of the respective embodiments described herein. In some embodiments, the physiological parameter is acquired by stimulating the nervous system to evoke an observable physiological response and/or a chain of responses, one or more of which are detectable and optionally measureable.

In some embodiments, a measurement of the physiological parameter acquired before denervation treatment is compared to a measurement of the same physiological parameter following treatment, to determine treatment effectiveness. For example, an increase in artery diameter above a certain threshold, measured following treatment, may indicate that the treatment was effective.

In some embodiments, immediate feedback is provided, and denervation treatment is modified and/or ceased based on the feedback. In an example, immediate feedback comprises assessing dilation of the bronchi, which may be observed shortly after denervation. In another example, immediate feedback comprises assessing arterial blood pressure.

In some embodiments of any of the respective embodiments described herein, a catheter device (according to any of the respective embodiments described herein) introduced to a subject's body is suitable for reducing unwanted movement of the catheter, and more specifically movement of at least a distal portion of the catheter when a more proximal portion of the catheter is passed through cardiac vasculature, where it is subjected to movement resulting from heart pulsation. In some embodiments, the catheter is passed through the right ventricle of the heart. In some cases, contraction of the ventricle may cause movement of the catheter shaft, thereby possibly moving the distal head of the catheter, which comprises one or more energy-emitting devices according to any of the respective embodiments described herein).

In some embodiments, a structure of the catheter shaft is selected to damp movement resulting from heart pulsation, potentially reducing a number of movements and/or a range of movement of at least a distal head of the catheter. In some embodiments, one or more locations along the catheter shaft are structured to provide a full or partial axial decoupling between axial segments of the catheter, for example so that movement of the head at a distal end of the device is least affected by movement of a more proximal portion of the catheter shaft. Additionally or alternatively, the catheter is anchored to a certain location in the artery and/or to other tissue or organs, to prevent or reduce movement of the catheter relative to the tissue, for example during

emission of energy, for example, ultrasound. Optionally, a small range of movement is permitted, such as movement to an extent which does not affect targeting. Additionally or alternatively, a "working frame" is provided, and the catheter is maneuvered within the working frame. Additionally or alternatively, movement of the catheter is synchronized with movement of the targeted tissue, for example by anchoring the catheter to a structure that moves in a similar pattern to the targeted tissue.

In some embodiments, at least a head of the catheter, comprising the one or more energy-emitting devices according to any of the respective embodiments described herein (ultrasound-emitting device(s)) is positioned and/or oriented within the lumen from which denervation treatment is applied at a predetermined location. Optionally, positioning of the catheter and/or directing of an energy (e.g., ultrasound) beam is selected based on one or more of: a distance from the tissue to be treated, a distance from the lumen wall, a position along the length of the lumen, parameters of the beam emitted by the energy-emitting devices (e.g., beam shape), and/or others. In some embodiments, positioning of the catheter and/or directing of the beam is performed by delivering the catheter over a pre-shaped guide wire, for example a spiral guide wire or a guide wire curved to a substantial Z shape. A potential advantage of the spiral configuration may include setting an advancement path for the catheter in which at any point along the path, at least the catheter head is maintained at a selected distance from the lumen wall, for example in proximity to the lumen wall. Optionally, the catheter is positioned a distance between 0.1 mm to 20 mm from the lumen wall. Optionally, the distance is selected in accordance with the intensity applied, for example a distance ranging from 0.1 mm to 5 mm, 5 mm to 10 mm, 15 mm to 20 mm or intermediate, larger or smaller distance ranges are used with an intensity between 20 W/cm^2 to 80 W/cm^2. In some embodiments, the spiral diameter (i.e. a diameter of a loop) is selected according to the lumen diameter. Additionally or alternatively, the spiral diameter is selected according to the catheter diameter, for example a diameter of the catheter head. In some embodiments, a similar effect to delivering the catheter over a helical structure may be obtained by delivering the catheter over the Z-shaped wire, and rotating the wire. Optionally, the catheter is introduced over the wire to a position in which the catheter head is proximal to the curved portion of the wire. Alternatively, the catheter is introduced over the wire to a position in which the catheter head is distal to the curved portion of the wire. Another potential advantage of the spiral and/or Z-shaped configurations (and/or any other configurations suitable to position the catheter away from the center of the lumen and in proximity to the walls) may include facilitating treating the lumen circumferentially. Optionally, when applying circumferential treatment by delivering the catheter over a curved guide wire, the curvature of

the wire can be selected to obtain a certain orientation of the energy-emitting device(s) at the head of the catheter, for example positioning an energy-emitting device such that a longer dimension of the energy-emitting device (for example being a rectangular energy-emitting device) extends at an angle relative to a longitudinal axis of the lumen.

In some embodiments of any of the embodiments described herein, denervation relates to a selected target tissue volume. In some embodiments, denervation relates to an anatomical treatment zone for positioning an energy-emitting device according to any of the respective embodiments described herein (optionally an ultrasonic transceiver), optionally of a catheter according to any of the respective embodiments described herein, such that the emitting device is positioned to treat the aforementioned selected target tissue volume, while damage to non-targeted tissue types and/or non-targeted organs is reduced.

In some embodiments, the selected treatment zone (for denervation) provides for targeting a tissue volume comprising a high nerve content as compared to other tissue volumes, while reducing a risk of damage to non-targeted tissue (such as adipose tissue, connective tissue) and/or to nearby organs (such as the aorta, vagus, esophagus and/or other organs). A potential advantage of positioning an energy-emitting device and/or catheter at the selected treatment zone may include optimizing a tradeoff between denervation efficacy and treatment safety, such as avoiding damage to non-targeted tissue. Other optimization methods can include treating the most efficient treatment location. It was found to be the most efficient due to highest nerve density, and it is also, a safe location to treat.

In some embodiments, the anatomical treatment zone (for denervation) comprises an ostial and/or near-ostial area within the lumen of the left pulmonary artery, in the vicinity of the bifurcation in which the main pulmonary trunk splits into the left pulmonary artery and the right pulmonary artery. In some embodiments, the anatomical treatment zone is located at a distance of less than 50 mm, 40 mm, 30 mm, less than 20 mm, less than 10 mm, or intermediate, longer or shorter distances from a central longitudinal axis of the main trunk of the pulmonary artery. Additionally or alternatively, the anatomical treatment zone is situated at an axial distance (measured along the length of the left pulmonary artery) from 5 to 50 mm, 0 to 10 mm, 10 to 30 mm or intermediate, longer or shorter distance ranges from the artery ostium. Additionally or alternatively, the anatomical treatment zone is situated at a distance of less than 10 mm, less than 7 mm, less than 3 mm from the point of maximal curvature of the left pulmonary artery. Additionally or alternatively, the anatomical treatment zone is situated within the range of the first 1/5, 1/4, 1/3 or intermediate, longer or shorter sections of the total length of the left pulmonary artery, measured for example between the long axis of the main pulmonary trunk to

the lateral bifurcation of the left pulmonary artery, where it splits into two or more branches, each extending towards one of the lobes of the left lung.

The "ostium" refers herein to the bifurcation point that is mutual to the main trunk, the left and the right pulmonary arteries.

In some embodiments the ostium point is first located by fluoroscopy prior to deciding the treatment zone for denervation.

In some embodiments, the anatomical treatment zone (for denervation) does not include the right pulmonary artery. A potential advantage of not treating from within the right pulmonary artery may include reducing potential damage (e.g. thermal damage) to the aorta, which ascends with the main pulmonary trunk and arches around the right pulmonary artery, and/or to reduce potential damage to the vagus nerve, which extends dorsally to the right pulmonary artery. Alternatively, the anatomical treatment zone comprises the right pulmonary artery.

In some embodiments, treatment for denervation (according to any of the respective embodiments described herein) is applied from the anatomical treatment zone to treat a selected target tissue volume. In some embodiments, the selected target tissue volume comprises one or more nerve plexuses situated to the left of the left pulmonary artery. In some embodiments, the selected target tissue volume is located laterally, posteriorly and/or anteriorly to the left pulmonary artery. In some embodiments, the selected target tissue volume is located within a distance range of 0.2-30 mm from a point of maximal curvature of the left pulmonary artery. Additionally or alternatively, the selected target tissue volume is located laterally to the main trunk of the pulmonary artery, inferior to the left pulmonary artery.

In some embodiments, energy is emitted towards a circumferential region of the left pulmonary artery. Optionally, the one or more energy-emitting devices (optionally ultrasound-emitting devices, e.g., transceivers) are activated and/or rotated during and/or between treatment sessions to cover different circumferential sections. In some embodiments, a line of energy-emitting devices (e.g., electrodes, ultrasonic transceivers) are aligned along the circumference of the artery and only the ones facing to target zone are activated. This may be potentially advantages to increasing safety.

In some embodiments, when emitting energy from the selected anatomical treatment zone towards the selected target tissue volume, a separation angle of at least 20 degrees, at least 30 degrees, at least 60 degrees or intermediate, larger or smaller angle is formed between the emitted energy beam and non-targeted organs. A potential advantage of emitting energy such that a separation angle is formed between the non-targeted organs and the emitted beam may

include increasing treatment safety, as even if the beam is emitted at an offset angle from the selected angle, at least to some extent, non-targeted tissue will remain substantially unharmed.

In some embodiments, a structure of the catheter is designed to provide for positioning one or more energy-emitting devices (e.g., ultrasonic transceivers) within the anatomical treatment zone, for example by the catheter comprising a shaft that is shaped and/or deformable to a curvature that matches the curvature of the left pulmonary artery.

In some embodiments, denervation is effected using a catheter which exhibits synergy with the anatomy of the selected treatment zone and/or the anatomy of a delivery path of the catheter. In some embodiments, the physician utilizes the anatomy to direct the catheter to a selected treatment location, such as within the anatomical treatment zone described herein. In some embodiments, the anatomy naturally "assists" in directing the catheter to the selected location, for example by defining boundaries which force the catheter to the selected location.

In some embodiments, a shaft of the catheter is shaped in a manner in which at least some portions of the shaft lean and/or anchor against walls of a lumen through which the catheter is introduced to the selected treatment location, for example a lumen of the pulmonary artery trunk and/or a lumen of the right and/or left pulmonary arteries, to provide for positioning a head of the catheter at a selected treatment zone. In an example, the catheter shaft is arched, allowing a more proximal portion of the shaft to lean against a right wall of the pulmonary artery trunk to thereby position a more distal portion of the catheter which includes an energy-emitting device (or other device for effecting denervation) within a treatment zone located in the ostial left pulmonary artery section.

In some embodiments, a path through which an energy-emitting device and/or catheter is introduced to the treatment zone follows the natural path of blood flow. Optionally, the flow of blood assists in directing the energy-emitting device and/or catheter to the selected treatment location, for example by using an inflatable balloon tip and/or sail tip providing for flow-directed flotation of the energy-emitting device and/or catheter to the selected location.

In some embodiments of any of the embodiments described herein, denervation relates to targeting nerves according to mapping of the nerves. In some embodiments, nerves are selected as target according to one or both of a distance of the nerve from the artery lumen and a cross sectional area of the nerve. In some embodiments, a number of target nerves is selected to reduce one or more of: mPAP (mean pulmonary arterial pressure), pulmonary vascular resistance, contractibility, and/or systemic pressure levels in the pulmonary artery as compared to mPAP levels measured before treatment. In some embodiments, right heart ejection fraction is

increased. Generally, the number of target nerves may be selected to improve (e.g. increase or decrease a level of) any parameter associated with pulmonary hypertension.

In some embodiments of any of the embodiments described herein, a catheter structure and/or a denervation protocol are selected based on an anatomy of the pulmonary artery region in which the catheter is intended to be positioned during treatment. For example, when positioning a catheter in the pulmonary artery trunk, in which the cross sectional area is relatively large (comprising a diameter which is about 1.5 times a diameter of the right or left pulmonary arteries), it may be desirable to position the catheter head closer to the lumen wall as compared to, for example, when treating in an artery region of smaller cross sectional area. Optionally, when treating an artery region having a relatively large cross sectional area, higher intensities are applied. In some embodiments, a high intensity is applied to compensate for undesired movement of the catheter within the large artery region. Optionally, by directing energy at a high intensity towards a large volume or cross section of tissue, the energy spreads over the large volume, thereby reducing the actual intensity of energy that effectively reaches the various tissue locations within the large volume.

In some embodiments of any of the embodiments described herein, denervation is effected (e.g., by selecting suitable parameters of energy emission) so as to reduce one or more of the following parameters: right atrial pressure (RAP), right ventricle pressures (RVP), systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressures (mPAP), pulmonary vascular resistance (PVR), and/or NT-pro-BNP levels (e.g., as exemplified herein).

In some embodiments of any of the embodiments described herein, denervation is effected (e.g., by selecting suitable parameters of energy emission) so as to increase one or more of the following parameters: cardiac output (CO), cardiac index (CI), ejection fraction (EF), pulmonary distensability, pulmonary compliance, pulmonary stiffness, exercise tolerance - 6 minutes walking distance (6MWD), quality of life (as assessed by questionnaire, e.g., emPHasis questionnaire), cardiopulmonary exercise testing and/or peak VO2 (e.g., as exemplified herein).

RAP, RVP, sPAP, mPAP, PVR, NT-pro-BNP levels, cardiac output, cardiac index, ejection fraction, pulmonary distensability, pulmonary compliance, pulmonary stiffness, exercise tolerance - 6 minutes walking distance (6MWD), cardiopulmonary exercise testing and/or peak VO2 may be determined using any suitable technique, procedure, and/or apparatus known in the art (e.g., for cardiac MRI and/or echocardiography), optionally as described below in the Examples section herein and/or FIGs. 1 and/or 2.

Formulation:

The therapeutically active agent(s) of any of the embodiments of the invention described herein can be administered to a subject *per se*, or in a pharmaceutical composition where it is mixed with suitable carriers or excipients.

As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active agents described herein with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier" which may be interchangeably used refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. An adjuvant is included under these phrases.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active agent. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, especially transnasal, intestinal or parenteral delivery, including intramuscular, subcutaneous and intramedullary injections as well as intrathecal, direct intraventricular, intracardiac, e.g., into the right or left ventricular cavity, into the common coronary artery, intravenous, intraperitoneal, intranasal, or intraocular injections.

Optionally, one may administer the pharmaceutical composition in a local rather than systemic manner, for example, via injection of the pharmaceutical composition directly into a tissue region (e.g., region of the vasculature) of a patient.

The term "tissue" refers to part of an organism consisting of cells designed to perform a function or functions. Examples include, but are not limited to, brain tissue, retina, skin tissue, hepatic tissue, pancreatic tissue, bone, cartilage, connective tissue, blood tissue, muscle tissue, cardiac tissue brain tissue, vascular tissue, renal tissue, pulmonary tissue, gonadal tissue, hematopoietic tissue.

Pharmaceutical compositions of some embodiments of the invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing,

dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with some embodiments of the invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active agents into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the active agents the pharmaceutical composition may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological salt buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the pharmaceutical composition to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active agents in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally,

stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by nasal inhalation, the active agents for use according to some embodiments of the invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in a dispenser may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The pharmaceutical composition described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. The compositions may be suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily or water based injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the active agents to allow for the preparation of highly concentrated solutions.

Alternatively, the active agent may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water based solution, before use.

The pharmaceutical composition of some embodiments of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

Pharmaceutical compositions suitable for use in context of some embodiments of the invention include compositions wherein the active agents are contained in an amount effective to achieve the intended purpose. More specifically, a therapeutically effective amount means an amount of active agent(s) effective to prevent, alleviate or ameliorate pulmonary arterial hypertension (or symptoms associated with pulmonary arterial hypertension), or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from *in vitro* and cell culture assays. For example, a dose can be formulated in animal models to achieve a desired concentration or titer. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the active agents described herein can be determined by standard pharmaceutical procedures *in vitro*, in cell cultures or experimental animals. The data obtained from these *in vitro* and cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1.

Dosage amount and interval may be adjusted individually to provide levels of the active agent(s) (e.g., in the blood) sufficient to induce or suppress the biological effect (minimal effective concentration, MEC). The MEC will vary for each preparation, but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. Detection assays can be used to determine plasma concentrations.

Depending on the severity and responsiveness of the condition to be treated, dosing can be of a single or a plurality of administrations, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

Compositions according to some embodiments of the invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or

more unit dosage forms containing the active agent(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accommodated by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation according to the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition (e.g., in combination with pulmonary artery denervation), as is further detailed above.

As used herein the term "about" refers to ± 20 %, wherein in some embodiments of any of the respective embodiments described herein, "about" refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first

indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

When reference is made to particular sequence listings, such reference is to be understood to also encompass sequences that substantially correspond to its complementary sequence as including minor sequence variations, resulting from, e.g., sequencing errors, cloning errors, or other alterations resulting in base substitution, base deletion or base addition, provided that the frequency of such variations is less than 1 in 50 nucleotides, alternatively, less than 1 in 100 nucleotides, alternatively, less than 1 in 200 nucleotides, alternatively, less than 1 in 500 nucleotides, alternatively, less than 1 in 1000 nucleotides, alternatively, less than 1 in 5,000 nucleotides, alternatively, less than 1 in 10,000 nucleotides.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non-limiting fashion.

EXAMPLE 1

Safety and effect of denervation of sympathetic nerves in combination with drug therapy on pulmonary arterial hypertension

The safety, performance and initial effectiveness of denervation of sympathetic nerves surrounding the pulmonary vasculature for treating PAH is evaluated. Denervation is effected using ultrasonic energy, optionally using a Therapeutic Intra-Vascular Ultra-Sound (TIVUS™) system.

Adult patients (e.g., about 15 patients) with idiopathic PAH, PAH associated with connective tissue disease, anorexigen-induced PAH and/or heritable PAH, are selected, in WHO functional class III (marked limitation of physical activity, comfortable at rest, less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope), with stable PAH on a stable drug regimen (i.e., with no changes of dose or medication for a minimum of 3 months prior to enrollment) of two PAH-specific medications other than parenteral prostanoids. The patients have eGFR levels of at least 30 ml per minute per 1.73 m^2 and/or serum creatinine levels of less than 150 μM.

PAH diagnosis is optionally confirmed by hemodynamic evaluation, which shows all of the following: mean pulmonary artery pressure (mPAP) of at least 25 mmHg at rest; pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of no more than 15 mmHg; pulmonary vascular resistance (PVR) at rest of over 3 Wood units; and not meeting the criteria for a positive vasodilator response (fall in mPAP of at least 10 mmHg to no more than 40 mmHg).

Patients treated with parenteral prostanoids; patients having an implantable cardiac pacemaker, ICD, neurostimulator or drug infusion device; patients who have experienced a recent (e.g., in the previous 6 months) myocardial infarction, unstable angina pectoris or a cerebrovascular accident patients with a pulmonary artery aneurysm, moderate to severe pulmonary artery stenosis, significant co-morbid conditions and/or short life expectancy (e.g., less than a year); patients with pulmonary artery anatomy that precludes treatment or patients unable to undergo an MRI scan; and/or women who are pregnant or planning a pregnancy soon (e.g., within 12 months), are optionally excluded from the study.

Safety is determined by evaluating procedural related adverse events (complications) (e.g., up to 30 days post-procedure), including pulmonary artery perforation/dissection, acute thrombus formation in pulmonary artery, pulmonary artery aneurysm, vascular stenosis, hemoptysis, and/or death (including PAH-related and/or procedural related).

Safety is also optionally determined by evaluating long-term (e.g., up to 12 months post-procedure) procedural related adverse events (as described hereinabove), PAH worsening adverse events and/or death.

Variables which are determined in the course of the study include:

a) Changes from baseline of:

PAH-specific medications (e.g., at 2 weeks, 1 month, 6 months and/or 12 months);

Physical examination parameters (e.g., at 2 weeks, 1 month, 6 months and/or 12 months);

ECG (electrocardiography) parameters (e.g., at 1 month, 6 months and/or 12 months);

6-minute walking distance (6MWD) (e.g., at 1 month and/or 12 months);

Activity monitored using an actigraphy device (e.g., at 6 months and/or 12 months);

Arterial vs. venous catecholamine concentration (e.g., at 6 months and/or 12 months); and/or

Hemodynamic response to inhaled nitric oxide, including mPAP and PVR (e.g., at 6 months and/or 12 months);

b) Cardiac and pulmonary MRI parameters (e.g., at 1 month);

c) Echocardiography parameters (e.g., at 12 months);

d) Quality of life, as determined by emPHasis questionnaire (e.g., at 12 months); and/or

e) Long-term surveillance (e.g., at 2, 3, 4 and/or 5 years) for determining survival (or cause of mortality), hospitalization due to PAH, interventional or surgical procedures such as atrial septostomy or lung transplantation, worsening of WHO functional class, and/or escalation of drug therapy.

Elements of a study and optional times thereof are presented in FIG. 1. An optional flow chart for a study is presented in FIG. 2.

Effectiveness of treatment is determined by evaluating changes in hemodynamic changes from baseline (e.g., mPAP, PVR, right atrial pressure and/or cardiac index), change in 6MWD, change in quality of life, change in right ventricular (RV) function as assessed by MRI (e.g., RV ejection fraction, RV end diastolic and systolic volume, wall thickness, aortic flow, PA flow, and/or main, left and right PA diameter), change in right ventricular (RV) function/structure as assessed by echocardiography (e.g., tricuspid annular plane systolic excursion, RV myocardial performance index, RV ejection fraction, and/or RV end diastolic and systolic volume), and/or NT-pro BNP (N-terminal prohormone of brain natriuretic peptide) serum levels (e.g., at 1, 6 and/or 12 months).

Effectiveness of denervation in combination with any given drug therapy (e.g., combination of drugs) is optionally observed as improvement of patient condition in comparison with what would have been expected in the absence of denervation, e.g., based on baseline parameters, patient history, and/or expected progression of PAH as reported in the art.

Improvement of patient condition is optionally evidenced as a reduction one or more of: right atrial pressure (RAP), right ventricle pressures (RVP), systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressures (mPAP), pulmonary vascular resistance (PVR), and/or NT-pro-BNP levels and/or

as an increase in one or more of: cardiac output (CO), cardiac index (CI), ejection fraction (EF), pulmonary distensability, exercise tolerance - 6 minutes walking distance (6MWD), quality of life (as assessed by questionnaire), cardiopulmonary exercise testing and/or peak VO2.

Comparison of results of different drug therapies (in combination with denervation) is optionally performed to determine a particularly effective drug or drug combination, in combination with denervation.

EXAMPLE 2

Effect of denervation of sympathetic nerves in combination with drug therapy on pulmonary arterial hypertension in randomized study

The clinical effectiveness of denervation of sympathetic nerves surrounding the pulmonary vasculature in the treatment of PAH is evaluated using a randomized, single blind study. Denervation is effected using ultrasonic energy, optionally using a Therapeutic Intra-Vascular Ultra-Sound (TIVUS™) system, with some of the patients (e.g., about half) undergoing a sham treatment with the ultrasonic system, as a control group.

Adult patients (e.g., about 120 patients) with idiopathic PAH, PAH associated with connective tissue disease, anorexigen-induced PAH and/or heritable PAH, are selected according to the criteria described hereinabove, on a stable drug regimen (as defined hereinabove) of at least two PAH-specific medications. Variables which are determined in the course of the study (in comparison with baseline values) include:

a) Cardiac MRI parameters relating to right ventricular (RV) function (e.g., at 6 and/or 12 months);

b) Peak VO_2 as evaluated by CPET (cardiopulmonary exercise testing) (e.g., at 6 and/or 12 months);

c) NT-pro BNP (N-terminal prohormone of brain natriuretic peptide) serum levels (e.g., at 6 and/or 12 months);

d) Activity monitored using an actigraphy device (e.g., at 6 and/or 12 months);

e) Quality of life, as determined by emPHasis questionnaire (e.g., at 6 and/or 12 months); and/or

f) Long-term surveillance (e.g., at 2 and/or 3 years) for determining survival (or cause of mortality), hospitalization due to PAH, interventional or surgical procedures such as atrial septostomy or lung transplantation, worsening of WHO functional class, and/or escalation of drug therapy.

Safety is optionally evaluated as described hereinabove (e.g., at up to 12 months post-procedure).

Effectiveness of treatment is determined by evaluating change in right ventricular (RV) function as assessed by MRI (e.g., RV ejection fraction, RV end diastolic and systolic volume, wall thickness, aortic flow, PA flow, and/or main, left and right PA diameter), change in peak VO_2, activity measured (e.g., by actigraphy) as steps per awake hours, change in quality of life, and/or NT-pro BNP serum levels.

Effectiveness of denervation in combination with any given drug therapy (e.g., combination of drugs) is optionally observed as improved patient condition in denervation-treated group relative to sham treatment.

Improvement of patient condition is optionally evidenced as a reduction one or more of: right atrial pressure (RAP), right ventricle pressures (RVP), systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressures (mPAP), pulmonary vascular resistance (PVR), and/or NT-pro-BNP levels and/or

as an increase in one or more of: cardiac output (CO), cardiac index (CI), ejection fraction (EF), pulmonary distensability, exercise tolerance - 6 minutes walking distance (6MWD), quality of life (as assessed by questionnaire), cardiopulmonary exercise testing and/or peak VO2.

Comparison of results of different drug therapies (in combination with denervation) is optionally performed to determine a particularly effective drug or drug combination, in combination with denervation.

EXAMPLE 3

Safety and effect of denervation of sympathetic nerves in combination with drug therapy on pulmonary arterial hypertension

The safety, performance and initial effectiveness of denervation of sympathetic nerves surrounding the pulmonary vasculature for treating PAH was evaluated according to procedures similar to those described in Example 1. Elements of a study are presented in FIG. 3. A flow chart for a study is presented in FIG. 4.

Denervation was effected using ultrasonic energy, using a Therapeutic Intra-Vascular Ultra-Sound (TIVUS™) system.

14 adult patients with PAH in WHO functional class II-III were tested, with stable PAH on a stable drug regimen (i.e., with no changes of dose or medication for a minimum of 3 months prior to enrollment) of two PAH-specific medications other than parenteral prostanoids.

The denervation procedure lasted 20-30 minutes on average, usability feedback from the operators was excellent, and no severe adverse events were recorded at 1, 4, 8 and 12 month follow-up; indicating that denervation using a TIVUS™ system is an easy to perform, straightforward, predictable and safe procedure. The number of denervation sites for each patient ranged from 6 to 16, according to patient anatomy.

11 of the patients continued their drug regimens for at least 4 months after treatment, at which time the following were determined:

Hemodynamic changes from baseline, for mPAP, PVR, right atrial pressure and cardiac index;

6-minute walking distance (6MWD);

Activity monitored using an actigraphy device; and

Quality of life, as determined by emPHasis-10 questionnaire (2 patients who did not complete 4 months of drug regimen were also included in quality of life analysis).

As shown in FIGs. 5A-5D, hemodynamic parameters were consistently improved 4 months after denervation treatment in subjects undergoing drug therapy for PAH, with mean pulmonary arterial pressure (mPAP) being reduced by an average of about 14 % (FIG. 5A), cardiac index values being increased by an average of about 2 % (FIG. 5B), pulmonary vascular resistance (PVR) values being reduced by an average of about 15 % (FIG. 5C), and right atrial pressure being reduced by an average of about 20 % (FIG. 5D), relative to baseline.

In addition, as shown in FIG. 6, 6-minute walking distance (6MWD) increased by an average of about 21 % relative to baseline, 4 months after denervation treatment in subjects undergoing drug therapy for PAH.

As shown in FIG. 7, subject activity (as determined by actigraphy) increased by an average of about 12 % relative to baseline, 4 months after denervation treatment in subjects undergoing drug therapy for PAH.

As shown in FIG. 8, subject emPHasis-10 questionnaire scores decreased by an average of about 21 % relative to baseline, indicating an increase of quality of life.

The above results, showing improvement in subjects on a stable drug therapy, indicate that denervation complements drug therapy of PAH, suggesting that denervation exhibit beneficial effects via a different mechanism than do therapeutically active agents for PAH.

As shown in FIG. 9, pulmonary vascular resistance (PVR) were reduced 4 months after denervation in subjects treated by an anticoagulant (warfarin, rivaroxaban, dabigatran, apixaban, edoxaban, enoxaparin and/or fondaparinux), but not in subjects not treated regularly by an anticoagulant.

This result indicates that denervation is particularly suitable for use in treating PAH in combination with anticoagulants, for example, in a subpopulation of subjects who are treated by anticoagulants.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising:

a) determining a responsiveness of the subject to at least one therapeutically active agent usable in treating pulmonary arterial hypertension; and

b) effecting pulmonary artery denervation in a subject responsive to said at least one therapeutically active agent,

thereby treating the pulmonary arterial hypertension.

2. The method of claim 1, wherein said at least one therapeutically active agent is selected from the group consisting of an anticoagulant, a prostacyclin receptor agonist, an endothelin inhibitor, and a guanylate cyclase activity enhancer.

3. The method of claim 1, wherein said at least one therapeutically active agent comprises a prostacyclin receptor agonist.

4. The method of claim 1, wherein said at least one therapeutically active agent comprises an endothelin inhibitor.

5. The method of claim 1, wherein said at least one therapeutically active agent comprises a guanylate cyclase activity enhancer.

6. The method of claim 1, wherein said therapeutically active agent comprises an anticoagulant.

7. The method of claim 2, wherein said anticoagulant is selected from the group consisting of warfarin, acenocoumarol, dicoumarol, ethylbiscoumacetate, phenprocoumon, tecarfarin, anisindione, fluindione, phenindione, atromentin, a heparin, fondaparinux, idraparinux, idrabiotaparinux, apixaban, betrixaban, darexaban, edoxaban, eribaxaban, letaxaban, otamixaban, rivaroxaban, hirudin, lepirudin, bivalirudin, desirudin, argatroban, inogatran, dabigatran, melagatran, ximelagatran, antithrombin, batroxobin, hementin, and vitamin E.

8. The method of claim 2, wherein said prostacyclin receptor agonist is selected from the group consisting of prostacyclin (epoprostenol), iloprost, beraprost, treprostinil and selexipag.

9. The method of claim 2, wherein said endothelin inhibitor comprises a selective ET_A receptor antagonist, optionally ambrisentan.

10. The method of claim 2, wherein said endothelin inhibitor comprises a dual ET_A/ET_B receptor antagonist, optionally bosentan and/or macitentan.

11. The method of claim 2, wherein said guanylate cyclase activity enhancer is selected from the group consisting of sildenafil, tadalafil, vardenafil and riociguat.

12. The method of claim 1, wherein effecting said pulmonary artery denervation comprises thermally damaging nerve tissue associated with a main pulmonary artery.

13. The method according to claim 12, wherein said thermally damaging nerve tissue comprises selectively damaging nerves that are not coated by myelin, by emitting energy at a frequency, intensity and duration sufficient to damage only nerves that are not coated by myelin, by producing a predetermined temperature profile in the treated tissue, said temperature profile ranging between 47-57 °C.

14. The method according to claim 12, wherein said thermally damaging nerve tissue is effected by cryotherapy and/or by emitting energy from at least one energy-emitting device introduced into the body.

15. The method according to claim 14, wherein said energy is selected from the group consisting of ultrasound energy and monopolar or bipolar radiofrequency energy.

16. The method according to claim 15, wherein said energy comprises unfocused ultrasound energy.

17. The method according to claim 14, wherein effecting said pulmonary artery denervation comprises introducing a catheter device comprising said at least one energy-emitting device into a main pulmonary artery lumen.

18. The method according to claim 14, wherein said energy-emitting device is a transceiver, and effecting said pulmonary artery denervation further comprises:

receiving, using said at least one energy-emitting transceiver, echo signals reflected from non-targeted tissue following emission of energy by said at least one transceiver;

analyzing said received echo signals to identify at least one of a type and location of said non-targeted tissue relative to said at least one transceiver; and

emitting energy from said at least one transceiver in accordance with said analyzing, to modify nerve activity without substantially damaging said identified non-targeted tissue.

19. The method according to claim 14, wherein effecting said pulmonary artery denervation further comprises:

positioning said at least one energy-emitting device within the left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk at a location which is in between the first bifurcation of the left pulmonary artery and the first bifurcation of the right pulmonary artery,

wherein said thermally damaging nerve tissue comprises emitting energy having parameters selected to damage nerves only within a distance window of between 0.2 mm and 10 mm from the intimal aspect of the pulmonary artery wall when said at least one device is positioned at said location.

20. A method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising:

a) effecting pulmonary artery denervation in the subject; and

b) administering to the subject at least one therapeutically active agent usable in treating pulmonary arterial hypertension,

wherein said administering is at a sub-therapeutically effective amount,

thereby treating the pulmonary arterial hypertension.

21. The method of claim 20, wherein said administering said sub-therapeutically effective amount comprises administering, subsequently to said denervation, a dosage of at least

one therapeutically active agent which is lower than a dosage of said agent administered to the subject prior to said denervation.

22. The method of claim 20, wherein said administering said sub-therapeutically effective amount comprises administering, subsequently to said denervation, fewer therapeutically active agents than are administered to the subject prior to said denervation, wherein at least two therapeutically active agent usable in treating pulmonary arterial hypertension are administered to the subject prior to said denervation.

23. The method of claim 20, wherein said at least one therapeutically active agent is selected from the group consisting of an anticoagulant, a prostacyclin receptor agonist, an endothelin inhibitor, and a guanylate cyclase activity enhancer.

24. The method of claim 20, wherein said at least one therapeutically active agent comprises a prostacyclin receptor agonist.

25. The method of claim 20, wherein said at least one therapeutically active agent comprises an endothelin inhibitor.

26. The method of claim 20, wherein said at least one therapeutically active agent comprises a guanylate cyclase activity enhancer.

27. The method of claim 20, wherein said therapeutically active agent comprises an anticoagulant.

28. The method of claim 23, wherein said anticoagulant is selected from the group consisting of warfarin, acenocoumarol, dicoumarol, ethylbiscoumacetate, phenprocoumon, tecarfarin, anisindione, fluindione, phenindione, atromentin, a heparin, fondaparinux, idraparinux, idrabiotaparinux, apixaban, betrixaban, darexaban, edoxaban, eribaxaban, letaxaban, otamixaban, rivaroxaban, hirudin, lepirudin, bivalirudin, desirudin, argatroban, inogatran, dabigatran, melagatran, ximelagatran, antithrombin, batroxobin, hementin, and vitamin E.

29. The method of claim 23, wherein said prostacyclin receptor agonist is selected from the group consisting of prostacyclin (epoprostenol), iloprost, beraprost, treprostinil and selexipag.

30. The method of claim 23, wherein said endothelin inhibitor comprises a selective ET_A receptor antagonist, optionally ambrisentan.

31. The method of claim 23, wherein said endothelin inhibitor comprises a dual ET_A/ET_B receptor antagonist, optionally bosentan and/or macitentan.

32. The method of claim 23, wherein said guanylate cyclase activity enhancer is selected from the group consisting of sildenafil, tadalafil, vardenafil and riociguat.

33. The method of claim 20, wherein effecting said pulmonary artery denervation comprises thermally damaging nerve tissue associated with a main pulmonary artery.

34. The method according to claim 33, wherein said thermally damaging nerve tissue comprises selectively damaging nerves that are not coated by myelin, by emitting energy at a frequency, intensity and duration sufficient to damage only nerves that are not coated by myelin, by producing a predetermined temperature profile in the treated tissue, said temperature profile ranging between 47-57 °C.

35. The method according to claim 33, wherein said thermally damaging nerve tissue is effected by cryotherapy and/or by emitting energy from at least one energy-emitting device introduced into the body.

36. The method according to claim 35, wherein said energy is selected from the group consisting of ultrasound energy and monopolar or bipolar radiofrequency energy.

37. The method according to claim 36, wherein said energy comprises unfocused ultrasound energy.

38. The method according to claim 35, wherein effecting said pulmonary artery denervation comprises introducing a catheter device comprising said at least one energy-emitting device into a main pulmonary artery lumen.

39. The method according to claim 35, wherein said energy-emitting device is a transceiver, and effecting said pulmonary artery denervation further comprises:

receiving, using said at least one energy-emitting transceiver, echo signals reflected from non-targeted tissue following emission of energy by said at least one transceiver;

analyzing said received echo signals to identify at least one of a type and location of said non-targeted tissue relative to said at least one transceiver; and

emitting energy from said at least one transceiver in accordance with said analyzing, to modify nerve activity without substantially damaging said identified non-targeted tissue.

40. The method according to claim 35, wherein effecting said pulmonary artery denervation further comprises:

positioning said at least one energy-emitting device within the left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk at a location which is in between the first bifurcation of the left pulmonary artery and the first bifurcation of the right pulmonary artery,

wherein said thermally damaging nerve tissue comprises emitting energy having parameters selected to damage nerves only within a distance window of between 0.2 mm and 10 mm from the intimal aspect of the pulmonary artery wall when said at least one device is positioned at said location.

41. A method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising effecting pulmonary artery denervation in the subject,

the method being devoid of administering to the subject a therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one month subsequent to said denervation,

thereby treating the pulmonary arterial hypertension.

42. The method of claim 41, wherein the method is devoid of administering to the subject said therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one year subsequent to said denervation.

43. The method of claim 41, wherein effecting said pulmonary artery denervation comprises thermally damaging nerve tissue associated with a main pulmonary artery.

44. The method according to claim 43, wherein said thermally damaging nerve tissue comprises selectively damaging nerves that are not coated by myelin, by emitting energy at a frequency, intensity and duration sufficient to damage only nerves that are not coated by myelin, by producing a predetermined temperature profile in the treated tissue, said temperature profile ranging between 47-57 °C.

45. The method according to claim 43, wherein said thermally damaging nerve tissue is effected by cryotherapy and/or by emitting energy from at least one energy-emitting device introduced into the body.

46. The method according to claim 45, wherein said energy is selected from the group consisting of ultrasound energy and monopolar or bipolar radiofrequency energy.

47. The method according to claim 46, wherein said energy comprises unfocused ultrasound energy.

48. The method according to claim 45, wherein effecting said pulmonary artery denervation comprises introducing a catheter device comprising said at least one energy-emitting device into a main pulmonary artery lumen.

49. The method according to claim 45, wherein said energy-emitting device is a transceiver, and effecting said pulmonary artery denervation further comprises:

receiving, using said at least one energy-emitting transceiver, echo signals reflected from non-targeted tissue following emission of energy by said at least one transceiver;

analyzing said received echo signals to identify at least one of a type and location of said non-targeted tissue relative to said at least one transceiver; and

emitting energy from said at least one transceiver in accordance with said analyzing, to modify nerve activity without substantially damaging said identified non-targeted tissue.

50. The method according to claim 45, wherein effecting said pulmonary artery denervation further comprises:

positioning said at least one energy-emitting device within the left pulmonary artery, right pulmonary artery and/or pulmonary artery trunk at a location which is in between the first bifurcation of the left pulmonary artery and the first bifurcation of the right pulmonary artery,

wherein said thermally damaging nerve tissue comprises emitting energy having parameters selected to damage nerves only within a distance window of between 0.2 mm and 10 mm from the intimal aspect of the pulmonary artery wall when said at least one device is positioned at said location.

	Screening	Eligibility I	Eligibility II + Procedure (RHC)[5]	Hospital discharge	2w ±5d	1m± 1w	6m± 1m	12m ±1m	24m ±3 m	36m ±3 m	48m ±3 m	60m ±3 m
Informed consent	X											
Medical history/demographics	X											
Physical examination inc. vital signs and FC	X	X	X	X	X	X	X	X				
Concomitant Medications	X	X	X	X	X	X	X	X				
REVEAL Risk Score			X									
DLCO Test		X										
Serum pregnancy test (only if child bearing potential)	X		X				X	X				
FBC,		X		X		X	X	X				
Liver enzyme		X				X	X	X				
Coagulation screen			X				X	X				
eGFR or serum creatinine		X				X	X	X				
12 lead ECG		X		X		X	X	X				
MRI		X				X	X					
Echocardiography		X					X	X	X	X	X	X
6MWD inc. Borg Dyspnea index, HR and O2 saturations		X				X	X	X				
serum NT-pro-BNP		X				X	X	X				
Right heart catheterization (RHC)			X				X	X				
Catecholamine Arterial vs.Venous			X				X	X				
Pulmonary artery denervation procedure			X									
Quality of life questionnaire		X					X	X				
Activity monitoring/actigraphy		X					X	X				
Adverse events		X	X	X	X	X	X	X				
Long term surveillance									X	X	X	X

FIG. 1

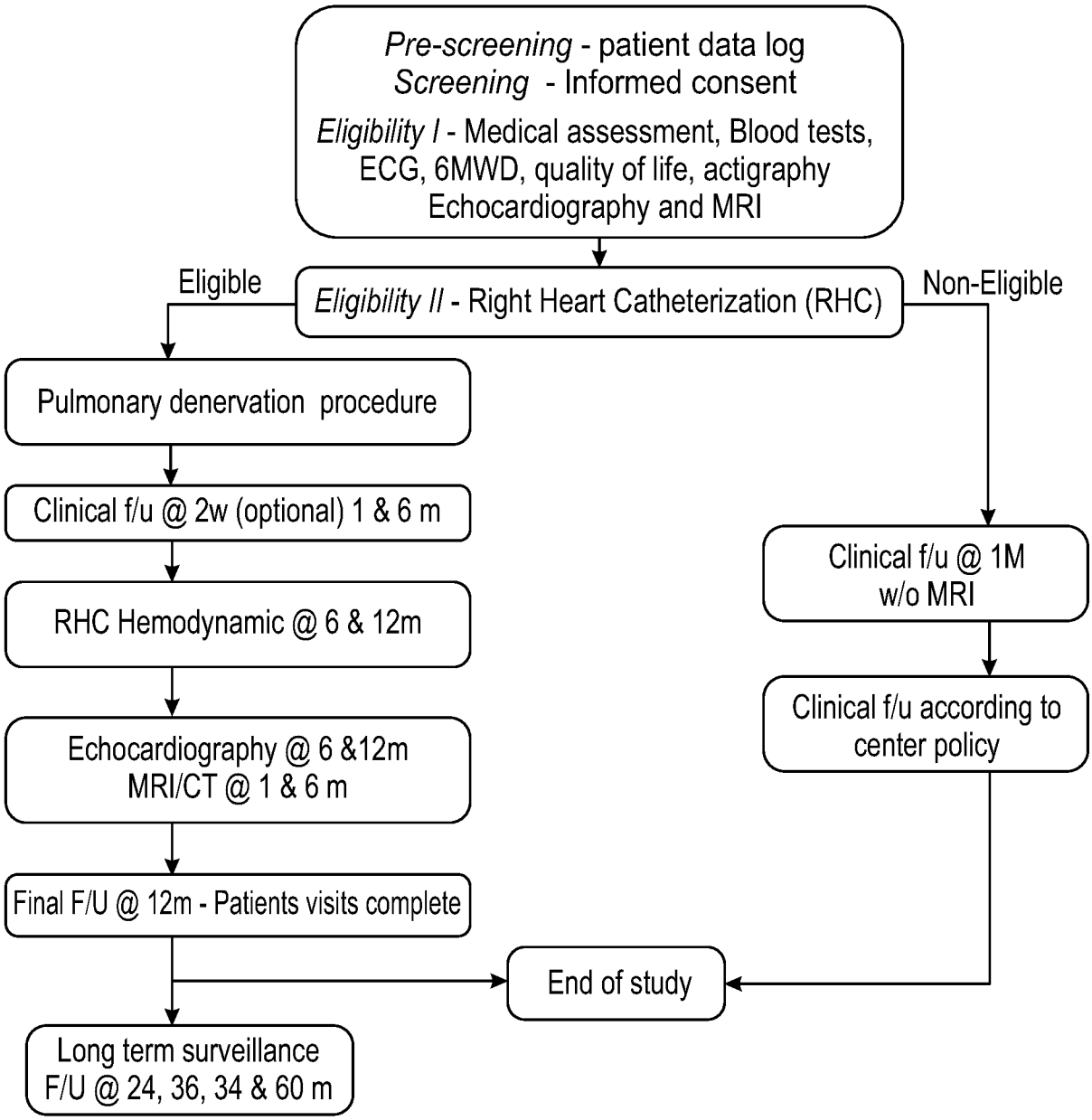

Pre-screening - patient data log
Screening - Informed consent
Eligibility I - Medical assessment, Blood tests, ECG, 6MWD, quality of life, actigraphy Echocardiography and MRI
Eligible
Eligibility II - Right Heart Catheterization (RHC)
Non-Eligible
Pulmonary denervation procedure
Clinical f/u @ 2w (optional) 1 & 6 m
RHC Hemodynamic @ 6 & 12m
Echocardiography @ 6 &12m MRI/CT @ 1 & 6 m
Final F/U @ 12m - Patients visits complete
Long term surveillance F/U @ 24, 36, 34 & 60 m
Clinical f/u @ 1M w/o MRI
Clinical f/u according to center policy
End of study

FIG. 2

	Screening	Eligibility I	Eligibility II + Procedure (RHC)[5]	Hospital discharge	2w[4] ±5d	1m± 1w	4m± 1m	8m± 1m	12m ±1m	24m ±3 m	36m ±3 m
Informed consent	x										
Medical history/demographics	x[1]										
Physical examination inc. vital sings and FC	x	x	x	x	x	x	x	x	x		
Concomitant Medications	x	x	x	x	x	x	x	x	x		
Serum pregnancy test (only if child bearing potential)	x		x			x	x		x		
FBC, Liver enzyme		x		x		x	x	x	x		
Coagulation screen			x				x		x		
eGFR or serum creatinine		x				x	x		x		
12 lead ECG		x		x		x	x	x	x		
MRI/CT angiography		x				x			x		
6MWD Inc. Borg Dyspnea index, HR and 02 saturations		x				x	x	x	x		
serum NT-pro-BNP		x		x		x	x	x	x		
Right heart catheterization (RHC)			x				x		x		
Catecholamine Arterial vs. Venous			x[2]				x		x		
Pulomonary artery denervation procedure			x								
Quality of life questionnaire		x					x	x	x		
Activity monitoring/actigraphy		x					x	x	x		
Adverse events		x	x	x	x	x	x	x	x		
Long term surveillance[3]										x	x

FIG. 3

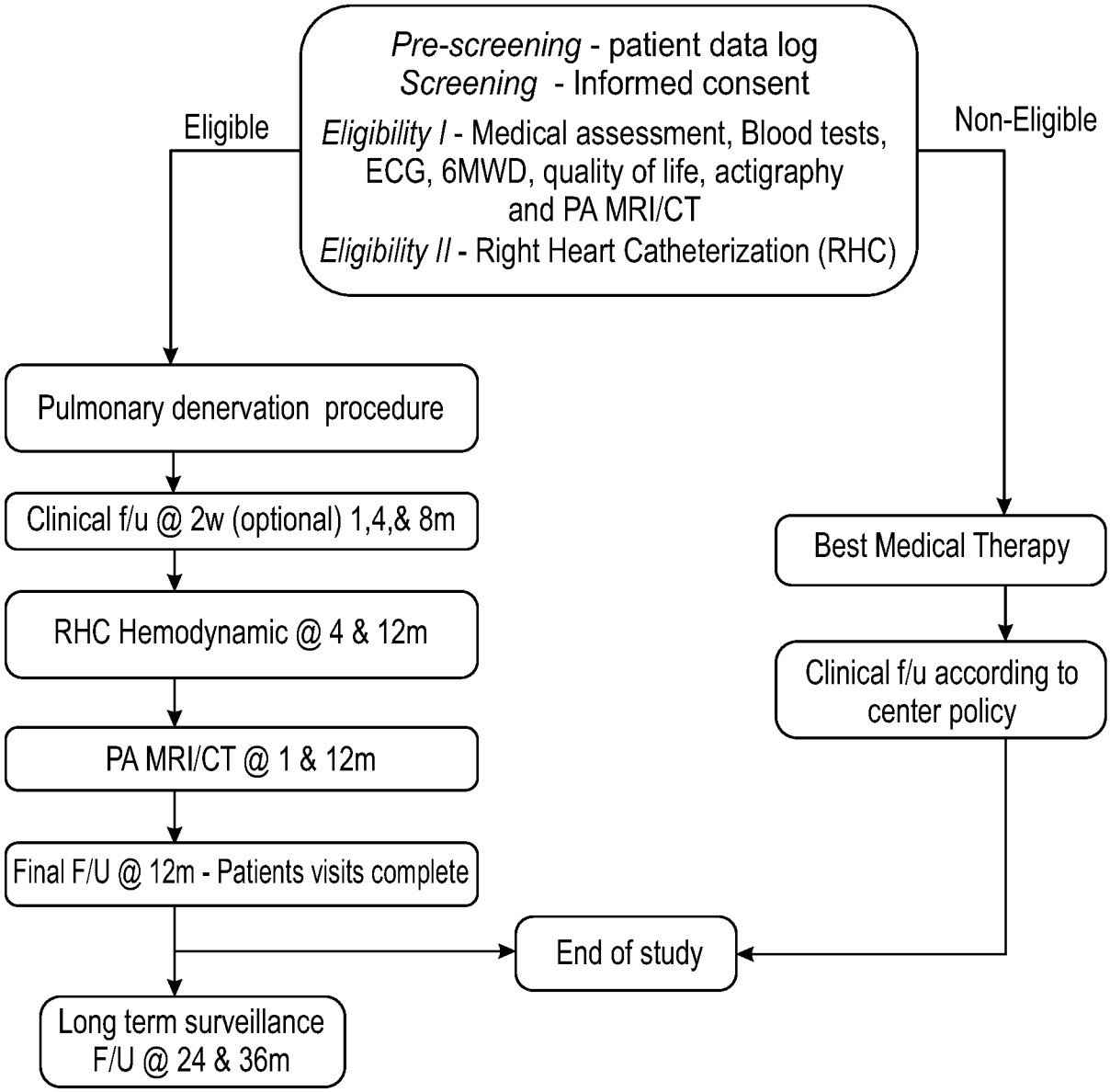

Pre-screening - patient data log
Screening - Informed consent
Eligibility I - Medical assessment, Blood tests, ECG, 6MWD, quality of life, actigraphy and PA MRI/CT
Eligibility II - Right Heart Catheterization (RHC)
Eligible
Non-Eligible
Pulmonary denervation procedure
Clinical f/u @ 2w (optional) 1,4,& 8m
RHC Hemodynamic @ 4 & 12m
PA MRI/CT @ 1 & 12m
Final F/U @ 12m - Patients visits complete
Long term surveillance F/U @ 24 & 36m
Best Medical Therapy
Clinical f/u according to center policy
End of study

FIG. 4

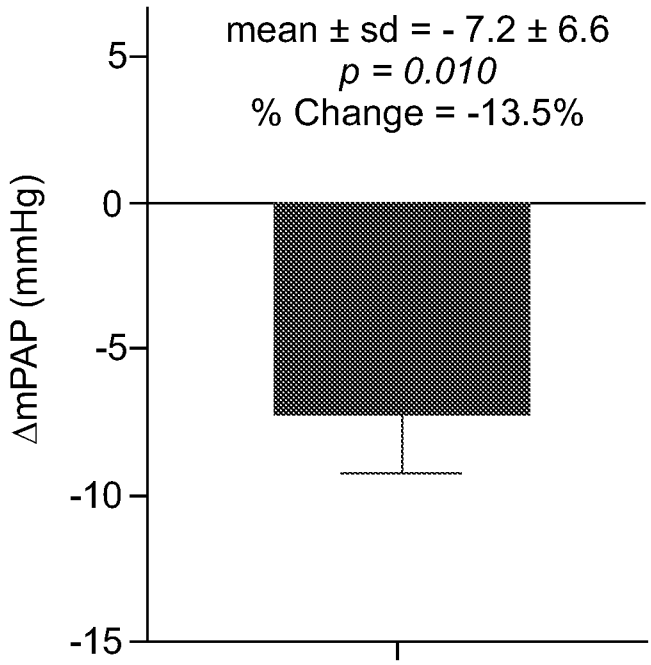

mean ± sd = - 7.2 ± 6.6
p = 0.010
% Change = -13.5%
ΔmPAP (mmHg)
5
0
-5
-10
-15

FIG. 5A

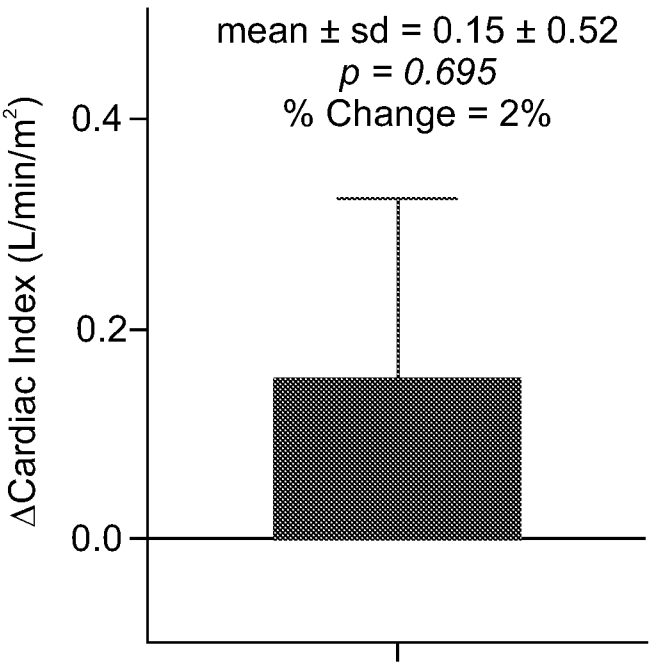

mean ± sd = 0.15 ± 0.52
p = 0.695
% Change = 2%
ΔCardiac Index (L/min/m²)
0.4
0.2
0.0

FIG. 5B

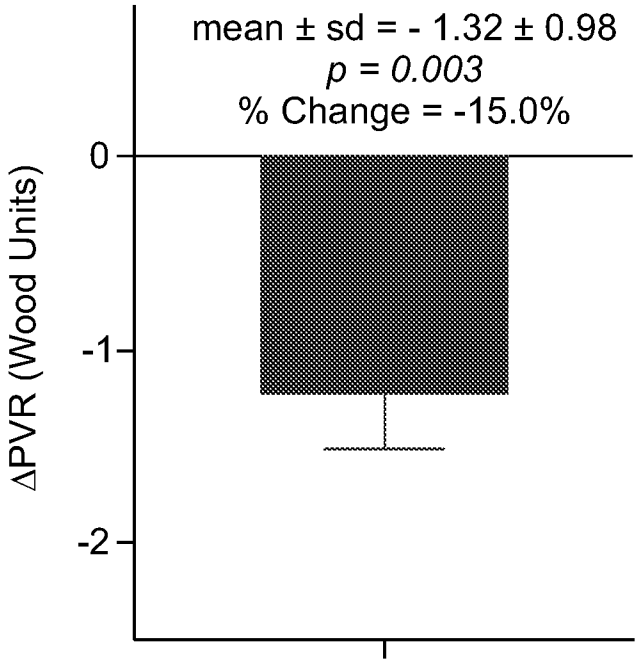

mean ± sd = - 1.32 ± 0.98
p = 0.003
% Change = -15.0%
0
-1
-2
ΔPVR (Wood Units)

FIG. 5C

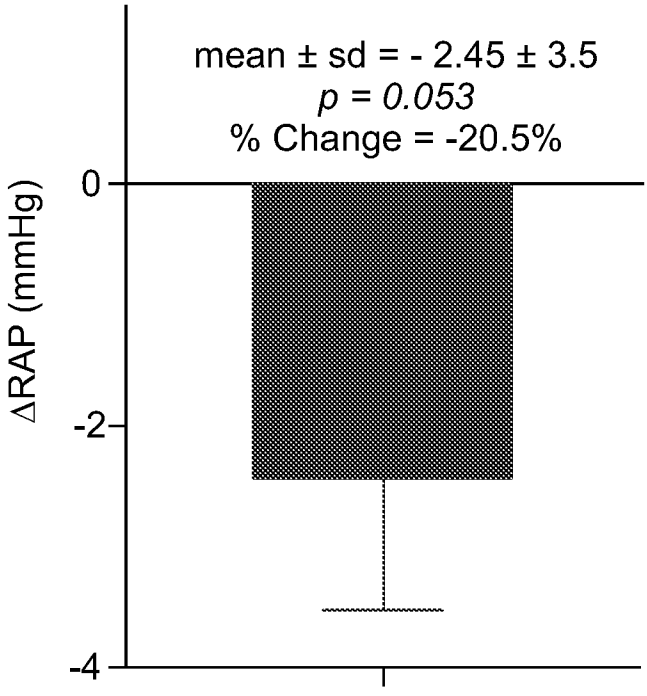

mean ± sd = - 2.45 ± 3.5
p = 0.053
% Change = -20.5%
0
-2
-4
ΔRAP (mmHg)

FIG. 5D

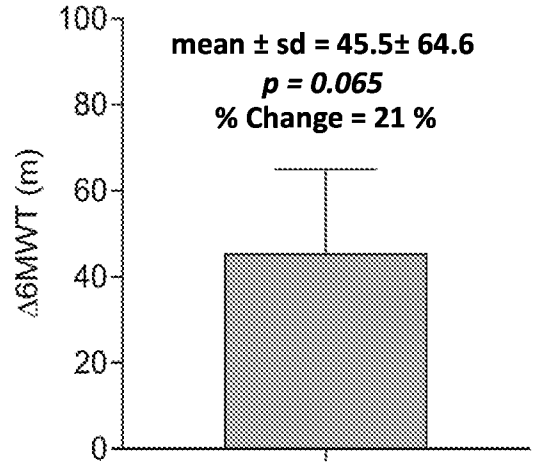


FIG. 6

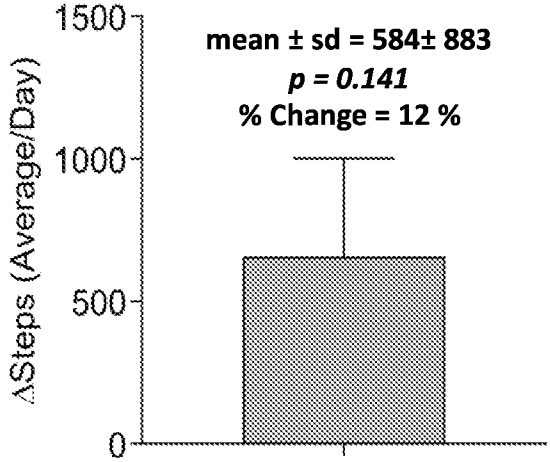


FIG. 7

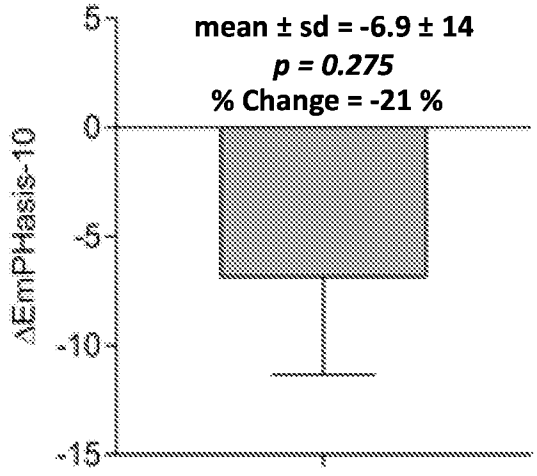


FIG. 8

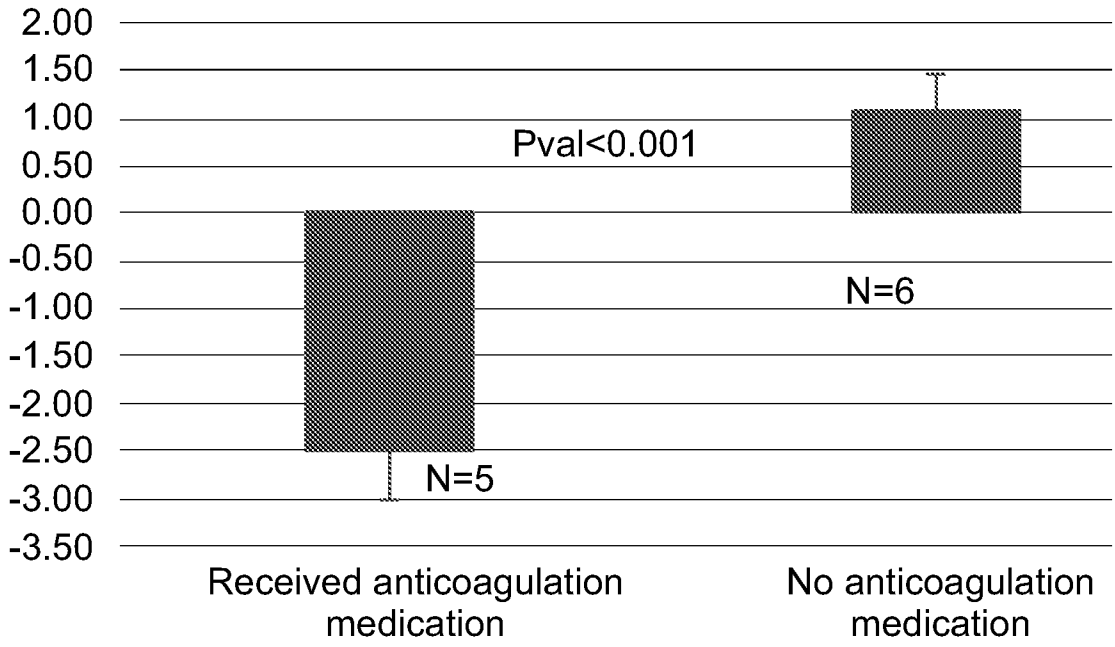

2.00
1.50
1.00
0.50
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
-3.50
Pval<0.001
N=6
N=5
Received anticoagulation medication
No anticoagulation medication

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2018/050321

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 45/06; A61K 31/4985; A61K 31/505; A61K 31/506; A61N 7/00 (2018.01)
CPC - A61K 45/06; A61K 31/4985; A61K 31/505; A61K 31/506; A61N 7/00 (2018.08)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0102361 A1 (BODIN) 27 May 2004 (27.05.2004) entire document	1-19
Y	WO 2016/084081 A2 (SONIEVIE LTD) 02 June 2016 (02.06.2016) entire document	1-19
Y	US 2013/0225595 A1 (GILEAD SCIENCES INC) 29 August 2013 (29.08.2013) entire document	5-7, 9, 11
A	US 2014/0180277 A1 (CHEN) 26 June 2014 (26.06.2014) entire document	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 August 2018	29 AUG 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2018/050321

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

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

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

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

See Extra Sheet

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-19

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: Claims 1-19 are drawn to methods of treating pulmonary arterial hypertension comprising determining a responsiveness of the subject to at least one therapeutically active agent usable in treating pulmonary arterial hypertension.

Group II: Claims 20-40 are drawn to methods of treating pulmonary arterial hypertension comprising administering a sub-therapeutically effective amount of a therapeutically active agent usable in treating pulmonary arterial hypertension.

Group III: Claims 41-50 are drawn to methods of treating pulmonary arterial hypertension, the methods being devoid of administering to a subject a therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one month subsequent to pulmonary artery denervation.

The inventions listed in Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, methods of treating pulmonary arterial hypertension comprising determining a responsiveness of the subject to at least one therapeutically active agent usable in treating pulmonary arterial hypertension, are not present in Groups II and III; the special technical features of Group II, methods of treating pulmonary arterial hypertension comprising administering a sub-therapeutically effective amount of a therapeutically active agent usable in treating pulmonary arterial hypertension, are not present in Groups I and III; and the special technical features of Group III, methods of treating pulmonary arterial hypertension, the methods being devoid of administering to a subject a therapeutically active agent usable in the treatment of pulmonary arterial hypertension for a time period of at least one month subsequent to pulmonary artery denervation, are not present in Groups I and II.

Groups I-III share the technical features of a method of treating pulmonary arterial hypertension in a subject in need thereof, the method comprising: effecting pulmonary artery denervation in the subject, thereby treating the pulmonary arterial hypertension; and providing at least one therapeutically active agent usable in treating pulmonary arterial hypertension. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2014/0180277 A1 to Chen discloses a method of treating pulmonary arterial hypertension in a subject in need thereof (Abstract, The device can be used to treat pulmonary hypertension with pulmonary denervation), the method comprising: effecting pulmonary artery denervation in the subject, thereby treating the pulmonary arterial hypertension (Para. [0154], In some embodiments, a method for sympathetic denervation can be used for treating pulmonary hypertension resulting from unilateral chronic thrombotic embolism; Para. [0106], This discovery provides a basis for more effective denervation of the pulmonary artery. For example, by selectively ablating only portions of the main pulmonary artery and the left and right pulmonary arteries, a higher success rate of denervation can be achieved with less unnecessary tissue damage. Such denervation can provide significant benefits in the treatment of diseases such as pulmonary hypertension, as described below).

Further, US 2004/0102361 A1 to Chen teaches a method of treating pulmonary arterial hypertension in a subject in need thereof (Abstract), the method comprising: providing at least one therapeutically active agent usable in treating pulmonary arterial hypertension (Para. [0001], The invention relates to pharmaceutical compositions for the treatment of pulmonary arterial hypertension comprising a prostacyclin or a prostacyclin analogue and an endothelin receptor antagonist...).

The inventions listed in Groups I-III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.