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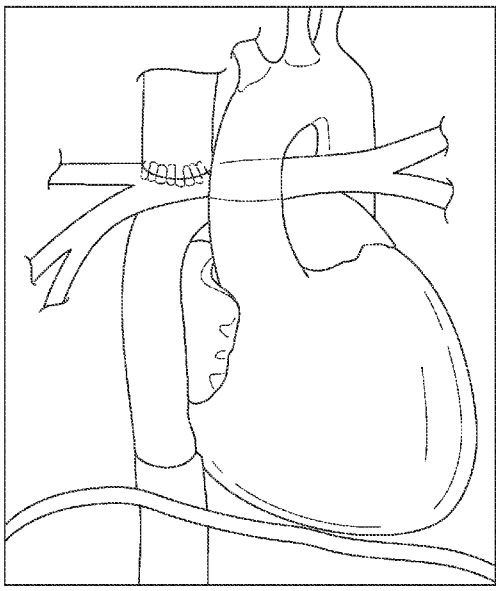


FIG. 1A

(57) Abstract: Various methods of treating single ventricle heart disease SVHD patients, including patients who have undergone Fontan surgery (Fontan patient), to improve exercise performance, single ventricular performance, cardiac output and myocardial performance index (MPI) in the SVHD patients, including the Fontan patients, using udenafil compositions. The methods of the present invention include administering an effective amount of udenafil or a pharmaceutically acceptable salt thereof to a SVHD patient, including a Fontan, to improve the ventricular performance of the SVHD patient's, including the Fontan patient's, single functioning ventricle. In addition, the methods of the present invention include administering an effective amount of udenafil or a pharmaceutically acceptable salt thereof to a SVHD patient, including a Fontan patient, to improve the SVHD patient's, including the Fontan patient's, MPI. IThe methods of the present invention further include administering an effective amount of udenafil or a pharmaceutically acceptable salt thereof to a SVHD patient, including a Fontan patient, to improve the SVHD patient's, including the Fontan patient's, cardiac output. The methods of the present invention further include administering an effective amount of udenafil or a pharmaceutically acceptable salt thereof to a SVHD patient, including a Fontan patient, who is at least 6 years old, to improve at least one or more or all of the following in the SVHD patient, including the Fontan patient: (a) ventricular performance of the SVHD patient's, including a Fontan patient's, single functioning ventricle as measured by MPI; (b) exercise capacity as measured by oxygen consumption at anaerobic threshold (VAT); (c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2; (d) work rate at VAT; (e) VE/VCO2 at VAT;

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diastolic blood pressure at rest; and (g) oxygen saturation (%) at rest.

METHODS OF IMPROVING EXERCISE PERFORMANCE, SINGLE VENTRICULAR PERFORMANCE, AND MYOCARDIAL PERFORMANCE INDEX (MPI) IN SINGLE VENTRICLE HEART DISEASE, USING UDENAFIL COMPOSITIONS

Statement of Government Interests

This work was funded, at least in part, by grants from the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health. The principal grant support was through NHLBI grant U24 HL135691 and/or U01 HL068270 to the New England Research Institutes, Inc. Grants to the Pediatric Heart Network clinical sites (UG1 HL135685, UG1 HL135680, UG1 HL135683, UG1 HL135689, UG1 HL135682, UG1 HL135665, UG1 HL135646, UG1 HL135678, UG1 HL135666). The government may have certain rights in the data and inventions disclosed herein.

Related Applications

The present application claims priority to U.S. Provisional No. 62/905,350 filed on September 24, 2019, U.S. Provisional No. 62/936,497 filed on November 16, 2019, and U.S. Provisional No. 63,023,070 filed on May 11, 2020. The foregoing provisional applications are incorporated herein by reference in their entireties.

Field of the Invention

Methods for improving exercise performance, single ventricular performance, and myocardial performance index (MPI) in single ventricle heart disease (SVHD) patients, including Fontan patients, using udenafil compositions are provided.

Background

The heart is a muscular organ that pumps blood through the blood vessels of the circulatory system. In humans, the heart is located between the lungs and the chest and is divided into left and right sides. The normal human heart has four chambers, a left atrium and left ventricle, the left side, and a right atrium and right ventricle, the right side. The oxygen-poor blood ("blue blood") enters the right side through the right atrium and freshly oxygenated blood ("red blood") exits the left side through the left ventricle. The heart has four valves, the tricuspid valve, the pulmonic valve, the mitral valve and the aortic valve. These valves

prevent backflow of blood within the heart and force blood to flow to the lungs and body in a forward direction.

A human heart beats (expands and contracts) approximately 100,000 times per day, pumping five to six quarts of blood each minute, or about 2,000 gallons per day. The left ventricle, the main pumping chamber of the heart, pumps freshly oxygenated blood (red blood) to the body through the aortic valve. The blood then circulates to all parts of the body through arteries and arterioles, delivering oxygen and nutrients. As the blood flows through the circulation, it exchanges oxygen and nutrients for carbon dioxide and metabolic wastes. In this process, the blood transitions from oxygen-rich blood (red blood) to oxygen-poor blood (blue blood). The oxygen-poor blood then returns to the right atrium through the veins of the body. The blue blood passes through the tricuspid valve from the right atrium to the right ventricle, and then it is pumped to the lungs by the right ventricle to exchange carbon dioxide for oxygen. The now freshly oxygenated blood (red blood) returns from the lungs to the left atrium via the pulmonary veins. The blood passes through the mitral valve from the left atrium to the left ventricle, and then is pumped to the body to start the circulation anew.

Thus, the normal human cardiovascular system consists of pulmonary and systemic circulations that are connected in series and powered by the pumping of the right and left ventricles. Gewillig M.: Congenital heart disease. THE FONTAN CIRCULATION. *Heart*, 91:839–846 (2005).

Single ventricle heart disease (SVHD) is a rare pediatric disease that includes a group of cardiac malformations, each of which results in the presence of only a single functional ventricle (pumping chamber). In other words, unlike newborns born with normal hearts (four chambers and two ventricles). SVHD newborns are born with only one functioning ventricle (one pumping chamber), i.e., single ventricle hearts. The non-functioning or missing ventricle (pumping chamber) may be smaller than the single ventricle such that it does not sufficiently function, it may be absent altogether, or it may be configured in such a way as to prevent it from contributing to the normal flow of blood through the circulation. Examples of SVHD include hypoplastic left heart syndrome, tricuspid atresia, double inlet left ventricle, and others.

Typically, SVHD newborns are cyanotic, blue in color, since a mixture of oxygen-poor blood (blue blood) and oxygen-rich blood (red blood) mix together in the single ventricle. The amount of oxygen within the blood mixture leaving the heart is very dependent upon the type, severity and location of the SVHD heart defect. Some SVHD newborns will be mildly cyanotic, whereas others will be severely cyanotic, requiring early intervention to meet the oxygen demands of the body to survive. Unfortunately, without surgical intervention most newborns born with SVHD will not survive.

SVHD can be thought of as having two primary subtypes. In the first subtype, the left ventricle and the aorta (the main artery to the body) are under-developed and the heart is not able to pump blood to the body without an interventional procedure. In the second subtype, the right ventricle and the pulmonary artery (the main artery to the lungs) are under-developed and the heart is not able to pump blood to the lungs.

For those infants born with an under-developed left ventricle and aorta, the first subtype, an urgent intervention is required within the first few days or weeks of life to stabilize blood flow to the body. This intervention is called the Norwood operation, see **FIG. 5**, and involves rebuilding the aorta (the main artery to the body) using the pulmonary valve and pulmonary artery along with patch material. Since the Norwood operation repurposes the pulmonary artery to supply blood to the body, it also must include a way for blood to get to the lungs. This is accomplished by the inclusion of a "shunt" of blood from the aortic circulation to the pulmonary circulation. This shunt is generally a tube graft that is placed between the right subclavian artery (the artery that supplies blood to the right arm) and the right pulmonary artery. The Norwood operation allow newborns to survive infancy, but is not a permanent solution. This temporary procedure forces the single pumping chamber of the heart to pump blood to both the body and to the lungs, putting it under stress. To relieve this stress, two additional procedures are performed. The first of these, the Glenn shunt or hemi-Fontan, see **FIG. 6**, occurs at 4-6 months and involves connecting the superior vena cava (the main vein of the upper body) directly to the pulmonary arteries. This allows the blue blood from the upper body to return to the lungs for oxygen repletion without the need for a ventricular pump. The final surgery, the Fontan operation, See **FIG. 1A and FIG. 7**, typically occurs at 18-48 months of age and involves connecting the inferior vena cava (the main vein of the lower body) directly to the pulmonary arteries. This allows blue blood from the lower body to return to the lungs for oxygen repletion without the need for a ventricular

pump specifically pumping the blood to the lungs. After the Fontan operation, all blue blood returns to the lungs and all red blood returns from the lungs to the heart but this is accomplished without the assistance of a ventricular pump dedicated to pumping blood through the lungs to the heart, as with a normal four-chamber heart.

For those infants born with an under-developed right ventricle and pulmonary artery, the second subtype, an urgent neonatal intervention is often not required. This group of babies requires close monitoring to determine if there is too little blood flow to the lungs, too much blood flow to the lungs, or an appropriate amount of blood flow to allow for growth and development. If there is too little blood flow to the lungs, a shunt is often placed, similar to what is done as part of the Norwood operation. If there is too much blood flow to the lungs, a restrictor may be placed around the pulmonary artery to reduce the amount of blood flow to the lungs to avoid the development of congestive heart failure. If the amount of blood flow to the lungs is appropriate, infants born with an under-developed right ventricle and pulmonary artery may go through their initial months of life without the need for a surgical intervention. Whether there is too little, too much, or an appropriate amount of blood flow to the lungs, infants born with this type of SVHD still require the Glenn shunt or hemi-Fontan at 4-6 months of age and the Fontan at 18-48 months of age to relieve the burden from the heart and to separate the blue blood from the red blood.

After the Fontan operation, the subtype of single ventricle heart disease is less important as all patients are left with a common physiology: (i) passive blood flow from the superior and inferior vena cava directly to the lungs bypassing the heart and (ii) a single ventricle that pumps blood to the body. Although this "Fontan circulation" has allowed for the survival of many thousands of patients over the last 40-50 years, it is far from normal. In the absence of a ventricular pump to push blood through the lungs and back to the heart, the Fontan circulation must rely on pressure generated in the veins of the body to accomplish this task. This results in a very elevated 'blood pressure' within the veins and also limits the amount of flow that can circulate through the body in a given amount of time – this is called reduced cardiac output.

Over time, the combination of elevated pressure in the veins and reduced cardiac output lead to a predictable set of long-term complications and, ultimately, to a significantly diminished duration of survival. Complications related to the Fontan circulation include: damage to the

kidneys and liver, overload of the lymphatic circulation leading to protein loss in the lungs or gastrointestinal tract, bleeding and blood clotting disorders including the risk of stroke, and progressive dysfunction of the pumping ability of the heart itself.

The ability to perform exercise is used in many forms of heart disease as a marker of the health of the circulation. For those with a Fontan circulation, exercise is likewise an important measure of health and a good predictor of outcomes. While exercise ability is often preserved for those with a Fontan circulation during childhood, it typically begins to drop during adolescence and early adulthood. This deterioration correlates with an increase in the prevalence of heart failure symptoms, hospitalizations, and mortality, often due to the complications of the Fontan circulation itself. In some cases, cardiac transplantation may remain a therapeutic option, but cardiac transplantation comes with its own sets of risks, and patients with Fontan circulation may often be poor candidates for a heart transplant due to chronic and progressive dysfunction of many organ systems.

Notwithstanding this long-standing very serious congenital heart disease, to date, no pharmacotherapy has been approved by the U.S. Food & Drug Administration (FDA) or any other equivalent agency through-out the world for the treatment of SVHD patients, including Fontan patients. Accordingly, there is a real need and demand for new pharmacotherapies for SVHD patients, including Fontan patients, relating to complications of SVHD and the Fontan circulation, with the goals of increasing the life span of SVHD patients, including Fontan patients, and avoiding or delaying the progression of the disease and the need for cardiac transplantation.

There is also a real need and demand for new pharmacotherapies for SVHD patients, including Fontan patients, to (i) improve the myocardial performance index ("MPI"), (ii) improve single ventricular performance, (iii) improve exercise capacity at the ventilatory anaerobic threshold (VAT) and/or the maximal aerobic capacity (max VO_2 or VO_2 max), (iv) improve the work rate at VAT, (v) improve the ventilatory equivalents of carbon dioxide (VE/VCO_2) at VAT, and/or (vi) improve cardiac performance of the single ventricle.

Summary of the Invention

The present invention overcomes the above-mentioned drawbacks and disadvantages associated with current treatments of SVHD patients, including Fontan patients, through the discovery of novel methods of treating SVHD patients, including Fontan patients.

Generally speaking, the methods of the present invention are directed to the use of udenafil or a pharmaceutically acceptable salt thereof, to treat SVHD patients, including Fontan patients. More specifically, methods of the present invention comprise administering, preferably daily, to a SVHD patient, including a Fontan patient, an effective amount of udenafil or a pharmaceutically acceptable salt thereof to improve, amongst other things, their MPI and exercise capacity or performance.

In general, the methods of the present invention include administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof, to the SVHD patient, including a Fontan patient, to improve:

(a) ventricular performance of the SVHD patient's single functioning ventricle as measured by MPI;
(b) exercise capacity as measured by oxygen consumption at VAT;
(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;
(d) work rate at VAT;
(e) VE/VCO_2 at VAT;
(f) diastolic blood pressure at rest; and
(g) oxygen saturation (%) at rest, each individually, collectively or in any combination.

Preferably, the methods of the present invention improve (a)-(g) listed above, including individually, collectively or in any combination thereof. Preferably, the methods of the present invention improve at least the combination of (a)-(e) listed above. Most preferably, (a)-(g) listed above, including individually, collectively or in any combination thereof, are improved in accordance with the present invention by administering daily to a SVHD patient, including a Fontan patient, an effective amount of udenafil or a pharmaceutical acceptable salt thereof.

Improvements in single ventricle performance in accordance with the methods of the present invention include improvements in both systolic and diastolic function. These can be demonstrated by improvements in, but not limited to, blood pool MPI, tissue Doppler MPI, cardiac output (estimated by the product of the integral under the Doppler derived outflow curve and the heart rate), and other measures of single ventricle heart performance. Improvements in exercise capacity or performance in accordance with the methods of the present invention include, but are not limited to, improvements in exercise capacity or performance at anaerobic threshold ("VAT") and/or improvements in exercise capacity or performance at maximal effort or max VO_2. Also in accordance with the present invention, there are improvements in work rate at VAT, ventilatory equivalents of carbon dioxide at VAT (VE/VCO_2), diastolic blood pressure at rest and/or oxygen saturation (%) at rest, when the methods of the present invention are practiced with regard to SVHD patients, including Fontan patients.

Generally, "effective amount" is used herein to mean an amount of udenafil or a pharmaceutically acceptable salt thereof, that is sufficient to elicit or induce a therapeutic or pharmacologic effect without causing treatment-limiting side effects.

More specifically, "effective amount" is used herein to mean an amount of udenafil or a pharmaceutically acceptable salt thereof, that is sufficient to elicit or induce a therapeutic or pharmacologic effect in a SVHD patient, including a Fontan patient, without causing treatment-limiting toxicity, treatment limiting side effects associated with inhibition of PDE6 and/or PDE11, and/or any other treatment-limiting side effects.

An example of an "effective amount" of udenafil or a pharmaceutically acceptable salt thereof in accordance with the present invention includes a total daily amount in a range that includes, but is not limited to, from about 87.5 mg to about 175 mg. More preferably, an "effective amount" of udenafil or a pharmaceutically acceptable salt thereof in accordance with the present invention includes a total daily amount in a range from about 125 mg to about 175 mg. Even more preferably, an "effective amount" of udenafil or a pharmaceutically acceptable salt thereof in accordance with the present invention includes an oral dosage amount that includes, but is not limited to, a single dosage amount administered

daily, including a single dosage amount of about 75 mg or 87.5 mg administered once or twice a day and a single dosage amount of about 125 mg administered once daily.

The present invention also contemplates methods which comprise administering, preferably daily, an effective amount of udenafil or a pharmaceutically acceptable salt thereof, to a SVHD patient, including a Fontan patient, for improving, amongst other things, MPI, ventricular performance, cardiac output, exercise capacity or performance at VAT, exercise capacity or performance at maximal effort or VO_2 max, work rate at VAT, VE/VCO_2 at VAT, diastolic blood pressure at rest and oxygen saturation (%) at rest, individually, collectively or in any combination, without causing treatment-limiting side effects, for example, interference with visual transduction or function, back pain, myalgia, sperm concentration or quality. In other words, the present invention contemplates treatments, preferably daily, of a SVHD patient, including a Fontan patient, with an effective amount of an effective PDE5 inhibitor, preferably udenafil or a pharmaceutically acceptable salt thereof, without causing treatment limiting side effects associated with inhibition of phosphodiesterase-6 ("PDE6") and/or phosphodiesterase-11 ("PDE11"). As used herein, PDE6 includes any isoenzyme, variant, catalytic subunit and/or inhibitory subunit of PDE6, such as PDE6α, PDE6β, PDE6γ, PDE6R and/or PDE6C, individually, collectively, or in any combination, As used herein PDE11, includes phosphodiesterase-11A (PDE11A) and any isoenzyme, variant, catalytic subunit and or inhibitory subunit of PDE11, such as PDE11A, including PDE11A1, PED11A2, PDE11A3 and/or PDE11A4, individually, collectively, or in any combination.

In one embodiment, the present invention is directed to a method of improving the MPI in a SVHD patient, including a Fontan patient. As used herein MPI measures both systolic and diastolic function for the assessment of global heart function. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

It is to be understood that by "improve, improving, improvement in or improved", with respect to MPI in accordance with the present invention, it means herein to improve single ventricle performance, i.e., to improve the diastolic and systolic function of the single functioning ventricle. In other words, the single functioning ventricle squeezes better or more efficiently per heartbeat. As a result, the cardiac output and the amount of blood flow

that can circulate in a given amount of time throughout the body of the SVHD patients, including Fontan patients, who practice or who are treated in accordance with the methods of the present invention are increased or improved, especially as compared to SVHD patients, including Fontan patients, who are not treated in accordance with the methods of the present invention. Thus, the methods of the present invention result in MPI, or other disclosed measures of ventricular performance, improvement in a SVHD patient, including a Fontan patient, as compared to MPI, or other disclosed measures of single ventricular performance in the absence of the methods of the present invention (e.g., in the absence of udenafil administration). For example, the improvement can be about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% or greater as compared to blood pool MPI, or other disclosed measures of single ventricular performance in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to a method of improving systolic function of the single functioning ventricle of a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof to the SVHD patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to a method of improving diastolic function of the single functioning ventricle of a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof to the SVHD patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to a method of improving cardiac output of the single functioning ventricle of a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor

or a pharmaceutically acceptable salt thereof to the SVHD patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to a method of improving the ability of the single functioning ventricle in a SVHD patient, including a Fontan patient to squeeze. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to a method of improving the venous pressure by decreasing the elevation in venous pressure in a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to a method of improving the amount of blood flow that can circulate through the body of the SVHD patient, including a Fontan patient, in a given amount of time. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

Thus, the present invention is directed to a method of improving global single ventricular performance of the single functioning ventricle in a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof to the SVHD patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention is directed to a method of improving diastolic blood pressure at rest in a SVHD patient, including a Fontan patient, whereby the SVHD patient's, including the Fontan patient's, diastolic blood pressure at rest is significantly lowered. The method comprises administering, preferably daily, an effective

amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention is directed to a method of improving oxygen saturation (%) at rest in a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention is directed to a method of improving exercise performance or capacity in a SVHD patient, including a Fontan patient. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to a method of improving exercise performance or capacity at the ventilatory anaerobic threshold ("VAT") in a SVHD patient, including a Fontan patient. The methods of the present invention result in improved VO_2 at VAT in SVHD patient, including the Fontan patient, as compared to VO_2 at VAT in SVHD patients, including Fontan patients, who are not treated with or do not practice the methods of the present invention (e.g., in the absence of daily udenafil administration in accordance with the methods of the present invention). For example, the improvement can be about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% or greater as compared to VO_2 at VAT in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to a method of improving exercise performance or capacity at maximal effort or max VO_2 in a SVHD patient, including a Fontan patient. The methods of the present invention result in improved VO_2 at the SVHD

patient's, including the Fontan patient's, maximal effort, as compared to VO_2 at maximal effort in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). For example, the improvement can be about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% or greater, as compared to VO_2 at maximal effort in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to a method of improving work rate at VAT in a SVHD patient, including a Fontan patient. The methods of the present invention result in improved work rate at the SVHD patient's, including the Fontan patient's, VAT, as compared to the work rate at VAT in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). For example, the improvement can be about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% or greater, as compared to VO_2 at VAT in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is directed to a method of improving ventilatory equivalents of carbon dioxide at the VAT ("VE/VCO_2") at VAT in a SVHD patient, including a Fontan patient. The methods of the present invention result in improved VE/VCO_2 at the SVHD patient's, including the Fontan patient's, VAT, as compared to the VE/VCO_2 at VAT in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). For example, the improvement can be about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21,

about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% or greater, as compared to VO_2 at VAT in the absence of the methods of the present invention (e.g., in the absence of daily udenafil administration). The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to improved methods for treating a SVHD patient, including a Fontan patient, who has undergone heart reconstruction of the abnormal SVHD heart, wherein the daily methods of the present invention result in fewer or less severe adverse events, as compared to conventional methods of treating such a SVHD patient, including a Fontan patient.

In another embodiment, the methods of the present invention result in few, if any, serious adverse events, moderate adverse events, or mild adverse events. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to improved methods for treating a SVHD patient who has undergone a Fontan procedure. In one such embodiment, the Fontan patient is diagnosed with hypoplastic left heart syndrome (HLHS), but first had a Norwood procedure, see, e.g., **FIG. 5**, followed by a Hemi-Fontan or Bi-directional Glenn procedure, see, e.g., **FIG. 6**, before undergoing the Fontan procedure, see, e.g., **FIG. 1A** and **FIG. 7**. In another such embodiment, the Fontan patient first had a Hemi-Fontan or Bi-directional Glenn procedure before undergoing the Fontan procedure. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention is directed to improved methods for treating a SVHD patient, including a Fontan patient, wherein the SVHD is selected from a group of SVHDs consisting of patients having an atrioventricular canal defect (AV Canal), a double inlet left ventricle (DILV), a double outlet right ventricle (DORV), Ebstein's anomaly,

HLHS, mitral valve atresia (usually associated with HLHS), pulmonary atresia with intact ventricular septum (PA/IVS), a single left ventricle, tricuspid valve atresia and tricuspid valve atresia with stenosis. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the methods of the present invention comprise administering an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof, once a day to a SVHD patient, including a Fontan patient.

In another embodiment, the methods of the present invention comprise administering an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof, twice a day to a SVHD patient, including a Fontan patient.

In another embodiment, the methods of the present invention comprise administering an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof, three or more times a day to a SVHD patient, including a Fontan patient.

In another embodiment, the SVHD patient, including a Fontan patient, is a pediatric patient of about 2 to about 18 years of age. Treatment of adult patients are also encompassed by the methods of the invention.

In yet another embodiment, the present invention is directed to improved methods for treating a SVHD patient, including a Fontan patient, wherein the methods of the present invention show an improvement in the SVHD patient's, including Fontan patient's, compliance with a dosing schedule of udenafil or a pharmaceutically acceptable salt thereof, as compared to SVHD patients, including Fontan patients, prescribed a non-udenafil drug.

Finally, in yet another embodiment, the methods of the present invention may result in a unique characteristic pharmacokinetic profile. The pharmacokinetic profile can comprises a C_{max} between 300 and 700 ng/ml, or more specifically, about 500 ng/ml; a T_{max} between 1 and 1.6 hr, or more specifically, about 1.3 hr; an AUC_{τ} between 2550 and 4150 nghr/ml or

more, specifically about 3350 nghr/ml; and an AUC_{0-24} between 5110 and 8290 nghr/ml or more, specifically about 6701 nghr/ml.

It is to be understood that present invention contemplates udenafil drug products that are therapeutically equivalent to the udenafil drug products of the present invention. In other words, the present invention contemplates udenafil drug products that (i) are therapeutically equivalent, (ii) are bioequivalent, (iii) are interchangeable, and (iv) have bioavailabilities that, when administered to a SVHD patient, including a Fontan patient in accordance with the methods of the present invention, are effective in carrying out or performing the objectives of the present invention.

Thus, in accordance with one embodiment of the present invention, the present invention contemplates drug formulations that have a 90% confidence interval (90% CI) for a pharmacokinetic profile wherein the ratio of the means lies within the range of between about 0.8 and about 1.25. In another embodiment in accordance with the present invention, the present invention contemplates interchangeable udenafil drug formulations that have a 90% confidence interval (90% CI) for a pharmacokinetic profile wherein the ratio of the means lies within the range of between about 0.8 and about 1.2. The present invention therefore contemplates SVHD patients, including Fontan patients, who are treated with or practice the methods of the present invention, having a udenafil plasma concentration that can vary by up to about 45% (i.e. -20 to +25%) of a pharmacokinetic profile, such as their C_{max}, T_{max} and AUC. More preferably, the present invention contemplates SVHD patients, including Fontan patients, who are treated with or practice the methods of the present invention, having a udenafil plasma concentration that can vary by up to about 40% (i.e. -20 to +20%) of a pharmacokinetic profile, such as their C_{max}, T_{max} , AUC_t and AUC_{0-24}. By way of example, the present invention contemplates SVHD patients, including Fontan patients, who are treated with or practice the methods of the present invention, having a udenafil pharmacokinetic profile:

(a) C_{max} plasma concentration of about -20 to about +25% of about 500 ng/ml, and more preferably a udenafil C_{max} plasma concentration of about -20 to about +20% of about 500 ng/ml;

(b) T_{max} of about -20 to about +25% of about 1.3 hr, and more preferably a udenafil T_{max} of about -20 to about +20% of 1.3 hr;

(c) AUC_t of about -20 to about +25% of about 3350 nghr/ml, and more preferably a udenafil AUC_t of about -20 to about +20% of about 3350 nghr/ml; and

(d) AUC_{0-24} of about -20 to about +25% of about 6701 nghr/ml, and more preferably a udenafil AUC_{0-24} of about -20 to about +20% of about 6701 nghr/ml, individually, collectively, or in any combination.

Thus, the present invention contemplates bioequivalent and interchangeable udenafil drug products for use in accordance with the methods of the present invention. In addtion, the present invetnion contmplates udenafil drug products that produce the above referenced C_{max}, T_{max} , AUC_t and/or AUC_{0-24} in SVHD patients, including Fontan patients, when administered to SVHD patients, including Fontan patients, in accordance with the methods of the present invention.

It should be further understood that the above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The foregoing description further exemplifies illustrative embodiments and provides explanation of the present invention as claimed. In several places throughout the specification, guidance is provided through examples, which examples can be used in various combinations. In each instance, the examples serve only as representative groups and should not be interpreted as exclusive examples.

Brief Description of the Drawings

The foregoing and other objects, advantages and features of the present invention, and the manner in which the same are accomplished, will be readily apparent to those of skill in the art from the following brief description of the drawings, the detailed description of the present invention and the examples, which illustrate embodiments, wherein:

FIG. 1A is a schematic drawing of an exemplary Fontan physiology;

FIG. 1B is a screening process (Randomization and Treatment of the Participants) used for the Fontan Udenafil Exercise Longitudinal (FUEL) Trial as described in the Examples 1-2. Peak VO_2 (VO_2 max) denotes oxygen consumption at peak exercise. RER denotes respiratory exchange ratio;

FIG. 2A demonstrates the difference in the change in mean peak or max VO_2 from Baseline to Week 26 along with the standard deviation for each treatment arm. **FIG. 2B** demonstrates the percentage of subjects (y axis) who demonstrated improvement in peak VO_2 by the reference percentage or greater (x axis);

FIG. 3A demonstrates the difference in the change in mean VO_2 at VAT from Baseline to Week 26 along with the standard deviation for each treatment arm. **FIG. 3B** demonstrates the percentage of subjects (y axis) who demonstrated improvement in VO_2 at VAT by the reference percentage or greater (x axis);

FIG. 4A demonstrates the difference in the change in mean work rate at VAT from Baseline to Week 26 along with the standard deviation for each treatment arm. **FIG. 4B** demonstrates the percentage of subjects (y axis) who demonstrated improvement in work rate by the reference percentage or greater (x axis);

FIG. 5 is a schematic drawing of an exemplary Norwood procedure (Stage 1) of a reconstructed SVHD heart with Hypoplastic Left Heart Syndrome (HLHS);

FIG. 6 is a schematic drawing of an exemplary Bidirectional Glenn procedure (Stage 2) of a reconstructed SVHD heart with Hypoplastic Left Heart Syndrome (HLHS); and

FIG. 7 is a schematic drawing of an exemplary Fontan procedure (Stage 3), an Extracardiac Fenestrated Fontan procedure, of a reconstructed SVHD heart with Hypoplastic Left Heart Syndrome (HLHS).

Detailed Description of the Invention

I. Fontan Physiology

The Fontan physiology is the definitive palliation for those classes of congenital heart defects that share the common feature of a functional single ventricle. They include defects that result in hypoplastic (malfunctioning) left or right ventricles. Usually through a series of 2 or 3 operations, the systemic and pulmonary circulations are separated to significantly eliminate the mixing of oxygenated and un-oxygenated blood caused by the congenital heart defects.

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This is accomplished by directly attaching the superior and inferior vena cavae to the pulmonary arteries, i.e., the total cavopulmonary connection. This results in a Fontan physiology that works as follows: (1) the single systemic ventricle pumps oxygenated blood (red blood) out the aorta to the body's systemic arterial vascular bed, (2) the systemic venous blood (blue blood) then returns by the vena cavae and the blue blood flows passively through the pulmonary vascular bed for oxygen uptake in the lungs without the aid of a sub-pulmonary ventricle to oxygenate the blue blood, and (3) the now oxygenated blood (red blood) then returns to the functioning single systemic ventricle pump via the common systemic functioning atrium and the red blood-blue blood circulation cycle is repeated. This anatomy is illustrated in **FIG.** 1A and **FIG. 7**.

The Fontan operation, which creates a total cavopulmonary connection, separates the systemic and pulmonary circuits and eliminates both hypoxemia and ventricular volume overload. However, following the Fontan operation there is no ventricular pump to propel the blue blood into the pulmonary arteries. Instead, the blue blood returns to the lungs via passive flow from the systemic veins. Thus, the major physiologic consequence of this type of palliation is that pulmonary blue blood flow is completely dependent upon the pressure gradient from the systemic venous bed to the atrium. The normal circulation flow through the pulmonary bed is augmented by the increased pressure generated by the right ventricle. In a healthy adolescent, this results in an increase of about 20 to 25 mm Hg in the pressure present in the pulmonary arteries at rest, which may double with exercise. With the Fontan physiology, there is no sub-pulmonary ventricle and thus no augmentation of pressure as the blue blood enters the pulmonary arteries. At rest, the pressure gradient across the pulmonary vascular bed is significantly less. The ability to increase this pressure gradient with exercise is extremely limited by the body's ability to tolerate increasingly elevated central venous pressures.

As a consequence of being entirely dependent upon the passive drop in venous pressure to drive pulmonary blood flow, the Fontan physiology is exquisitely sensitive to changes in pulmonary vascular resistance. Even increases that are well within the normal range for pulmonary resistance in normal physiology will have detrimental effects on the Fontan physiology. The use of udenafil offers a potential therapy that is unique to this class of palliated congenital heart defects. Unlike other uses for PDE-5 inhibitors, this therapy would be to lower pulmonary vascular resistance in a population without elevated pulmonary

vascular resistances or pressures. This is a distinctly different use of this class of agents as compared to patients with (i) structurally normal hearts and pulmonary vascular disease, such as pulmonary arterial hypertension (PAH) and chronic obstructive pulmonary disease (COPD), (ii) heart failure, such as congestive heart disease, or (iii) the very rare patient with congenital heart disease palliated with a two ventricle repair (and thus having a sub-pulmonary ventricle) and associated pulmonary vascular disease.

II. Clinical Measurements Relevant to Fontan Patients

For children born with functional single ventricle or single ventricular congenital heart disease, the Fontan procedure is the current standard of care. The Fontan procedure is palliative, rather than curative, and while it has greatly increased the survival of pediatric subjects with functional single ventricle heart disease, the procedure also results in a series of side effects and complications that can lead to attrition of patients, with complications such as arrhythmias, ventricular dysfunction, and unusual clinical syndromes of protein-losing enteropathy (PLE) and plastic bronchitis, as well as hepatic and kidney complications.

In certain embodiments, the disclosed present invention relates to improving or preventing the decline of specific clinically relevant physiological measurements that are indicative of a patient's health following a Fontan procedure. Such measurements include, but are not limited to, exercise testing, vascular function testing, and echocardiographic assessment of ventricular performance.

III. Exercise Testing

Exercise testing can include assessment of VO_2 values during maximal effort or at the ventilator anaerobic threshold (VAT). VO_2 max, or maximal oxygen consumption, refers to the maximum amount of oxygen that an individual can utilize during intense exercise. This measurement is generally considered a reliable indicator of cardiovascular fitness and aerobic endurance. The more oxygen a person can use during high level exercise, the more energy that person can produce. This test has been the standard for cardiorespiratory fitness because muscles need oxygen for prolonged (aerobic) exercise; blood carries oxygen to the muscles and the heart must pump adequate amounts of blood to meet the demands of aerobic exercise.

VO_2 is often measured by putting a mask on a subject, and measuring the volume and gas concentrations of inhaled and expired air. This measurement is often used in both clinical settings and research and is considered the most accurate. Testing commonly involves either exercising on a treadmill or riding a cycle ergometer at increasing intensity until exhaustion, and is designed to provide readings at a maximal effort of the subject and/or at the subject's anaerobic threshold.

SVHD patients, including SVHD patients that have previously undergone a Fontan procedure, will generally see a decline in VO_2 measurements over time. However, when practicing or treating a SVHD patient, including a Fontan patient, is treated with a method according to the present invention, the VO_2 measurement (i) is maintained at a similar level, demonstrating that there has been no further decline in VO_2 measurement, or (ii) improved with therapy, demonstrating that there has been an increase in VO_2, and/or the rate of decline in VO_2 measurement is reduced, thus, improved, each indicating that the treatments or methods of the present invention are clinically beneficial . In some SVHD patients, treatment in accordance with the present invention may significantly slow or decrease the decline in VO_2 measured during exercise.

In one embodiment, the present invention is directed to a method of improving or maintaining VO_2 measurements of a SVHD patient or a subject who has previously had a Fontan procedure. The method of the present invention comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to a SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof. In some embodiments of the present invention, VO_2 is measured at maximal effort, while in other embodiments, VO_2 is measured at the subject's anaerobic threshold (VAT).

In some embodiments, the disclosed methods and compositions of the present invention are administered to a SVHD patient, including a Fontan patient, and result in no decrease, or a minimal decrease, in exercise capacity over time. More specifically, the disclosed methods and compositions of the present invention may result in a decrease in exercise capacity of less than about 40, less than about 35, less than about 30, less than about 35, less than about 20, less than about 15, less than about 10, or less than about 5% over time. The time period between a first and second measurement used to calculate the decrease in exercise capacity

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can be, for example, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 months; about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 years, or any combination thereof, e.g., 1 year, 3 months; 4 years, 7 months, etc.

In some embodiments, the disclosed methods and compositions of the present invention may be administered to a SVHD patient, including a Fontan patient, and result in an improvement of exercise capacity. More specifically, the disclosed methods and compositions of the present invention may result in a 1, 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50% or more improvement in VO_2 at maximal effort. Alternatively, the disclosed methods and compositions of the present invention may result in a 1, 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50% or more improvement in VO_2 at the SVHD patient's, including the Fontan patient's, ventilatory anaerobic threshold (VAT).

IV. Vascular Function Testing

Vascular endothelial dysfunction is an important outcome for assessing vascular health in intervention studies. It is now well established that vascular endothelial dysfunction is positively associated with traditional cardiovascular disease (CVD) risk factors, and independently predicts cardiovascular events over intervals of 1 to 6 years.

Pulse amplitude tonometry (PAT), a FDA-approved method for assessing vascular function, is increasingly being used as an alternative measure of endothelium-dependent dilation in response to reactive hyperemia and flow-mediated dilation (FMD). The PAT device records digital pulse wave amplitude (PWA) using fingertip plethysmography. PWA can be measured continuously during three phases: a quiet baseline period, 5-min forearm occlusion, and reactive hyperemia following cuff release. Unlike FMD, PAT testing is not dependent upon a highly skilled technician and post-test analysis is largely automated. Most importantly, at least one longitudinal study has shown that PAT measures of endothelial function predict CVD events over a 6-year follow-up period. These significant advantages may make PAT testing suitable for clinical practice if prognostic significance and reliability can be verified.

SVHD patients, including SVHD patients that have previously undergone a Fontan procedure, will generally see a decline in vascular function over time. Treating a SVHD

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patient, including a Fontan patient, that improves or prevents further decline in vascular function of a SVHD patient, including a Fontan patient, would indicate that the treatment is clinically beneficial and may improve the SVHD patient's, including the Fontan patient's, quality of life or prevent decline in cardiovascular function.

In one embodiment, the present invention is directed to a method of improving or maintaining vascular function of SVHD patients, including SVHD patients that have previously undergone a Fontan procedure. The method comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to a SVHD patient, including a Fontan patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof. In some embodiments, vascular function is measured using a PAT index.

In some embodiments, the disclosed methods and compositions of the present invention are administered to a SVHD patient, including a Fontan patient, and result in no decrease, or a minimal decrease, in vascular function over time. Vascular function can be measured using any conventional known technique, including but not limited to pulse amplitude tonometry measurements, the natural log of reactive hyperemia index, Reactive Hyperemia Index, Framingham (RHI), area under the curve to max-occlusion/control, average up to max-occlusion/control, and other known EndoPAT indices. In some embodiments of the present invention, vascular function is measured using a PAT index. More specifically, the disclosed methods and compositions of the present invention may result in a decrease in vascular function of less than about 40, less than about 35, less than about 30, less than about 35, less than about 20, less than about 15, less than about 10, or less than about 5% over time. The time period between a first and second measurement used to calculate the decrease in vascular function can be, for example, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 months; about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 years, or any combination thereof, e.g., 1 year, 3 months; 4 years, 7 months, etc.

In some embodiments, the disclosed methods and compositions of the present invention may be administered to a SVHD patient, including a Fontan patient and result in an improvement of vascular function. Vascular function can be measured using any conventional known

technique, including but not limited to pulse amplitude tonometry measurements, the natural log of reactive hyperemia index, Reactive Hyperemia Index, Framingham RHI, area under the curve to max-occlusion/control, average up to max-occlusion/control, and other known EndoPAT indices. In some embodiments of the present invention, vascular function is measured using a PAT index. More specifically, the disclosed methods and compositions may result in about a 1, about 2, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, or about 50% or more improvement in one or more measurements of vascular function, including but not limited to pulse amplitude tonometry measurement, the natural log of reactive hyperemia index, Reactive Hyperemia Index, Framingham RHI, area under the curve to max-occlusion/control, average up to max-occlusion/control, and other known EndoPAT indices.

V. Echocardiographic Assessment of Ventricular Performance

Ventricular performance and cardiac contractility are important measurements that can reveal impairment of cardiovascular health before overt heart failure is present. Ventricular performance can be assessed using echocardiographic methods and quantified via a myocardial performance index or MPI. MPI is an index that combines systolic and diastolic function. Specifically, MPI is defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time.

Various versions of MPI are known in the art, and each version of MPI may be used to assess ventricular performance. For instance, MPI indices may include, but are not limited to, blood pool MPI and tissue Doppler MPI. MPI can be measured by using pulsed-wave tissue Doppler echocardiography (TDE). To calculate MPI using TDE, isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) of the functioning single ventricle are measured. MPI is then determined by adding together the IVCT and the IVRT and dividing the sum by ET.

Patients that have previously undergone a Fontan procedure will generally see a decline in ventricular performance over time. Treating a patient such that the patient's ventricular performance is maintained, exhibits minimal decrease over time, or increases indicates that the treatment is clinically beneficial and may improve patient quality of life or prevent decline in cardiovascular function.

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In one embodiment, the present invention is directed to a method of maintaining, producing a minimal decrease in, or increasing ventricular performance of a subject who has previously had a Fontan procedure. The method of the present invention comprises administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the patient, where the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof. In some embodiments of the present invention, ventricular performance is measured using a myocardial performance index (MPI). In some embodiments, the MPI may be a blood pool MPI, while in other embodiments the MPI may be a tissue Doppler MPI.

In some embodiments, the disclosed methods and compositions of the present invention may be administered to a Fontan patient and result in minimal or no decrease in ventricular performance over time. Ventricular performance can be measured using any conventional known technique, including but not limited to myocardial performance index (MPI), blood pool MPI, tissue doppler MPI, average isovolumetric contraction and relaxation, and other known ventricular performance indices. More specifically, the disclosed methods and compositions of the present invention may result in a decrease in ventricular performance of less than about 40, less than about 35, less than about 30, less than about 35, less than about 20, less than about 15, less than about 10, or less than about 5% over time. The time period between a first and second measurement used to calculate the decrease in ventricular performance can be, for example, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 months; about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 years, or any combination thereof, e.g., 1 year, 3 months; 4 years, 7 months, etc.

In some embodiments, the disclosed methods and compositions of the present invention may be administered to a SVHD patient, including a Fontan patient, and result in an improvement of ventricular performance over time. Ventricular performance can be measured using any conventional known technique, including but not limited to myocardial performance index (MPI), blood pool MPI, tissue doppler MPI, average isovolumetric contraction and relaxation, and other known ventricular performance indices. For example, the disclosed methods and compositions of the present invention may result in about a 1, about 2, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, or about 50%

or more improvement in ventricular performance, as measured by any known technique, including but not limited to myocardial performance index (MPI), blood pool MPI, tissue doppler MPI, average isovolumetric contraction and relaxation, and other known ventricular performance indices.

VI. Methods According to the Invention

The disclosed methods of the present invention relate to improving exercise and ventricular performance in a SVHD patient, including a Fontan patient, and who is in need of improvement in exercise capacity and/or ventricular performance. In general, the methods include administering daily an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof, preferably as udenafil or a pharmaceutically acceptable salt thereof, to the SVHD patient, including a Fontan patient, to improve:

(a) ventricular performance of the SVHD patient's single functioning ventricle as measured by MPI;
(b) exercise capacity as measured by oxygen consumption at VAT;
(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;
(d) work rate at VAT;
(e) VE/VCO_2 at VAT, each individually or in any combination;
(f) diastolic blood pressure at rest; and
(g) oxygen saturation (%) at rest, each individually, collectively or in any combination.

Preferably, the methods of the present invention improve (a)-(g) listed above, including individually, collectively or in any combination thereof. More preferably, (a)-(g) listed above, including individually, collectively or in any combination thereof, is improved in accordance with the present invention by administering daily to a SVHD patient, including a Fontan patient, an effective amount of udenafil or a pharmaceutical acceptable sat thereof.

As discussed above and used herein, an effective PDE5 inhibitor inhibits the degradative action of cGMP-specific phosphodiesterase type 5 (PDE5) on cyclic GMP in the smooth muscle cells lining the blood vessels that supply blood to various tissues.

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As also discussed above and used herein, MPI is a measure of ventricular systolic and diastolic function and a prognostic and progression marker for various heart diseases, as determined by a focused echocardiogram. This numeric value is defined as the sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET) and can be calculated for a single ventricle. The change in the myocardial performance index is determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the single functioning ventricle. In other words, MPI is a measure of global systolic and diastolic time intervals to assess global cardiac dysfunction and ventricular performance. Moreover, because the MPI is a Doppler index, it is independent of ventricular geometry and can be applied to either left and right ventricular function, depending upon which ventricle is the single functioning ventricle in the SVHD patients.

More specifically, the methods include administering daily an effective amount of an effective PDE5 inhibitor or a pharmaceutically acceptable salt thereof, preferably udenafil or a pharmaceutically acceptable salt thereof, to effect one or more of the above improvements without causing treatment-limiting side effects including, but not limited to, blindness or loss of vision via inhibition of photoreceptor phosphodiesterase enzyme (PDE6), back pain and/or myalgia via inhibition of PDE11, such as 11A1 (PDE11**A1**) and/or decrease in sperm concentration via inhibition of PDE11, such 11A3 (PDE11A3). Kayık, G. *et al.*: Investigation of PDE5/PDE6 and PDE5/PDE11 selective potent tadalafil-like PDE5 inhibitors using combination of molecular modeling approaches, molecular fingerprint-based virtual screening protocols and structure-based pharmacophore development. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1):311–330 (2017); Pomara G. and Morelli G.: Inhibition of phosphodiesterase 11 (PDE11) impacts on sperm quality. *Int J Impot Res*, 17:385–386 (2005), and Huang S.A. and Lie, J.D.: Phosphodiesterase-5 (PDE5) Inhibitors. In the Management of Erectile Dysfunction. *Pharmacy and Therapeutics*, 38(7):407-419 (July 2013).

Quite uniquely and surprisingly, the methods of the present invention increase and/or maximize oxygen consumption at the ventilatory anaerobic threshold (VAT) and at maximum effort or max VO_2 to improve exercise capacity, and increase and/or maximize work rate at VAT and VE/VCO_2 at VAT in SVHD patients, including Fontan patients.

Also, quite uniquely and surprisingly, the methods of the present invention improve the MPI of the SVHD patients, namely, the Fontan patients. In other words, the methods of the present invention improve both systolic and diastolic function of the single functioning ventricle and the global heart function. In other words, the methods of the present invention improve the filling and emptying characteristics, i.e., the squeezing ability of the single functioning ventricle and the overall ability of the reconstructed abnormal SVHD heart of the SVHD patients, including the Fontan patients, to pump the freshly oxygenated blood to the body for peripheral tissue needs.

The clinical value of the MPI improvement is evidenced by the statistically significant improvement in the MPI in those SVHD patients, and in particular the Fontan patients, who were treated with the methods of the present invention, as compared to those SVHD patients, namely the Fontan patients, who were treated with placebo during the FUEL Trial.

The clinical value of the MPI improvement is also evidenced by the improvement of the single ventricular performance as measured by the isovolumic contraction time, isovolumic relaxation time and ejection time using TDE, as discussed above.

By "isovolumetric contraction time" (IVCT), it is meant herein to mean a single ventricular event that occurs early in systole, during which the single ventricle contracts without volume change (isovolumetrically). This period of the cardiac cycle, the squeeze event, takes place while all heart valves are closed.

By "isovolumic relaxation time" (IVRT), it is meant herein to mean the interval period of the cardiac cycle, i.e., the squeeze and relax cycle, that concerns the second heart sound emanating from the closure of the valve to the onset filling of the functioning single ventricle by following the opening of the valve. The IVRT may indicate diastolic dysfunction of the functioning single ventricle.

By "ejection time" (ET), it is meant herein to mean the single ventricular ejection time (UVET) of the reconstructed abnormal heart determined by the opening and closing of the valve during which the pressure differences across the valve are measured.

By "stroke volume," it is meant herein to mean the amount of freshly oxygenated blood that the single functioning ventricle can pump out into the circulatory system in one contraction.

By "cardiac output," it is meant herein to mean the amount of blood the single functioning ventricle in an SVHD patient, including a Fontan patient, can pump through the circulatory system in one minute.[1] The stroke volume and the heart rate determine cardiac output.

While each of the improvements in the treatment of SVHD patients, including Fontan patients, in accordance with the methods of the present invention are individually unique and surprising, the combination of improvements in the treatment of SVHD patients, including Fontan patients, is especially unique and surprising.

In another embodiment, it was surprising that that the methods of the invention show improved results when udenafil is administered as compared to prior very limited studies using a non-udenafil PDE5 inhibitor, such as sildenafil or tadalafil. In yet another embodiment, it was surprising that the methods of the invention show fewer side effects, and/or less severe side effects when udenafil is administered, as compared to other prior treatments using a non-udenafil PDE5 inhibitor, such as sildenafil or tadalafil.

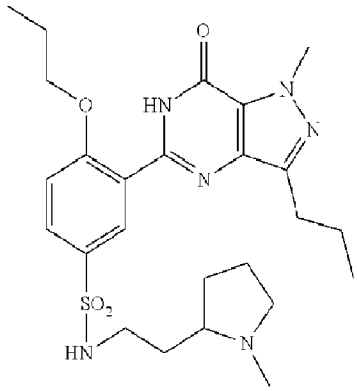
In some embodiments, the Fontan patient can be an adult human, whereas in other embodiments, the Fontan patient can be an adolescent human. In some embodiments, the Fontan patient can be between about 12 and about 19 years old, whereas in other embodiments, the Fontan patient can between about 12 and 18 years old. In yet other embodiments, the Fontan patient can be from about 12 to about 16 years old. In yet other embodiments, the Fontan patient can be from about 6 years old to adult. In one embodiment, the Fontan patient can be less than 18 years old.

VII. Doses and Dosage Forms

The structure of udenafil is shown below:

[1] A normal adult has a cardiac output on average of about 4.7 liters (5 quarts) of blood per minute.

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In some embodiments, udenafil or a pharmaceutically acceptable salt thereof can be administered at total daily dosage amounts of about 0.01 to about 150 mg/kg. In another embodiment, the udenafil or a pharmaceutically acceptable salt thereof can be administered at total daily doses of about 0.01 mg/kg up to about 30 mg/kg. In another embodiment, udenafil or a pharmaceutically acceptable salt thereof can be administered in a dosage amount of from about 2.5 mg to about 275 mg, such as about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27.5 mg, about 30 mg, about 32.5, about 35 mg, about 37.5 mg, about 40 mg, about 42.5 mg, about 45 mg, about 47.5 mg, about 50 mg, about 52.5 mg, about 55 mg, about 57.5 mg, about 60 mg, about 62.5 mg, about 65 mg, about 67.5 mg, about 70 mg, about 72.5 mg, about 75 mg, about 77.5 mg, about 80 mg, about 82.5 mg, about 85 mg, about 87.5 mg, about 90 mg, about 92.5 mg, about 95 mg, about 97.5 mg, about 100 mg, about 102.5 mg, about 105 mg, about 107.5 mg, about 110 mg, about 112.5 mg, about 115 mg, bout 117.5 mg, about 120 mg, about 122.5 mg, about 125 mg, about 127.5 mg, about 130 mg, about 132.5 mg, about 135 mg, about 137.5 mg, about 140 mg, about 142.5 mg, about 145 mg, about 147.5 mg, about 150 mg, about 152.5 mg, about 155 mg, about 157.5 mg, about 160 mg, about 162.5 mg, about 165 mg, about 167.5 g, about 170 mg, about 172.5 mg, about 175 mg, about 180 mg, about 182.5 mg, about 185 mg, about 187.5 mg, about 190 mg, about 192.5 mg, about 195 mg, about 197.5 mg, about 200 mg, about 202.5 mg, about 205 mg, about 207.5 mg, about 210 mg, about 212.5 mg, about 215 mg, about 217.5 mg, about 220 mg, about 222.5 mg, about 225 mg, about 227.5 mg, about 230 mg, about 232.5 mg, about 235 mg, about 237.5 mg, about 240 mg, about 242.5 mg, about 245 mg, about 247.5 mg, about 250 mg, about 252.5 mg, about 255 mg, about 257.5 mg, about 260 mg, about 262.5 mg, about 265 mg, about 267.5 mg, about 270 mg, about 272.5 mg or about 275 mg, so long as any such

individual dosage amount does not cause treatment-limiting toxicity or treatment-limiting side effects to the extent that the drug product would not be approved for market. In yet another embodiment, udenafil or a pharmaceutically acceptable salt thereof can be administered at total daily doses of from about 5 mg to about 275 mg, such as about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 27.5 mg, about 30 mg, about 32.5, about 35 mg, about 37.5 mg, about 40 mg, about 42.5 mg, about 45 mg, about 47.5 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 87.5 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, or about 275 mg, so long as any such individual total daily dose does not cause treatment-limiting toxicity or treatment-limiting side effects to the extent that the total daily dose would not be approved for market.

In still another embodiment, udenafil or a pharmaceutically acceptable salt thereof can be administered in total daily doses of from about 25 mg to about 700 mg, such as about 25 mg, about 37.5 mg, about 50 mg, about 75 mg, about 87.5 mg, 125 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, or about 700 mg, so long as any such individual total daily dose does not cause treatment-limiting toxicity or treatment-limiting side effects to the extent that the total daily dose would not be approved for market.

In a further embodiment, udenafil or a pharmaceutically acceptable salt thereof can be administered at a total daily dose of about 37.5 mg, about 75 mg, about 87.5 mg, 125 mg, or about 175 mg. In a further embodiment, udenafil or a pharmaceutically acceptable salt thereof can be administered at a total daily dose range of from about 37.5 mg to about 175 mg, preferably, a total daily dose range of from 75 mg to about 175 mg, more preferably, a total daily dose range of from about 87.5 mg to about 175 mg and, most preferably, a total daily dose range of from 125 mg to about 175 mg. In a preferred embodiment, udenafil or any pharmaceutically acceptable salt thereof can be administered to a Fontan patient in any dosage amount or in any total daily dose, so long as any selected individual dosage amount or any selected individual total daily dose does not cause treatment-limiting toxicity or treatment-limiting side effects to the extent that the total daily dose would not be approved

for market.

Thus, the present invention contemplates administration of udenafil or a pharmaceutically acceptable salt thereof to SVHD patients, including Fontan patients, at any dosage amount, at any total daily dose, at any treatment regimen and in any dosage form, so long as when any such dosage amount, total daily dose, treatment regimen or dosage form is selected, it does not cause treatment-limiting toxicity or treatment-limiting side effects to the extent that such would not be approved for market. In particular, the present invention contemplates administration of udenafil or a pharmaceutically acceptable salt thereof in an effective amount to SVHD patients, including Fontan patients to improve MPI, single ventricular performance, systolic and/or diastolic function, ventricular squeeze capability, cardiac output, exercise capacity or performance at VAT and/or max VO_2, work rate at VAT, VE/CO_2 at VAT, diastolic blood pressure at rest, oxygen saturation (%) at rest and/or decrease the rate of decline of progression of SVHD, as compared to untreated SVHD patients, so long as the therapeutically effective amount does not cause treatment-limiting toxicity, treatment limiting side effects associated with inhibition of PDE6 and/or PDE11, and/or treatment-limiting side effects to the extent that the drug product would not be approved for market.

In one embodiment, the udenafil or a pharmaceutically acceptable salt thereof can be administered once a day.

In another embodiment, the udenafil or a pharmaceutically acceptable salt thereof can be administered once daily or in divided multiple dosages, such as twice a day, three times a day, four times a day or more.

In yet another embodiment, the udenafil or a pharmaceutically acceptable salt thereof can be administered twice a day such that therapeutically effective blood levels are maintained for at least about 1.5 to about 24 hours, more particularly at least about 1.5, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, abut 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 hours of a 24 hour dosing period. Thus, the present invention therefore contemplates udenafil and/or any udenafil active metabolite, such as DA8164 active metabolite, maintaining an effective blood level for any period of time within a 24 hour dosing period.

In some embodiments, the total daily dosage amount of udenafil or a pharmaceutically

acceptable salt administered twice a day can be less than the total daily dosage amount of udenafil or a pharmaceutically acceptable salt thereof administered once a day.

In some embodiments, the total daily dosage amount of udenafil or a pharmaceutically acceptable salt thereof administered twice a day, can maintain therapeutically effective blood levels for the same number of hours in a 24 hour period as a higher dosage of udenafil or a pharmaceutically acceptable salt thereof when administered once a day. In other embodiments, the total daily dosage amount of udenafil or a pharmaceutically acceptable salt thereof administered twice a day, can maintain therapeutically effective blood levels for a higher number of hours in a 24 hour period as the same dosage of udenafil or a pharmaceutically acceptable salt thereof when administered once a day. Thus, the present invention contemplates administration of any total daily dosage amount of udenafil or any acceptable salt thereof once daily or in divided doses multiple times a day, such as twice daily, three times daily, four times daily or more, to maintain therapeutically effective blood levels throughout a 24 hour period.

In one embodiment, it is surprising that the administration of twice a day udenafil or a pharmaceutically acceptable salt thereof results in fewer side effects than the administration of once a day udenafil or a pharmaceutically acceptable salt thereof. In another embodiment, it is surprising that twice a day administration of udenafil or a pharmaceutically acceptable salt thereof can achieve therapeutically effective levels of udenafil at a lower total daily dosage than a once a day administration.

In some embodiments, the pharmaceutically acceptable salt of udenafil can be an acid addition salt. In one embodiment, the acid addition salt of udenafil can be an inorganic acid addition salt such as, hydrochloric, hydrobromic, sulfuric, or phosphoric acid addition salt. In another embodiment, the acid addition salt can be an organic acid addition salt such as citrate, tartarate, acetate, lactate, maleate, fumarate, gluconate, methanesulfonate (mesylate), glycolate, succinate, p-toluenesulfonate (tosylate), galacturonate, embonate, glutamate, aspartate, oxalate, benzensulfonate, camphorsulfonate, cinnamate, adipate, or cyclamate. In a particular embodiment, the pharmaceutically acceptable salt of udenafil can be an oxalate, benzensulfonate, camphorsulfonate, cinnamate, adipate, or cyclamate salt.

In some embodiments, the udenafil or a pharmaceutically acceptable salt thereof can be administered as a pharmaceutical composition. In one embodiment, the pharmaceutical

composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated in a wide variety of oral or parenteral dosage forms on clinical application. Each of the dosage forms can contain various disintegrating agents, surfactants, fillers, thickeners, binders, diluents such as wetting agents or other pharmaceutically acceptable excipients.

The udenafil composition can be administered using any pharmaceutically acceptable method, such as intranasal, buccal, sublingual, oral, rectal, ocular, parenteral (intravenously, intradermally, intramuscularly, subcutaneously, intracisternally, intraperitoneally), pulmonary, intravaginal, locally administered, topically administered, topically administered after scarification, mucosally administered, via an aerosol, or via a buccal or nasal gel or spray formulation.

Further, the udenafil composition can be formulated into any pharmaceutically acceptable dosage form, such as a solid dosage form, including but not limited to a tablet, pill, lozenge, capsule, caplet, orally-disintegrating dosage form, sublingual dosage form, buccal dosage form, liquid, liquid dispersion, liquid suspension, solution, aerosol, pulmonary aerosol, nasal aerosol and semi-solid, namely, ointment, cream, thin film, and gel, and patches such as transdermal patches. Further, the composition may be a controlled release formulation, sustained release formulation, immediate release formulation, modified release formulation or any combination thereof. Further, the composition may be a transdermal delivery system.

In another embodiment, the pharmaceutical composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated into a solid dosage form for oral administration, and the solid dosage form can be powders, granules, capsules, tablets, caplets, caches, orally-disintegrating dosage forms, sublingual dosage forms, buccal dosage forms, lozenges or pills. In yet another embodiment, the solid dosage form can include one or more excipients such as calcium carbonate, starch, sucrose, lactose, microcrystalline cellulose or gelatin. In addition, the solid dosage form can include, in addition to the excipients, a lubricant such as talc or magnesium stearate. In some embodiments, the oral dosage form can be immediate release, or a modified release form. Modified release dosage forms include controlled, sustained, modified or extended release, enteric release, and the like. The excipients used in the modified release dosage forms are commonly known to a person of ordinary skill in the art.

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For example, a solid carrier may be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, oral dosage form disintegrating agents, or an encapsulating material. The oral dosage forms, such as powders, granules, capsules, tablets, caplets, caches, lozenges or pills, preferably contain from 5% to 70% of the udenafil. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose (e.g., lactose monohydrate), pectin, dextrin, starch (e.g., corn starch), gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, silicon dioxide (e.g., colloidal silicon dioxide), a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the udenafil solid, liquid or semi-solid matrix with or without encapsulating material.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution. For example, aqueous solutions suitable for oral use can be prepared by dissolving the udenafil in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. In another example, aqueous suspensions suitable for oral use can be made by dispersing the finely divided udenafil in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In one embodiment, the pharmaceutical composition can be formulated in a liquid dosage form for oral administration, such as suspensions, emulsions or syrups, which may contain, in addition to the udenafil, colorants, flavors, stabilizers, buffers (e.g., buffers to adjust the pH to a desirable range for intravenous use such as salts of inorganic acids such as phosphate, borate, and sulfate), artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. In other embodiments, the liquid dosage form can include, in addition to commonly used simple diluents such as water and liquid paraffin, various excipients such as humectants, sweeteners, aromatics or preservatives. In particular embodiments, the composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated to be suitable for administration to a pediatric patient.

In one embodiment, the pharmaceutical composition can be formulated in a dosage form for parenteral administration, such as sterile aqueous solutions, suspensions, emulsions or non-aqueous solutions. In other embodiments, the non-aqueous solutions or suspensions can include propyleneglycol, polyethyleneglycol, vegetable oils such as olive oil or injectable esters such as ethyl oleate. Alternatively, the pharmaceutical composition can be formulated in a dosage form for rectal or vaginal administration. As a base for suppositories, witepsol, macrogol, tween 61, cacao oil, laurin oil or glycerinated gelatin can be used.

The pharmaceutical preparation may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight. Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the udenafil or any acceptable pharmaceutical salt thereof. The unit dosage form can be a packaged preparation, such as a sachet, the package containing discrete quantities of preparation, such as packeted tablets, caplets, capsules, orally-disintegrating dosage forms, sublingual dosage forms, buccal dosage forms and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, caplets, pills, orally-disintegrating dosage forms, sublingual dosage forms, buccal dosage forms, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The pharmaceutical compositions may include components to provide immediate release, sustained release, extended release, modified release, convenience and/or comfort. Such

components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates.

In a further embodiment, the pharmaceutical composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated as an orally-disintegrating, sublingual or buccal dosage form. Such dosage forms comprise sublingual tablets or solution compositions that are administered under the tongue and buccal tablets that are placed between the cheek and gum.

The pharmaceutical preparation may be prepared by further containing a coating agent for example, the light shielding agent capable of generating free radical by UV light, metal oxides such as titanium oxide and the like are described, and as the free radical scavenger, for example, organic acids such as benzoic acid and the like. In addition, the coating agent may further include, but not be limited to, an water-soluble polymer (e.g., hypromellose or hydroxypropyl cellulose,), an enteric coating layer containing polyethylene glycol, triethyl citrate, cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, methyl methacrylate-methacrylic acid copolymers, shellac, cellulose acetate succinate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose phthalate, zein, sodium alginate, and mannitol, and/or enteric coating aqueous solution including, for example, ethylcellulose, medium chain triglycerides, oleic acid, sodium alginate, stearic acid.

In yet a further embodiment, the pharmaceutical composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated as a nasal dosage form. Such dosage forms of the present invention comprise solution, suspension, emulsion, and gel compositions for nasal delivery.

In one embodiment, the pharmaceutical composition can be formulated in a liquid dosage form for oral administration, such as solutions, suspensions, emulsions or syrups. In other embodiments, the liquid dosage form can include, in addition to commonly used simple diluents such as water and liquid paraffin, various excipients such as humectants, sweeteners, aromatics or preservatives. In particular embodiments, the composition comprising udenafil or a pharmaceutically acceptable salt thereof can be formulated to be suitable for administration to a pediatric patient.

The dosage of the pharmaceutical composition can vary depending on the patient's weight, age, gender, administration time and mode, excretion rate, and the severity of disease.

VIII. Exercise Testing

Exercise testing can include assessment of VO_2 values during maximal effort or at ventilator anaerobic threshold ("VAT"). VO_2 max ("peak VO_2"), or maximal ("peak") oxygen consumption, refers to the maximum amount of oxygen that an individual can utilize during intense exercise. This measurement is generally considered a reliable indicator of cardiovascular fitness and aerobic endurance. Theoretically, the more oxygen a person can use during exercise, the more energy that person can produce. This test is often used for cardiorespiratory fitness because muscles need oxygen for prolonged (aerobic) exercise; blood carries oxygen to the muscles and the heart must pump adequate amounts of blood to meet the demands of aerobic exercise. However, while peak VO_2 may be useful as a surrogate for many cardiovascular disease states, it may not be as relevant an endpoint after the Fontan operation. In this unique physiology, central venous pressure, rather than right ventricular contraction (pumping), is the primary driver of transpulmonary blood flow and, therefore, cardiac output. Gewillig M and Goldberg DJ. Failure of the fontan circulation. Heart Fail Clin. 10(1):105-116 (Jan 2014); Egbe AC, Connolly HM, Miranda WR, Ammash NM, Hagler DJ, Veldtman GR and Borlaug BA. Hemodynamics of Fontan Failure: The Role of Pulmonary Vascular Disease. Circ Heart Fail. 10(12): e004515 (Sept. 2017); Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A and Gorenflo M. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg. 10(3):428-433 (Mar 2010); and Goldberg DJ, Avitabile CM, McBride MG and Paridon SM. Exercise capacity in the Fontan circulation. Cardiol Young. 23(6):824-830 (Dec 2013). As the demand for cardiac output increases with exertion, central venous pressure in the Fontan circulation must rise to meet that demand, but eventually reaches a critical ceiling beyond which it can rise no further. Navaratnam D, Fitzsimmons S, Grocott M, Rossiter HB, Emmanuel Y, Diller GP, Gordon-Walker T, Jack S, Sheron N, Pappachan J, Pratap JN, Vettukattil JJ and Veldtman G. Exercise-Induced Systemic Venous Hypertension in the Fontan Circulation. *Am J Cardiol.* 117(10):1667-1671 (May 15, 2016). At submaximal exertion, the elevation in central venous pressure does not reach this physiologic ceiling and thus outcomes at this level of exercise may be more sensitive to pharmacologic manipulation of the pulmonary vasculature.

VO_2 is often measured by putting a mask on a subject, and measuring the volume and gas concentrations of inhaled and expired air. This measurement is often used in both clinical settings and research and has been considered the most accurate. Testing commonly involves either exercising on a treadmill or riding a cycle ergometer at increasing intensity until exhaustion, and is designed to provide readings at a maximal effort of the subject and/or at the subject's anaerobic threshold.

Patients that have previously undergone a Fontan procedure will generally see a decline in VO_2 measurements over time. Treating a patient with methods disclosed herein such that the patient's VO_2 measurement is either maintained at a similar level, demonstrating that there has been no further decline in VO_2 function, or improved with therapy indicates that the treatment is clinically beneficial and may improve cardiovascular function or prevent or slow the rate of decline in cardiovascular function.

IX. Myocardial Performance Index (MPI)

Generally speaking, MPI (also referred to as the Doppler-derived index or Tei Index) is a measure of ventricular systolic and diastolic function as determined by a focused echocardiogram. It combines systolic and diastolic time intervals to assess heart function. More specifically, MPI can be used to assess ventricular performance represented by a numeric value using cardiac time intervals. This numeric value equals the sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET) and can be determined for either the left or right ventricle. Pellett, A.A., et al.: The Tei Index: Methodology and Disease. State Values. Echocardiography: A Jrnl. of CV Ultrasound & Allied Tech. 21(7):669-672 (2004); and Uluçay, A., Tatli E.: Myocardial performance index. Anadolu Kardiyol Derg. 8(2):143-8 (April, 2008), both of which are incorporated herein by reference in their entireties. In the FUEL Trial, the MPI measured the performance of the single functioning ventricle. Thus, the MPI results from the FUEL Trial were determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the functioning single ventricle. In other words, the FUEL Trial MPI was determined by measuring the cardiac time intervals using pulsed-wave Doppler velocity spectra of the ventricular inflow and outflow of the single functioning ventricle.

X. Echocardiogram Testing

Echocardiograms were performed by sonographers with specific training for this protocol.

The primary outcome of interest was MPI using Doppler-based measures of inflow and outflow duration. The duration of inflow into the dominant ventricle and outflow across the dominant semilunar valve were measured and used to calculate MPI using the standard formula. Tei C, Ling LH, Hodge DO, *et al.*: New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function–a study in normals and dilated cardiomyopathy. *J Cardiol,* 26(6):357-66 (1995); and Pellet AA *et al.*: The Tei Index: Methodology and Disease State Values. *Echocardiography: A Jrnl Of CV Ultrasound & Allied Tech*, 21(7):669-672 (2004). Additional tissue Doppler images were obtained and used to calculate the tissue Doppler based MPI as previously described. Harada K, Tamura M, Toyono M *et al.*: Comparison of the right ventricular Tei index by tissue Doppler imaging to that obtained by pulsed Doppler in children without heart disease. *Am J Cardiol*, 90(5):566-9 (2002). Whenever possible, three measurements were made and the mean duration was used for the calculation.

The methods may be further understood with the following non-limiting examples.

EXAMPLE 1

The Fontan Udenafil Exercise Longitudinal (FUEL) Trial

The FUEL Trial was conducted at 30 centers around the world. The FUEL Trial was a Phase 3, randomized, double-blind, placebo-controlled trial of udenafil in adolescents with SVHD who had undergone Fontan palliation. (Funded by Mezzion Pharma Co. Ltd., and conducted by the National Heart, Lung, and Blood Institute-funded Pediatric Heart Network; ClinicalTrials.gov number NCT02741115).

The primary aim was to determine the effect of udenafil on exercise capacity in adolescents with Fontan physiology over a six-month period. The primary outcome was the change in oxygen consumption at peak exercise (max or peak VO_2) from baseline to the 26-week visit. Secondary exercise outcomes included change in additional measures at maximal exertion, as well as change in measures of submaximal exercise at the ventilatory anaerobic threshold (VAT). The primary outcome for clinical secondary aims included change in myocardial performance index (MPI), an echocardiographically-derived measure of systolic and diastolic ventricular function, change in log-transformed reactive hyperemia index (lnRHI), a PAT-derived measure of peripheral vascular function, and change in log-transformed serum BNP

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level. Safety was monitored through adverse event reports, which were collected according to a pre-specified protocol of study coordinator outreach, and through *ad hoc* patient and family communication with members of the study team at each site.

Trial Population

Individuals between the ages of 12 and 18 years (inclusive) who had undergone the Fontan procedure, who were not receiving treatment with a PDE5 inhibitor, who were ≥40 kg, and who met the minimum height requirement for cycle ergometry (≥132 cm) were eligible for enrollment. To isolate the effect of udenafil on exercise performance, patients with severe ventricular dysfunction, severe atrioventricular valve insufficiency, or those with a prior clinical exercise test in which peak oxygen consumption was <50% of predicted for age and gender, were excluded. The full list of inclusion and exclusion criteria are listed in **Table 1**.

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Table 1

FUEL Inclusion and Exclusion Criteria
Inclusion Criteria 1. Males and females with Fontan physiology 12-<19 y of age at enrollment 2. Participant consent or parental/guardian consent with participant assent 3. Participant fuelt in English, Spanish or Korean
Exclusion Criteria 1. Weight <40kg 2. Height <132 Cm 3. Hospitalization for acute decompenated heart failure within the last 12 m 4. Current intravenous intropic drugs 5. Undergoing evaluation for heart transplantation or listed for transplantation 6. Diagnosis of acive protein-losing enteropathy or plastic bronchitits within the last 3 y, or a hstroy of liver cirrhosis 7. Known Fontan baffle obstruction, branch pulmonary artery stenosis, or pulmonary vein stenosis resulting in a mean gradient of >4mm Hg between the regions proximal and distal to the obstruction as measured by either catheterization or echocardiography, obtained prior to screening for the trial 8. Single lung physiology with greater then 80% flow to 1 lung 9. V02 max less then 50% of predicted for age and gender at enrollment 10. Severe ventricular dysfunction assessed qualitatively by clinical echocardiography within 6 m prior to enrollment 11. Severe valve regurgitation, ventricular outflow obstruction, or aortic arch obstruction assessed by clinical echocardiography within 6 m prior to enrollement 12. Siginificant renal (serum creatinine >2.0), hepatic (serum AST and/or ALT >3 times upper limit of normal), gastrointestinal, or biliary disorders that could impair absorbtion, metabolism, or excretion of orally administered medications based on laboratory assessment 6 wk prior to screening for the trial 13. Inability to compelte exercise testing at baseline screening 14. History of PDE-5 inhibitor use within 3 m before study onset 15. History of any other medication for treatment of pulmonary hypertension within 3 m before the study 16. Known intolerany to oral udenafil 17. Frequent use of medication or other substances that inhibit or induce CYP34A 18. Currentus of α-blockers or nitrates 19. Ongoing or planned participation in another research protocol that would either prevent successful completeion of planned study trasting or invalidate its results 20. Noncardiac medical, psychiatric, and/or social disorder that would prevent successful completion of planned study testing or would invalidate its results 21. Cardiac care, ongoing or planned, at a nonstudy center that would impede study completeion 22. For females; pregnancy at the time of screening, pregnancy planned before study completion, or refusal to use an acceptavle method of contraception for study duration if sexually active 23. Inability to abstain from or limit intake of grapefruit juice during the duration of the trial 24. Refusal to provide written informed consent/assent

25. In the opinon of the primary care physician, the subject is likely to be noncompliant with the study protocol
*ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP3A4, cytochrome P450 34A

Randomization and Study Procedures

Enrolled participants were assigned to udenafil or placebo in a 1:1 ratio using randomly permuted blocks and stratified by ventricular morphology (left ventricle versus right ventricle or mixed). Randomization assignments were generated by a web-based algorithm after confirmation of trial eligibility and consent.

Baseline clinical testing completed before drug initiation included a blood draw to measure brain-type natriuretic peptide (BNP) level, a cardiopulmonary exercise test (CPET) using a standardized cycle ergometer ramp protocol, a standardized echocardiogram, and an assessment of peripheral vascular function using peripheral arterial tonometry (PAT) measured by finger cuff (EndoPAT; Itamar Medical, Israel). Participants who achieved maximal effort, defined as respiratory exchange ratio (RER) $\geq$1.10 at peak exercise during CPET, were eligible for randomization and study drug initiation. Participants who did not achieve maximal effort were given a subsequent opportunity to repeat the exercise test within two weeks of the initial attempt. End-of-study clinical testing included repeat measurement of serum BNP, CPET, echocardiogram, and PAT.

Statistical Analysis

A sample size of 200 participants per arm was chosen to allow for 90% power to detect a mean treatment difference in change from baseline to 26-week testing in max VO_2 of 10% with a type 1 error of 0.05. The following assumption were made: a baseline standard deviation of 7.235 ml/kg/min, a correlation between max VO_2 measurements of 0.33, a drop-out and incomplete testing rate of 10%, and failure to reach maximal effort at the 26-week exercise testing in 15% of participants. These assumptions were based on historical data and reflect a conservative approach to assessing within-participant correlations and failure to reach maximal effort.

The primary analysis used the intention-to-treat population to evaluate the difference in the change in the primary outcome between treatment arms. This difference was assessed with

an analysis of covariance (ANCOVA) with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group, with a continuous covariate of baseline max VO_2. For those without data at the 26-week visit, this value was imputed as equal to the baseline value (no change). Secondary analyses included participants who successfully completed the protocol with measurable values at each of the secondary endpoints. Secondary outcomes of continuous data points were analyzed in the manner described for the primary outcome. In order to assess the generalizability of findings at the ventilatory anaerobic threshold, demographic and clinical characteristics were compared between participants without paired VO_2 at VAT data and those comprising the remainder of the cohort.

Trial Results

From July 2016 to May 2018, 1376 patients at 30 centers were screened. **FIG. 1B**. Of these, 200 were randomly assigned to udenafil and 200 to placebo. Mean age at randomization was 15.5 years, mean height was 163.6 cm, and mean weight was 58.1 kg. Sixty percent of participants were male and 81% described their racial identity as white. Those in the placebo group were taller, compared to those in the udenafil group, but baseline characteristics were otherwise similar between groups.

Primary Aim - Exercise Measures

Maximal exercise data (VO_2 max) were available for all participants at baseline testing, and for 379 participants at 26-week testing (189 in the udenafil group and 190 in the placebo group). Reasons for absence of data at 26-week testing included patient dropout or errors in data capture (n=14), and participant inability to generate an RER $\geq$1.10 (n=7). There was no difference in the change from baseline to 26-week testing in resting heart rate, respiratory rate, or systolic blood pressure between the udenafil and placebo groups. There was a small but statistically significant increase in resting oxygen saturation and a small but statistically significant decrease in diastolic blood pressure in the udenafil group.

Resting data and exercise performance results are provided in **Table 2**.

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Table 2: Resting Data and Exercise performance with comparison based on treatment arm. Summaries presented as mean ± standard deviation (n)*.

	Udenafil			Placebo			*p* value
Resting data	Baseline	26-week	Change	Baseline	26-week	Change	
Heart rate (bpm)	87.5±15.3 (200)	86.6±15.4 (191)	**-0.9±12.7 (191)**	88.1±14.1 (200)	87.4±16.1 (195)	**-0.6±12.7 (195)**	**0.78**
Systolic blood pressure (mmHg)	112.3±12.1 (200)	110.5±12.0 (191)	**-1.8±12.2 (191)**	113.2±12.9 (200)	112.8±11.6 (195)	**-0.2±12.2 (195)**	**0.18**
Diastolic blood pressure (mmHg)	68.4±9.5 (200)	65.3±9.9 (191)	**-2.9±9.7 (191)**	69.3±10.1 (200)	69.4±9.1 (195)	**0.2±10.7 (195)**	**0.003**
Oxygen saturation (%)	92.8±3.9 (200)	93.3±3.5 (191)	**0.5±2.4 (191)**	93.2±3.8 (200)	92.9±3.7 (195)	**-0.3±2.8 (195)**	**0.002**
Peak exercise							
Oxygen consumption (mL/min)*	1562±437 (200)	1606±452 (200)	**44±245 (200)**	1627±414 (200)	1623±432 (200)	**-3.7±228 (200)**	**0.071**
Work rate (W)	120±32 (198)	124±32 (187)	**3.2±14 (186)**	123±32 (199)	127±32 (189)	**2.6±14 (188)**	**0.85**
Heart rate (bpm)	165±20 (200)	165±20 (189)	**-1.4±11 (189)**	168±22 (199)	166±21 (190)	**-2.5±13 (189)**	**0.56**
Respiratory rate (breaths/min)	51±11 (199)	50±12 (188)	**-1.1±10 (187)**	51±13 (200)	50±12 (189)	**-1.5±10 (189)**	**0.72**
Minute ventilation (L/min)	71±21 (199)	73±22 (189)	**1.2±14 (188)**	76±22 (200)	76±21 (190)	**-0.1±14 (190)**	**0.84**
Oxygen saturation (%)	89.2±5.3 (195)	89.6±4.9 (190)	**0.4±3.4 (186)**	89.8±5.0 (197)	89.7±5.0 (192)	**-0.1±3.4 (190)**	**0.21**
Anaerobic Threshold							
Oxygen consumption (mL/min)	1039±301 (170)	1059±292 (185)	**29.7±177 (170)**	1021±280 (181)	1014±277 (191)	**-8.0±183 (181)**	**0.023**
Work (W)	66.2=26 (167)	69.2±26 (181)	**3.5±15 (167)**	66.1±23 (177)	66.6±23 (186)	**0.31±13.3 (177)**	**0.029**
VE/VCO2	34.3±4.9 (170)	33.6±4.8 (185)	**-0.76±3.6 (155)**	34.8±5.2 (181)	34.7±4.9 (191)	**-0.06±3.1 (162)**	**0.011**

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*P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO2. Note: Last observation carried forward was used to impute missing values at Week 26.

Analysis at resting of the diastolic blood pressure demonstrated a statistically significant change (a decrease shows improvement) in diastolic blood pressure in the udenafil group (-2.9 decrease, improvement) compared to the placebo group (+0.2 increase, no improvement) (p=0.003).

Analysis at resting of the oxygen saturation (%) demonstrated a statistically significant change (an increase shows improvement) in oxygen saturation (%) in the udenafil group (+0.5 increase, improvement) compared to the placebo group (-0.3 decrease, no improvement) (p=0.002).

Analysis at maximal exercise demonstrated an increase in VO_2 max of 44 mL/min (2.8%) in the udenafil group compared to a decline of 3.7 mL/min (-0.2%) in the placebo group, although the difference did not reach statistical significance (p=0.071).

Further, metabolic data for the calculation of VO_2 at VAT were available for 317 participants; 170 in the udenafil group and 181 in the placebo group, as shown in **Table 2** above. There was no difference in the baseline demographic or clinical characteristics of this subgroup compared to the larger cohort. For those with paired VO_2 at VAT data, there was a statistically significant improvement of 30 mL/min (1.92%) in the udenafil group compared to a decrease of 8 mL/min (-0.7%) in the placebo group (p=0.023). Ventilatory equivalents of carbon dioxide measured at VAT (VE/VCO_2) significantly decreased (improved ventilatory efficiency) by 0.8 (2.1%) in the udenafil group compared to 0.05 (0.2%) in the placebo group (p=0.011), while the work rate significantly improved by 3.5 Watts (5.5%) in the udenafil group compared to 0.31 Watts (0.78%) in the placebo group (p=0.029). Thus, treatment of Fontan patients with 87.5 mg, twice daily, demonstrated statistically significant improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold.

Secondary Aims Measures

Paired echocardiographic data for the measure of MPI were available in 250 participants (63%); 122 in the udenafil group and 128 in the placebo group. **Table 3**. There was a

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statistically significant change (a decrease shows improvement) in MPI in the udenafil treated group (-0.02 decrease, improvement) as compared to the placebo group +0.01 increase, no improvement) (p=0.028).

Paired PAT-derived vascular function data were available in 328 participants (81%); 163 in the udenafil group and 165 in the placebo group. There were non-significant improvements in lnRHI in both the udenafil and placebo groups (0.07 vs 0.05, p=0.59). Paired measures of serum BNP level were available in 378 participants (95%); 187 in the udenafil group and 191 in the placebo group. The change in log serum BNP level was not different between groups (p=0.18). The paired echocardiographic data, the paired PAT-derived vascular function data, and the paired measure of serum BNP level is provided in **Table 3**.

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Table 3: Secondary Outcomes with Comparison Based on Treatment Arm

Endocardiography				
Myocardial Performance Index (MPI) by Visit and Treatment Arm Difference Between Week 26 and Baseline Visits (ITT Population)				
	Udenafil	**Placebo**	**LS Mean Dif A-B(SE)*** **	**P-Value**
Baseline, N: Mean (SD)	150: 0.45 (0.173)	155: 0.45 (0.156)	-0.0 (0.018)	0.818*
Week 26, N: Mean (SD)	146: 0.42 (0.147)	148: 0.46 (0.177)	-0.04 (0.018)	0.024*
Difference, Week 26-Baseline N: Mean (SD)	122: -0.02 (0.113)	128: 0.01 (0.133)	-0.03 (0.014)	0.028**
Median (Interquartile Range) of the difference	-0.01 (-0.11, 0.05)	0.01 (-0.08, 0.08)		
Min, Max of the difference	(-.3, 0.2)	(-0.5, 0.4)		

*P value was assessed using ANOVA with the fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group

**P value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2

***LS Mean (least square mean) was the estimated treatment mean difference from the analysis model

Endpoint	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value[a]
Log-transformed reactive hyperemia index	n=170	n=173		
Difference, Week 26 – baseline, mean (SD)	0.06 (0.301)	0.04 (0.370)	0.02 (0.030)	0.591
Log brain natriuretic peptide (pg/mL)	n=187	n=191		
Difference, Week 26 – baseline, mean (SD)	0.08 (0.905)	0.03 (1.137)	0.13 (0.094)	0.169

ANCOVA = analysis of covariance; ITT = intent-to-treat; LS = least squares; SD = standard deviation; SE = standard error

a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal minute oxygen consumption.

Note: Brain natriuretic peptide values reported by the laboratory as <2.0 were imputed as 1.0.

Safety and Tolerability

Table 4: Non-Serious Adverse Events. Number of participants that experienced an adverse event presented as n (%).

	Udenafil (200)	Placebo (200)
Headache	79 (39.5)	51 (25.5)
Flushing	32 (16.0)	12 (6.0)
Dizziness	16 (8.0)	17 (8.5)
Nausea / vomiting	31 (15.5)	14 (7.0)
Increased erection*	13 (11.7)	2 (1.6)
Epistaxis	21 (10.5)	5 (2.5)

*Percentage of male participants.

Udenafil and placebo were well tolerated by study participants. There were no deaths in the study cohort. A total of 24 participants (6%) experienced a serious adverse event; 14 in the udenafil group and 10 in the placebo group. There were 3 events in the udenafil group and 2 events in the placebo group that were thought to have a possible, probable, or definite relationship to study drug. Those that occurred in the udenafil group included unilateral retinal artery and vein thrombosis, transient lower extremity diplegia, and transient dyspnea. Frequent non-serious adverse events thought to have a possible, probable, or definite relationship to study drug that occurred in at least 5% of participants in either treatment group are provided in **Table 4**. Headache, facial flushing, abdominal pain, epistaxis, and erection (male participants) were more common in the udenafil group. All other adverse events occurred with similar frequency between the groups.

EXAMPLE 2

Additional FUEL Trial Results

The following example additionally describes the above-referenced FUEL trial, as referenced in Goldberg, DJ, et al.: Results of the Fontan Udenafil Exercise Longitudinal (FUEL) Trial. *Circulation*, 141(8):141:641–651 (2020), which is hereby incorporated herein by reference in its entirety.

The Fontan operation creates a total cavopulmonary connection, a circulation in which the importance of pulmonary vascular resistance is magnified. Over time, this circulation leads to deterioration of cardiovascular efficiency associated with a decline in exercise

performance. Rigorous clinical trials aimed at improving physiology and guiding pharmacotherapy are lacking.

The FUEL Trial was a Phase III clinical trial conducted at 30 centers. Participants were randomly assigned udenafil, 87.5 mg twice daily, or placebo in a 1:1 ratio. The primary outcome was the between group difference in change in oxygen consumption at peak exercise. Secondary outcomes included between group differences in changes in sub-maximal exercise at the ventilatory anaerobic threshold (VAT), the myocardial performance index (MPI), the natural log of the reactive hyperemia index (lnRHI), and serum brain-type natriuretic peptide (BNP).

Between 2017 and 2019, 30 clinical sites in North America and the Republic of Korea randomized 400 participants with Fontan physiology. The mean age at randomization was 15.5 ±2 years; 60% of participants were male and 81% were White. All 400 subjects were included in the primary analysis with imputation of the 26-week endpoint for 21 participants with missing data (11 randomized to udenafil and 10 to placebo). Among randomized participants, peak oxygen consumption increased by 44 ±245 mL/min (2.8%) in the udenafil group and declined by 3.7 ±228 mL/min (-0.2%) in the placebo group (p=0.071). Analysis at VAT demonstrated statistically significant improvements in the udenafil group versus the placebo group in oxygen consumption (+33 ±185 (3.2%) vs -9 ±193 (-0.9%) mL/min, p=0.012), ventilatory equivalents of carbon dioxide (-0.8 vs -0.06, p=0.014), and work rate (+3.8 vs +0.34 Watts, p=0.021). Analysis of MPI also demonstrated statistically significant improvement in the udenafil treated group (p=0.028) compared to the group taking placebo over the same time period. There was no difference in change in lnRHI, or serum BNP level.

In the FUEL trial, treatment with udenafil (87.5 mg twice daily) was associated with an improvement in oxygen consumption at peak exercise (p=0.071) and statistically significant improvements in (i) multiple measures of exercise performance at the ventilatory anaerobic threshold (VAT), (ii) MPI, (iii) diastolic blood pressure at rest, and (iv) oxygen saturation (%) at rest.

The FUEL trial was Funded by Mezzion Pharma Co. Ltd., and conducted by the National Heart, Lung, and Blood Institute-funded Pediatric Heart Network. ClinicalTrials.gov number NCT02741115, which is hereby incorporated herein by reference in its entirety.

Clinical Perspective

New aspects

- The Circulation publication describes the results of the Fontan Udenafil Exercise Longitudinal (FUEL) Trial, the largest medical intervention trial in congenital heart disease. Goldberg D.J. *et al.*: Results of the FUEL Trial. *Circulation*, 141(8):141:641–651 (2020)
- The Circulation errata to Goldberg D.J. *et al.*: Results of the FUEL Trial. *Circulation*, 141(8):141:641–651 (2020), as incorporated in Example 4, describes the corrected MPI results of the FUEL Trial.
- While treatment with udenafil did not result in a statistically significant increase in peak oxygen consumption, it did result in a notable increase in peak oxygen consumption.
- Treatment with udenafil did result in statistically significant improvements in measures of exercise performance at the ventilator anaerobic threshold (VAT), work rate at VAT, ventilatory equivalents of carbon dioxide (VE/VCO_2) at VAT, MPI, diastolic blood pressure at rest, and oxygen saturation at rest.
- Udenafil was well tolerated by the FUEL Trial subjects with side effects limited to those previously known to be associated with phosphodiesterase type 5 inhibitors.

Clinical Implications

- Udenafil is the first medication evaluated in a large-scale, phase III clinical trial to demonstrate a quantifiable benefit in measures of exercise capacity in adolescents after Fontan palliation.
- These findings suggest that therapy with udenafil may improve the physiology, the exercise capacity, the work rate, the VE/VCO_2, the MPI, the cardiac output, the squeezing performance, the amount of flow that can circulate through the body in a given amount of time, diastolic blood pressure and/or oxygen saturation at rest, and the performance of the single functioning ventricles of the cohort of patients who have undergone a total cavopulmonary connection.
- Ongoing surveillance is needed to determine the effect of chronic treatment with udenafil on the long-term clinical course of those living with single ventricle congenital heart disease.

Children born with single ventricle congenital heart disease (SVHD) require a series of staged surgical interventions to reconstruct their defective hearts for long-term survival. The

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Methods

The FUEL trial was an international, multicenter, randomized, double-blind, placebo-controlled trial of udenafil, in addition to standard care, in adolescents with SVHD who had undergone Fontan palliation. The trial was supported by the National Heart, Lung, and Blood Institute (NHLBI)-funded PHN in partnership with the regulatory sponsor, Mezzion Pharma Co. Ltd., under a Special Protocol Assessment through the Food and Drug Administration. The FUEL protocol and consent forms and all subsequent amendments were approved by the DSMB, the institution review board or equivalent at each study center, and regulatory agencies from the United States, Canada, and the Republic of Korea. Consent was obtained from the study participant, or the legal guardian for those <18 years of age. Assent was obtained from participants >18 years of age. The trial design has been published previously. Goldberg DJ, Zak V, Goldstein BH, McCrindle BW, Menon SC, Schumacher KR, Payne RM, Rhodes J, McHugh KE, Penny DJ, Trachtenberg F, Hamstra MS, Richmond ME, Frommelt PC, Files MD, Yeager JL, Pemberton VL, Stylianou MP, Pearson GD, Paridon SM

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Trial Population

Individuals between the ages of 12 and 18 years (inclusive) who had undergone the Fontan procedure, who were not receiving treatment with a PDE5 inhibitor, who were ≥40 kg, and who met the minimum height requirement for cycle ergometry (≥132 cm) were eligible for enrollment. To isolate the effect of udenafil on exercise performance, patients with severe ventricular dysfunction, severe atrioventricular valve insufficiency, or those with a prior clinical exercise test in which peak oxygen consumption was <50% of predicted for age and sex, were excluded. The full list of inclusion and exclusion criteria are listed in **Table 1** above for the study protocol.

Randomization and Study Procedures

Enrolled participants were assigned to udenafil or placebo in a 1:1 ratio in a double-blind manner using randomly permuted blocks and stratified by ventricular morphology (left ventricle versus right ventricle or mixed). Randomization assignments were generated by a web-based algorithm after confirmation of trial eligibility and consent.

Baseline clinical testing completed before drug initiation included a blood draw to measure brain-type natriuretic peptide (BNP) level, a cardiopulmonary exercise test (CPET) using a standardized cycle ergometer ramp protocol (previously described in children and adolescents with Fontan physiology, Sleeper LA, Anderson P, Hsu DT, Mahony L, McCrindle BW, Roth SJ, Saul JP, Williams RV, Geva T, Colan SD, Clark BJ and Pediatric Heart Network I. Design of a large cross-sectional study to facilitate future clinical trials in children with the Fontan palliation. *Am Heart J.* 152(3):427-433 (Sep 2006), a standardized echocardiogram, and an assessment of peripheral vascular function using peripheral arterial tonometry (PAT) measured by finger cuff (EndoPAT; Itamar Medical, Israel). Participants who achieved maximal effort, defined as respiratory exchange ratio (RER) ≥1.10 at peak exercise during CPET, were eligible for randomization and study drug initiation. Participants who did not achieve maximal effort were given a subsequent opportunity to repeat the exercise test within two weeks of the initial attempt. End-of-study clinical testing included repeat measurement of serum BNP, CPET, echocardiogram, and PAT.

Primary and Secondary End Points

The primary aim was to determine the effect of udenafil on exercise capacity in adolescents with Fontan physiology over a six-month period. The primary outcome was the between group difference in the change in oxygen consumption at peak exercise (peak VO_2) from baseline to the 26-week visit. Secondary exercise outcomes included between group differences in change in additional measures at maximal exertion, as well as change in measures of submaximal exercise at the ventilatory anaerobic threshold (VAT). All measurement of values for exercise testing were initially made by the exercise physiologists and physicians at the individual participating sites. These were subsequently reviewed for accuracy in a blinded fashion at each site by one of two trained reviewers (MGM, SMP) in conjunction with the sites' exercise teams prior to finalization. For both peak VO_2 and VO_2 at VAT, unindexed oxygen consumption was evaluated to avoid the introduction of confounding based on short-term change in body habits. An analysis of oxygen consumption corrected for body weight is included in **Table 5**.

Table 5: Oxygen consumption indexed to weight for peak exercise and the anaerobic threshold with comparison based on treatment arm. Summaries presented as mean ± standard deviation (n).

		Peak exercise Oxygen consumption (mL/kg/min)	*Anaerobic Threshold* Oxygen consumption (mL/kg/min)
Udenafil	Baseline	27.84±6.88 (200)	18.35±4.63 (170)
	26-week	27.61±6.87 (200)	18.20±4.51 (185)
	Change	**-0.23±4.06 (200)**	**-0.07±3.0 (170)**
Placebo	Baseline	28.01±6.13 (200)	17.71±4.30 (181)
	26-week	27.12±6.63 (200)	16.99±4.13 (191)
	Change	**-0.89±3.67 (200)**	**-0.68±3.2 (181)**
	p value	**0.092****	**0.012****

**P_value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO2.
Imputations were done as follows:
• Subjects who were known to be alive, but who discontinued from the study (and were missing maximal VO2 at Week 26) were assigned the latest value available (e.g., value from end of study visit if available and from baseline visit otherwise).
• Subjects who completed Week 26, but were physically unable to reach maximum effort in cardiopulmonary exercise testing after two attempts, were assigned their baseline value when the subject met maximum effort in Baseline exercise testing. One exception was subject 330011 who was adjudicated to be included as RER was 1.10

The primary outcome for clinical secondary aims included the between group differences in change in myocardial performance index (MPI), an echocardiographically-derived measure of systolic and diastolic ventricular function, change in log-transformed reactive hyperemia index (lnRHI), a PAT-derived measure of peripheral vascular function, and change in log-transformed serum BNP level. Measurements for each of these secondary outcomes were performed at core labs. Safety was monitored through adverse event reports, which were collected according to a pre-specified protocol of study coordinator outreach, and through *ad hoc* patient and family communication with members of the study team at each site.

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Statistical Analysis

A sample size of 200 participants per arm was chosen to allow for 90% power to detect a mean treatment difference in change from baseline to 26-week testing in peak VO_2 of 10% with a type 1 error of 0.05. We assumed a baseline standard deviation of 7.235 ml/kg/min, a correlation between peak VO_2 measurements of 0.33, a drop-out and incomplete testing rate of 10%, and failure to reach maximal effort at the 26-week exercise testing in 15% of participants. These assumptions were based on historical data and reflect a conservative approach to assessing within-participant correlations and failure to reach maximal effort and the analysis was performed using a two-sample, independent means t-test. The primary analysis used the intention-to-treat population to evaluate the difference in the change in the primary outcome between treatment arms. This difference was assessed with an analysis of covariance (ANCOVA) with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group, with a continuous covariate of baseline peak VO_2. For those without data at the 26-week visit, this value was imputed as equal to the baseline value (no change). The alpha level was set at 0.05 with two-sided testing. All statistical analyses were performed using SAS statistical software 9.4 (SAS Institute, Inc., Cary, North Carolina). Secondary analyses included participants who successfully completed the protocol with measurable values at each of the secondary endpoints. Secondary outcomes of continuous data points were analyzed in the manner described for the primary outcome. In order to assess the generalizability of findings at the ventilatory anaerobic threshold, demographic and clinical characteristics were compared between participants without paired VO_2 at VAT data and those comprising the remainder of the cohort using the Student's t-test and Fisher's exact test. Fisher's exact test was used to compare adverse events between the udenafil and placebo cohorts.

Results

Participants: From July 2016 to May 2018, 1376 patients at 30 centers were screened. **FIG. 1B**. Of these, 200 were randomly assigned to udenafil and 200 to placebo. Mean age at randomization was 15.5 years, mean height was 163.6 cm, and mean weight was 58.1 kg. Sixty percent of participants were male and 81% described their racial identity as white. Those in the placebo group were taller, compared to those in the udenafil group, but baseline characteristics were otherwise similar between groups in **Table 6**.

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Table 6: Demographic and clinical baseline characteristics for the 400 subjects randomized to a treatment arm; summaries presented as mean (standard deviation) unless otherwise noted as n (%).

	Total (n=400)	Udenafil (n=200)	Placebo (n=200)
Age, years	15.5 (2.0)	15.4 (2.0)	15.6 (2.0)
Female, n (%)	161 (40.3)	89 (44.5)	72 (36.0)
Race, n (%)			
White	324 (81.0)	169 (84.5)	155 (77.5)
Asian	38 (9.5)	17 (8.5)	21 (10.5)
Black	23 (5.8)	10 (5.0)	13 (6.5)
Other	15 (3.8)	4 (2.0)	11 (5.5)
Predominant Ventricular morphology, n (%)			
Right	176 (44.0)	89 (44.5)	87 (43.5)
Left	189 (47.3)	94 (47.0)	95 (47.5)
Other (indeterminant and biventricular)	35 (8.8)	17 (8.5)	18 (9.0)
Subjects with a patent fenestration, n (%)	131 (32.8)	73 (36.5)	58 (29.0)
Height, cm	163.6 (9.6)	162.5 (10.4)	164.7 (8.7)
Weight, kg	58.1 (13.6)	57.1 (13.9)	59.0 (13.2)
Body mass index, kg/m^2	21.6 (4.1)	21.5 (3.9)	21.7 (4.2)

*t-test for continuous variables, Fisher exact test for categorical

Exercise measures

Resting, submaximal, and maximal exercise measures are presented in **Table 2**. Maximal exercise data were available for all participants at baseline testing, and for 379 participants at 26-week testing (189 in the udenafil group and 190 in the placebo group). Reasons for absence of data at 26-week testing included patient dropout or errors in data capture (n=14) and participant inability to generate an RER ≥1.10 (n=7). There was no difference in the change from baseline to 26-week testing in resting heart rate, respiratory rate, or systolic blood pressure between the udenafil and placebo groups. Peak minute ventilation at baseline (pre-drug exposure) was higher in the placebo group, but there was no difference in the change in minute ventilation between groups. There was a small but statistically significant increase in resting oxygen saturation and a small but statistically significant decrease in diastolic blood pressure in the udenafil group.

Analysis at maximal exercise demonstrated an increase in peak VO_2 of 44 mL/min (2.8%) in the udenafil group compared to a decline of 3.7 mL/min (-0.2%) in the placebo group, although the difference did not reach statistical significance. **FIGS. 2A- 2B, p=0.071**.

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Metabolic data for the calculation of VO_2 at VAT were available for 351 participants; 170 in the udenafil group and 181 in the placebo group. There was no difference in the baseline demographic or clinical characteristics of this subgroup compared to the larger cohort. **Table 7**. For those with paired VO_2 at VAT data, there was a statistically significant improvement of 29.7 mL/min (2.85%) in the udenafil group compared to a decrease of 9 mL/min (-0.8%) in the placebo group. **FIGS. 3A-3B**, p=0.023. Ventilatory equivalents of carbon dioxide measured at VAT (VE/VCO_2) significantly decreased (improved ventilatory efficiency) by 0.8 in the udenafil group compared to 0.05 in the placebo group (p=0.0114), while the work rate significantly improved by 3.5 Watts (5.2%) in the udenafil group compared to 0.31 Watts (0.5%) in the placebo group. **FIGS. 4A-4B**, p=0.029.

Table 7: Demographic and clinical baseline characteristics for subjects with versus without paired data for VO_2 at VAT; summaries presented as mean (standard deviation) unless otherwise noted as n (%).

	Total (n=400)	Paired Data (n=317)	No Paired Data (n=83)	*p* value*
Age, years	15.5 (2.0)	15.6 (2.0)	15.4 (2.2)	0.50
Female, n (%)	161 (40.3%)	128 (40.4%)	33 (39.8%)	1.0
Race, n (%)				0.16
White	324 (81.0%)	256 (80.8%)	68 (81.9%)	
Asian	38 (9.5%)	34 (10.7%)	4 (4.8%)	
Black	23 (5.8%)	15 (4.7%)	8 (9.6%)	
Other	15 (3.8%)	12 (3.8%)	3 (3.6%)	
Predominant Ventricular morphology, n (%)				0.97
Right	176 (44.0%)	138 (43.5%)	38 (45.8%)	
Left	189 (47.3%)	151 (47.6%)	38 (45.8%)	
Other (indeterminant and biventricular)	35 (8.8%)	28 (8.8%)	7 (8.4%)	
Subjects with a patent fenestration, n (%)	131 (32.8%)	104 (32.8%)	27 (32.5%)	1.0
Height, cm	163.6 (9.6)	164.0 (9.5)	162.0 (10.0)	0.095
Weight, kg	58.1 (13.6)	58.0 (13.6)	58.3 (13.5)	0.85
Body mass index, kg/m^2	21.6 (4.1)	21.5 (4.0)	22.1 (4.3)	0.19
Baseline VO_2 at peak exercise	1594 (426)	1614 (432)	1518 (400)	0.07
Baseline VO_2 at the anaerobic threshold	1030 (290)	1034 (294)	993 (251)	0.44

*t-test for continuous variables, Fisher exact test for categorical. Differences between those with and without paired data.

Secondary aims

Paired echocardiographic data for the measure of MPI were available in 250 participants (63%); 122 in the udenafil group and 128 in the placebo group. **Table 3**. There was a statistically significant change (decrease shows improvement) in MPI in the udenafil-treated group (-0.02 decrease, improvement) as compared to the placebo group (+0.01 increase, no improvement) (p=0.028). Paired PAT-derived vascular function data were available in 328 participants (81%); 163 in the udenafil group and 165 in the placebo group. There were non-significant improvements in lnRHI in both the udenafil and placebo groups (0.07 vs 0.05, p=0.59). Paired measures of serum BNP level were available in 378 participants (95%); 187 in the udenafil group and 191 in the placebo group. The change in log serum BNP level was not different between groups (p=0.18).

Safety and tolerability

Udenafil and placebo were well tolerated by study participants. There were no deaths in the study cohort. A total of 24 participants (6%) experienced a serious adverse event; 14 in the udenafil group and 10 in the placebo group. There were 3 events in the udenafil group and 2 events in the placebo group that were thought to have a possible, probable, or definite relationship to study drug. Those that occurred in the udenafil group included unilateral retinal artery and vein thrombosis, transient lower extremity diplegia, and transient dyspnea. Frequent non-serious adverse events thought to have a possible, probable, or definite relationship to study drug are listed in **Table 4**. Headache, facial flushing, abdominal pain, epistaxis, and erection (male participants) were more common in the udenafil group. There were no reported episodes of priapism. All other adverse events occurred with similar frequency between the groups.

Discussion

The FUEL trial was a phase III clinical trial of udenafil in children with SVHD who have undergone the Fontan operation. Although the relative improvement in peak VO_2 in the udenafil group did not reach statistical significance when compared between treatment arms, treatment with udenafil did lead to statistically significant improvements in pre-specified secondary outcome measures of sub-maximal exercise. Participants randomized to udenafil had superior gains in oxygen consumption, work rate, ventilatory efficiency at the anaerobic threshold, and the myocardial performance index. A relative improvement in the PAT-

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derived reactive hyperemia index was not seen. Overall, udenafil was well tolerated with few serious adverse events and side effects limited to those known to be associated with PDE5 inhibitor therapy. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM and Rychik J. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. *Circulation*. 123(11):1185-1193 (May 22 2011); Goldberg DJ, Zak V, Goldstein BH, McCrindle BW, Menon SC, Schumacher KR, Payne RM, Rhodes J, McHugh KE, Penny DJ, Trachtenberg F, Hamstra MS, Richmond ME, Frommelt PC, Files MD, Yeager JL, Pemberton VL, Stylianou MP, Pearson GD, Paridon SM and Pediatric Heart Network I. Design and rationale of the Fontan Udenafil Exercise Longitudinal (FUEL) trial. *Am Heart J*. 201:1-8 (Jul 2018); and Chang HJ, Song S, Chang SA, Kim HK, Jung HO, Choi JH, Lee JS, Kim KH, Jeong JO, Lee JH and Kim DK. Efficacy and Safety of Udenafil for the Treatment of Pulmonary Arterial Hypertension: a Placebo-controlled, Double-blind, Phase IIb Clinical Trial. *Clin Ther*. 41(8):1499-1507 (Aug 2019).

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threshold compared to peak exercise, and is different from the physiology for those with a sub-pulmonary ventricle in whom central venous pressure changes very little during exercise and for whom trends in improvement or decline in VO_2 at VAT and peak VO_2 are usually equivalent.

Despite the importance of the findings reported here, there are limitations to this trial. First, to minimize burden to participants, the study design did not include detailed measures of hemodynamics such as might be obtained with cardiac magnetic resonance imaging or invasive catheterization study. Additionally, evaluation of the PAT outcome did not reveal a benefit to udenafil over placebo. [?] Further interrogation of the multiple measures provided by these studies was not performed in this initial analysis but will be the subject of future analyses. Finally, the duration of the FUEL trial precluded a long-term assessment of safety, although this is being addressed by the ongoing FUEL open-label extension study.

Treatment with udenafil (87.5 mg twice daily), in addition to standard therapy, was not associated with a statistically significant improvement in oxygen consumption at peak exercise but did demonstrate statistically significant improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold. As the first large, multicenter, placebo-controlled, randomized trial to demonstrate a measurable physiologic benefit for Fontan patients, the FUEL trial represents a milestone in the nearly 50-year experience with the Fontan circulation and serves as a model of how public-private partnership can advance science in congenital heart disease. Further study is warranted to determine if udenafil is selectively beneficial for subpopulations within the larger cohort with SVHD, and to evaluate the long-term tolerability and safety of treatment.

The disclosures cited in this **EXAMPLE 2** are incorporated herein by reference in their entireties as if fully set forth herein.

EXAMPLE 3

Formulation of Udenafil Tablet

An exemplary formulation of a tablet containing 87.5 mg of the udenafil is detailed in **Table 11**. The udenafil formulation as reported in Table 11 was used with Fontan patients enrolled in the FUEL trial, which is discussed in Examples 1 and 2 above.

Table 11: Composition of Udenafil Tablets, 87.5 mg.

Component	Quality Standard	Function	Quantity (mg/tablet)
Core tablet			
Udenafil	In-house	Active	about 87.5
Lactose monohydrate	NF	Diluent	about 100.00
Corn starch	NF	Diluent	about 20.00
Low substituted hydroxypropyl cellulose	NF	Disintegrant	about 12.50
Colloidal silicon dioxide	NF	Disintegrant	about 12.50
Hydroxypropyl cellulose	NF	Binder	about 7.50
Purified water	USP	Granulating solvent	NA[1]
Talc	USP	Glidant	about 7.50
Magnesium stearate	NF	Lubricant	about 2.50
		Total core tablet weight	about ***250.0 mg***
Tablet coating			
Purified water	USP	Solvent	NA[1]
Opadry white[3]	In-house	Coating material	about 8.00[2]
		Total Tablet Weight	about ***258.00***

[1] Purified Water, USP is removed during the manufacturing process and is not part of the final formulation.
[2] Based on a nominal coating weight gain of 3.2% w/w
[3] Opadry white contains hypromellose, hydroxypropyl cellulose, titanium dioxide, and polyethylene glycol

EXAMPLE 4

Udenafil effect on echocardiographic indices of myocardial performance in SVHD subjects with Fontan Palliation

An objective of the FUEL Trial was to determine the effect of udenafil on echocardiographic measures of myocardial performance in adolescents, ages about 12 to about 18, with a functional single-ventricle physiology after Fontan surgery. The FUEL Trial was a randomized, double-blind, placebo-controlled, trial and was conducted in adolescents, ages about 12 to about 18, after the Fontan operation, at 30 different sites located in the United

States (26), Canada (2) and South Korea (2). The Fontan patients were randomized to receive placebo or udenafil (87.5 mg twice daily) for 26 weeks.

Each subject underwent an echocardiogram at the start and finish of the 26 weeks. Paired echocardiographic data for the measure of MPI were available in 250 participants (63%); 122 in the udenafil group and 128 in the placebo group. **Table 3**. There was a statistically significant change in MPI in the udenafil treated group (-0.02 decrease, improvement) as compared to the placebo group (+0.01 increase, no improvement) (p=0.028). The change in the MPI was determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the single functioning dominant ventricle. All measurements were made by the echocardiography core lab at the Children's Hospital of Wisconsin. The subjects treated with udenafil demonstrated statistically significant improvement (decrease shows improvement) in their myocardial performance index (MPI), p=0.028, compared to subjects taking placebo over the same time period.

These data demonstrate an improvement in MPI in the udenafil group relative to the placebo group (-0.02 vs +0.01, p=0.028). Myocardial performance is an important factor in the long-term health of those with SVHD, including those with SVHD who have undergone Fontan surgery, and improvement in this aspect of physiology complements the improvement noted in exercise performance and suggests that the benefit of treatment with udenafil may be multifactorial.

All disclosures, including all patents, patent documents, articles, abstracts, errata and publications, that are referenced or cited herein, including application for U.S. patent, Serial Number 14/788,211, U.S. Patent Publication No. 2019/0030037, U.S. Patent No. 10,137,128, and application for U.S. Patent, Serial Number 15/887,523, U.S. Patent Publication No. 2018/0169103 and U.S. Patent No. 10,653,698, are incorporated herein by reference in their entireties, as if each were individually and completely incorporated.

In case of conflict with other related earlier filed applications cited under "Related Applications," this present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative

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embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

Having described our invention, we claim:

1. A method of treating a patient who has undergone Fontan surgery (Fontan patient) to improve the patient's exercise capacity, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the Fontan patient to increase oxygen consumption at the ventilatory anaerobic threshold (VAT) to improve the Fontan patient's exercise capacity.

2. The method of claim 1, wherein said method improves ventilatory equivalents of carbon dioxide (VE/VCO2) at VAT to improve the Fontan patient's exercise capacity.

3. The method of claim 1, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

4. The method of claim 2, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

5. The method according to claim 1, wherein said method increases oxygen consumption at peak exercise capacity to improve the Fontan patient's exercise capacity.

6. The method according to claim 5, wherein said method improves ventilatory equivalents of carbon dioxide (VE/VCO2) at VAT to improve the Fontan patient's exercise capacity.

7. The method according to claim 5, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

8. The method according to claim 6, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

9. The method according to claim 1, wherein the patient is an adolescent.

10. The method according to claim 1, wherein the patient is between about 12 and about 19 years old.

11. The method according to claim 1, wherein the patient is between about 12 and about 18 years old.

12. A method of treating a Fontan patient's exercise capacity, comprising:

administering 87.5 mg of udenafil or a pharmaceutically acceptable salt thereof twice daily to the patient to increase oxygen consumption at VAT to improve the Fontan patient's exercise capacity.

13. The method according to claim 12, wherein said method improves ventilatory equivalents of carbon dioxide (VE/VCO2) at VAT to improve the Fontan patient's exercise capacity.

14. The method according to claim 12, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

15. The method according to claim 13, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

16. The method according to claim 12, wherein said method increases oxygen consumption at peak exercise capacity to improve the Fontan patient's exercise capacity.

17. The method according to claim 16, wherein said method improves ventilatory equivalents of carbon dioxide (VE/VCO2) at VAT to improve the Fontan patient's exercise capacity.

18. The method according to claim 16, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

19. The method according to claim 17, wherein said method increases work rate at VAT to improve the Fontan patient's exercise capacity.

20. The method according to any one of claims 1 to 11, wherein said method results in minimal or no side effects caused to the Fontan patient.

21. The method according to any one of claims 12 to 19, wherein said method results in minimal or no side effects caused to the Fontan patient.

22. The method according to any one of claims 1 to 11, wherein said method results in beneficial effects comprising decreasing the rate of physiological functional decline in the Fontan patient.

23. The method according to any one of claims 1 to 11, wherein said method results in beneficial effects for the Fontan patient comprising increasing the duration of symptom-free survival of the Fontan patient.

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24. The method according to any one of claims 12 to 19, wherein said method results in beneficial effects for the Fontan patient comprising decreasing the rate of physiological functional decline in the Fontan patient.

25. The method according to any one of claims 12 to 19, wherein said method results in beneficial effects for the Fontan patient comprising increasing the duration of symptom-free survival of the Fontan patient.

26. A daily method of increasing venous capacitance in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle, to increase oxygen consumption at ventilatory anaerobic threshold (VAT) to improve daily the patient's exercise capacity at VAT, said method comprising:

administering to the Fontan patient daily an effective daily dose of a phosphodiesterase type 5 inhibitor (PDE5i) to increase the Fontan patient's venous capacitance to increase the Fontan patient's oxygen consumption at VAT to improve daily the Fontan patient's exercise capacity at VAT.

27. A daily method of inducing venous vasodilation in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle, to increase the patient's venous capacitance to enable the patient to increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to improve daily the patient's exercise capacity at VAT, said method comprising:

inducing daily the patient's venous vasodilation to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to improve daily the patient's exercise capacity at VAT.

28. A daily method of interfering with the conversion of cyclic guanosine monophosphate (cGMP) to 5'-guanosine monophosphate (5'-GMP) in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle, to induce venous vasodilation in the patient to increase the patient's venous capacitance to enable the patient to increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to improve daily the patient's exercise capacity at VAT, said method comprising:

interfering daily with the conversion of cGMP to 5'-GMP in the patient to induce venous vasodilation to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to improve daily the patient's exercise capacity at VAT.

29. A daily method of potentiating the nitric oxide –stimulated cyclic guanosine monophosphate (cGMP) signal in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle, to induce venous vasodilation in the patient to increase the patient's venous capacitance to enable the patient to increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to daily improve the patient's exercise capacity at VAT, said method comprising:

potentiating daily the cGMP signal in a patient to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to daily improve the patient's exercise capacity at VAT.

30. A daily method of inhibiting cyclic guanosine monophosphate (cGMP) degradation in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle, to induce venous vasodilation in the patient to increase the patient's venous capacitance to enable the patient to increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to daily improve the patient's exercise capacity at VAT, said method comprising:

inhibiting daily cGMP degradation in a patient to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to daily improve the patient's exercise capacity at VAT.

31. A daily method of achieving peak venous capacitance in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to enable the Fontan patient to achieve daily peak oxygen consumption at ventilatory anaerobic threshold (VAT) to further enable the Fontan patient to achieve peak exercise capacity at VAT daily, said method comprising:

administering to the Fontan patient daily an effective daily dose of a phosphodiesterase type 5 inhibitor (PDE5i) to achieve peak venous capacitance in the Fontan

patient to enable the Fontan patient to achieve peak oxygen consumption at VAT daily, so that the Fontan patient can achieve peak exercise capacity at VAT on a daily basis.

32. A daily method of inducing peak venous vasodilation in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to enable the Fontan patient to achieve peak venous capacitance daily to further enable the Fontan patient to achieve peak oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to enable the Fontan patient to achieve daily peak exercise capacity at VAT, said method comprising:

inducing daily peak venous vasodilation in the Fontan patient to achieve peak venous capacitance in the Fontan patient to enable the Fontan patient to achieve daily peak oxygen consumption at the Fontan patient's VAT, so that peak exercise capacity at VAT is achieved daily by the Fontan patient.

33. A daily method of interfering with the conversion of cyclic guanosine monophosphate (cGMP) to guanosine 5'-monophosphate (5'-GMP) in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to induce daily peak venous vasodilation to achieve peak venous capacitance in the Fontan patient to enable the Fontan patient to achieve peak oxygen consumption at the Fontan patient's ventilatory anaerobic threshold (VAT) so that the Fontan patient can achieve daily peak exercise capacity at VAT, said method comprising:

interfering daily with the conversion of cGMP to 5'-GMP in the Fontan patient to induce daily peak venous vasodilation to achieve daily peak venous capacitance in the Fontan patient to achieve daily peak oxygen consumption by the Fontan patient so that, whenever the Fontan patient exercises, the Fontan patient can achieve peak oxygen consumption and exercise capacity at VAT.

34. A daily method of potentiating the nitric oxide –stimulated cyclic guanosine monophosphate (cGMP) signal in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to induce venous vasodilation in the patient to increase the patient's venous capacitance to enable the patient to

increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to daily improve the patient's exercise capacity at VAT, said method comprising:

potentiating daily the cGMP signal in a patient to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to daily improve the patient's exercise capacity at VAT.

35. A daily method of inhibiting cyclic guanosine monophosphate (cGMP) degradation in a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to induce venous vasodilation in the patient to increase the patient's venous capacitance to enable the patient to increase oxygen consumption at the patient's ventilatory anaerobic threshold (VAT) to daily improve the patient's exercise capacity at VAT, said method comprising:

inhibiting daily cGMP degradation in a patient to increase the patient's venous capacitance to increase oxygen consumption by the patient at the patient's VAT to daily improve the patient's exercise capacity at VAT.

36. A daily method for providing increased on demand oxygen to a patient, who is in need of oxygen and who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle and whose venous, atrial, ventricular and arterial shunts are inoperative, so that the patient in need of oxygen has increased oxygen available to achieve on demand improved exercise capacity, as measured at ventilatory anaerobic threshold (VAT), said method comprising:

enabling daily in the patient increased venous capacitance to provide daily increased transpulmonary blood flow, in which the patient's increased transpulmonary blood flow through the patient's lungs is assisted by the patient's central venous pressure, to enable the patient to achieve daily increased oxygen uptake by the patient's increased transpulmonary blood flow to provide increased on demand oxygen in the patient, so that the patient in need of oxygen has increased on demand oxygen available to achieve on demand increased exercise capacity, as measured at VAT.

37. The daily method of claim 36, wherein the patient's maximum rate of oxygen consumption measured during the patient's increasing exercise intensity (max VO2) is improved, as compared to the patient's max VO2 without said increased on demand oxygen.

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38. A daily method for providing increased on demand oxygen to a patient, who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle and whose venous, atrial, ventricular and arterial shunts are inoperative, so that the patient, when in need of increased oxygen for exercise, has sufficient oxygen to achieve on demand increased work rate at ventilatory anaerobic threshold (VAT), said method comprising:

inducing daily in the patient increased venous capacitance to provide daily increased transpulmonary blood flow in the patient, assisted by the patient's central venous pressure, to enable the patient to achieve increased oxygen uptake by the patient's lungs to provide sufficient on demand oxygen in the patient, so that the patient, when in need of oxygen for exercise, has sufficient on demand oxygen available to achieve increased work rate at the patient's VAT.

39. The daily method of claim 38, wherein the patient's maximum rate of oxygen consumption measured during the patient's increasing exercise intensity (max VO2) is improved.

40. A daily method for providing increased on demand oxygen to a patient who has a single functioning ventricle in which the patient's systemic venous return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle and whose venous, atrial, ventricular and arterial shunts are inoperative, so that the patient, when in need of oxygen, has sufficient oxygen to achieve on demand increased ventilator efficiency during exercise (VE/CO2 slope) at ventilatory anaerobic threshold (VAT), said method comprising:

inducing daily in the patient increased venous capacitance to provide daily increased transpulmonary blood flow in the patient, assisted by the patient's central venous pressure, to enable the patient to achieve increased oxygen uptake by the patient's lungs to provide sufficient on demand oxygen in the patient, so that the patient, when in need of oxygen for exercise, has sufficient on demand oxygen available to achieve increased VE/CO2 slope at the patient's VAT.

41. The daily method of claim 40, wherein the patient's oxygen consumption at peak exercise capacity is increased.

42. A method of increasing or to increase the likelihood of increasing venous capacitance in a patient, who has a single functioning ventricle in which the patient's systemic venous

return is connected directly to the pulmonary arteries without the interposition of a second functioning ventricle (Fontan patient), to increase or to increase the likelihood of increasing the Fontan patient's oxygen consumption at ventilatory anaerobic threshold (VAT), said method comprising:

administering to the Fontan patient an effective daily dose of a phosphodiesterase type 5 inhibitor (PDE5i) to increase or to increase the likelihood of increasing the Fontan patient's venous capacitance to increase or to increase the likelihood of increasing the Fontan patient's oxygen consumption at VAT.

43. A method of increasing oxygen availability in a Fontan patient by both increasing peak VO2 to or near its physiological ceiling and increasing VO2 at VAT by a statistically significant amount comprising administration of an effective PDE5 inhibitor (PDE5i).

44. The method of claim 43 where in the PDE5i is udenafil or a pharmacologically acceptable salt thereof.

45. A method of treating SVHD in a patient who has had a Fontan procedure by improving exercise capacity at both VAT and peak VO_2 comprising administering an effective amount of an effective PDE5 inhibitor (PDE5i).

46. The method of claim 45 wherein the PDE5i is udenafil or a pharmacologically acceptable salt thereof.

47. A method of improving exercise capacity in a Fontan patient by both increasing peak VO2 to or near its physiological ceiling and increasing VO2 at VAT by a statistically significant amount comprising administering an effective PDE5 inhibitor (PDE5i).

48. The method of claim 47 where in the PDE5i is udenafil or its pharmacologically acceptable salt.

49. The method according to any one of claims 1 to 19, wherein said method increases the Fontan patient's oxygen saturation.

50. The method according to any one of claims 1 to 19, wherein said method decreases the Fontan patient's diastolic blood pressure.

51. The method according to any one of claims 1 to 19, wherein said method results in beneficial effects for the Fontan patient comprising decreasing the rate of deterioration of cardiovascular efficiency in the Fontan patient.

52. The method according to any one of claims 1 to 19, wherein the udenafil or its pharmaceutically acceptable salt is administered in a daily dose comprising 87.5 mg of udenafil or its pharmacologically acceptable salt, administered twice daily.

53. A pharmaceutical composition comprising the composition of Table 11.

54. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle to improve ventricular performance of the SVHD patient's single functioning ventricle, wherein the SVHD patient is in need of the treatment to improve ventricular performance of the SVHD patient's single functioning ventricle, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the ventricular performance of the SVHD patient's single functioning ventricle.

55. The method of claim 54, wherein the SVHD patient's ventricular performance is measured by the SVHD patient's myocardial performance index (MPI).

56. The method of claim 55, wherein said administration step comprises:

administering 87.5 mg of udenafil or a pharmaceutically acceptable salt thereof twice daily to administer said effective amount of udenafil to the SVHD patient.

57. The method of claim 56, wherein said method results in minimal or no side effects caused to the SVHD patient.

58. The method of claim 54, wherein the effective amount udenafil or a pharmaceutically acceptable salt thereof ranges from about 125 mg to about 175 mg.

59. The method of claim 54, wherein the effective amount of udenafil or a pharmaceutically acceptable salt thereof is about 175 mg.

60. The method of claim 54, wherein the ventricular performance improvement is increased in the SVHD patient, as compared to ventricular performance of a single functioning ventricle in a SVHD patient who is not treated daily with the effective amount of udenafil or a pharmaceutically acceptable salt thereof.

61. The method of any one of claims 54-60, wherein the effective amount does not cause treatment-limiting side effects.

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62. The method of claim 61, wherein the treatment-limiting side effects are associated with inhibition of PDE6 and/or PDE11.

63. The method of any one of claims 54 to 62, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

64. The method of any one of claims 54 to 62, wherein the SVHD patient underwent Norwood surgery.

65. The method of any one of claims 54 to 62, wherein the SVHD patient underwent Bi-lateral Glenn surgery.

66. The method of any one of claims 54 to 62, wherein the SVHD patient is at least 6 years of age.

67. The method of any one of claims 54 to 62, wherein the SVHD patient is at least 8 years of age.

68. The method of any one of claims 54 to 62, wherein the SVHD patient is at least 10 years of age.

69. The method of any one of claims 54 to 62, wherein the SVHD patient is at least 12 years of age.

70. The method of any one of claims 54 to 62, wherein the SVHD patient is an adolescent.

71. The method of any one of claims 54 to 62, wherein the SVHD patient is an adult.

72. The method of any one of claims 63 to 65, wherein the SVHD patient is at least 8 years of age.

73. The method of any one of claims 63-65, wherein the SVHD patient is at least 10 years of age.

74. The method of any one of claims 63-65, wherein the SVHD patient is at least 12 years of age.

75. The method of any one of claims 63-65, wherein the SVHD patient is an adolescent.

76. The method of any one of claims 63-65, wherein the SVHD patient is an adult.

77. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of treatment to improve ventricular performance of the single functioning ventricle as measured by myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at ventilatory anaerobic threshold (VAT), exercise capacity as measured by oxygen consumption at maximal effort or max VO_2, work rate at VAT, ventilatory equivalents of

carbon dioxide (VE/VCO_2), diastolic blood pressure at rest and/or oxygen saturation (%) at rest, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHDn patient, to improve the SVHD patient's:

(a) ventricular performance of the SVHD patient's single functioning ventricle as measured by MPI;

(b) exercise capacity as measured by oxygen consumption at VAT;

(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;

(d) work rate at VAT;

(e) VE/VCO_2 at VAT;

(f) diastolic blood pressure at rest; and

(g) oxygen saturation (%) at rest, each individually, collectively or in any combination.

78. The method of claim 77, wherein said (a), (b), (d), (e) and (f) are improved.

79. The method of claim 77, wherein said (a), (b), (d), (e) and (g) are improved.

80. The method of claim 77, wherein said (a), (b), (d), (e), (f) and (g) are improved.

81. The method of any one of claims 70-81, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

82. The method of any one of claims 70-81, wherein the SVHD patient underwent Norwood surgery.

83. The method of any one of claims 70-81, wherein the SVHD patient underwent Bi-lateral Glenn surgery.

84. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle who is in need of treatment to improve ventricular performance of the single functioning ventricle as measured by myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at ventilatory anaerobic threshold (VAT), exercise capacity as measured by oxygen consumption at maximal effort or max VO_2, work rate at VAT and ventilatory equivalents of carbon dioxide (VE/VCO_2, comprising

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the Fontan patient, to improve the SVHD patient's:

(a) Ventricular performance of the SVHD patient's single functioning ventricle as measured by MPI;

(b) exercise capacity as measured by oxygen consumption at VAT;

(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;

(d) work rate at VAT; and

(e) VE/VCO_2 at VAT, each individually, collectively or in any combination.

85. The method of claim 84, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

86. The method of claim 84, wherein the SVHD patient is a Fontan patient, who underwent Norwood surgery.

87. The method of claims 84, wherein the SVHD patient is a Fontan patient, who underwent Bi-lateral Glenn surgery.

88. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle who is in need of treatment to improve ventricular performance of the single functioning ventricle as measured by myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at ventilatory anaerobic threshold (VAT), work rate at VAT and ventilatory equivalents of carbon dioxide (VE/VCO_2, comprising

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the SVHD patient's:

(a) Ventricular performance of the SVDHD patient's single functioning ventricle as measured by MPI;

(b) exercise capacity as measured by oxygen consumption at VAT;

(c) work rate at VAT; and

(d) VE/VCO_2 at VAT, each individually, collectively or in any combination.

89. The method of claim 88, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

90. The method of claim 88, wherein the SVHD patient underwent Norwood surgery.

91. The method of claims 84, wherein the SVHD patient underwent Bi-lateral Glenn surgery.

92. A method of improving myocardial performance index (MPI) in a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of improvement in the MPI, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the SVHD patient's MPI.

93. The method of claim 92, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

94. The method of claim 92, wherein the SVHD patient underwent Norwood surgery.

95. The method of claim 92, wherein the SVHD patient underwent Bi-lateral Glenn surgery.

96. The method of any one of claims 92-95, wherein the MPI is measured by pulsed-wave tissue Doppler echocardiography (TDE).

97. The method of any one of claims 92-95, wherein said method includes the further step of:

using pulsed-wave tissue Doppler echocardiography (TDE) to measure the MPI.

98. A method of improving cardiac output in a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of improvement in cardiac output, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the SVHD patient's cardiac output.

99. The method of claim 98, wherein the SVHD patient's cardiac output is measured by myocardia performance index (MPI).

100. The method of claim 99, wherein the MPI is measured by pulsed-wave tissue Doppler echocardiography (TDE).

101. The method of claim 98, wherein said method includes the further step of:

using pulsed-wave tissue Doppler echocardiography (TDE) to measure the MPI.

102. The method of any one of claims 99-101, wherein the SVHD patient is a Fontan patient, who underwent Fontan surgery.

103. The method of any one of claims 99-101, wherein the SVHD patient underwent Norwood surgery.

104. The method of any one of claims 99-101, wherein the SVHD patient underwent Bi-lateral Glenn surgery.

105. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle to improve ventricular performance of the SVHD patient's single functioning ventricle, wherein the SVHD patient is in need of the treatment to improve ventricular performance of the SVHD patient's single functioning ventricle, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the ventricular performance of the SVHD patient's single functioning ventricle, wherein the effective amount produces a udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient of between 300 and 700 ng/ml.

106. The method of claim 105, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml, and more preferably about -20 to about +20% of about 500 ng/ml.

107. The method of claim 105, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml

108. The method of claim 105, wherein the effective amount further produces a udenafil T_{max} pharmacokinetic blood plasma profile in the SVHD patient of between about 1 hour and 1.6 hours.

109. The method of claim 108, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

110. The method of claim 108, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

111. The method of claim 105, wherein the effective amount produces a udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient of between about 2550 and about 4150 nghr/ml.

112. The method of claim 111, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

113. The method of claim 111, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

114. The method of claim 105, wherein the effective amount produces a udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient of between about 5110 and about 8290 nghr/ml.

115. The method of claim 114, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

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116. The method of claim 114, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

117. The method of any one of claims 105-116, wherein the SVHD patient is a Fontan patient, who has undergone Fontan surgery.

118. The method of any one of claims 105-116, wherein the SVHD patient has undergone Norwood surgery.

119. The method of any one of claims 105-116, wherein the SVHD patient has undergone Bi-lateral Glenn surgery.

120. A method of treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of treatment to improve ventricular performance of the single functioning ventricle as measured by myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at ventilatory anaerobic threshold (VAT), exercise capacity as measured by oxygen consumption at maximal effort or max VO_2, work rate at VAT, ventilatory equivalents of carbon dioxide (VE/VCO_2), diastolic blood pressure at rest and/or oxygen saturation (%) at rest, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHDn patient, to improve the SVHD patient's:

(b) ventricular performance of the SVHD's patient's single functioning ventricle as measured by MPI;

(b) exercise capacity as measured by oxygen consumption at VAT;

(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;

(d) work rate at VAT;

(e) VE/VCO_2 at VAT;

(f) diastolic blood pressure at rest; and

(g) oxygen saturation (%) at rest, each individually, collectively or in any combination;

wherein, the effective amount produces a udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient of between 300 and 700 ng/ml.

121. The method of claim 120, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml, and more preferably about -20 to about +20% of about 500 ng/ml.

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122. The method of claim 120, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

123. The method of claim 120, wherein the effective amount further produces a udenafil T_{max} pharmacokinetic blood plasma profile in the SVHD patient of between about 1 hour and 1.6 hours.

124. The method of claim 123, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

125. The method of claim 123, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

126. The method of claim 120, wherein the effective amount produces a udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient of between about 2550 and about 4150 nghr/ml.

127. The method of claim 126, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

128. The method of claim 126, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

129. The method of claim 120, wherein the effective amount produces a udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient of between about 5110 and about 8290 nghr/ml.

130. The method of claim 129, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

131. The method of claim 129, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

132. The method of any one of claims 120-131, wherein the SVHD patient is a Fontan patient, who has undergone Fontan surgery.

133. The method of any one of claims 120-131, wherein the SVHD patient has undergone Norwood surgery.

134. The method of any one of claims 120-131, wherein the SVHD patient has undergone Bi-lateral Glenn surgery.

135. A method of improving myocardial performance index (MPI) in a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of improvement in the MPI, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the SVHD patient's MPI, wherein, the effective amount produces a udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient of between 300 and 700 ng/ml.

136. The method of claim 135, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml, and more preferably about -20 to about +20% of about 500 ng/ml.

137. The method of claim 135, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

138. The method of claim 135, wherein the effective amount further produces a udenafil T_{max} pharmacokinetic blood plasma profile in the SVHD patient of between about 1 hour and 1.6 hours.

139. The method of claim 138, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

140. The method of claim 138, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

141. The method of claim 135, wherein the effective amount produces a udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient of between about 2550 and about 4150 nghr/ml.

142. The method of claim 141, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

143. The method of claim 141, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

144. The method of claim 135, wherein the effective amount produces a udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient of between about 5110 and about 8290 nghr/ml.

145. The method of claim 144, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

146. The method of claim 144, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

147. The method of any one of claims 135-146, wherein the SVHD patient is a Fontan patient, who has undergone Fontan surgery.

148. The method of any one of claims 135-146, wherein the SVHD patient has undergone Norwood surgery.

149. The method of any one of claims 145-146, wherein the SVHD patient has undergone Bi-lateral Glenn surgery.

150. A method of improving cardiac output in a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of improvement in cardiac output, comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the SVHD patient to improve the SVHD patient's cardiac output, wherein, the effective amount produces a udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient of between 300 and 700 ng/ml.

151. The method of claim 150, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml, and more preferably about -20 to about +20% of about 500 ng/ml.

152. The method of claim 150, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

153. The method of claim 150, wherein the effective amount further produces a udenafil T_{max} pharmacokinetic blood plasma profile in the SVHD patient of between about 1 hour and 1.6 hours.

154. The method of claim 153, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

155. The method of claim 153, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

156. The method of claim 150, wherein the effective amount produces a udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient of between about 2550 and about 4150 nghr/ml.

157. The method of claim 156, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

158. The method of claim 156, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

159. The method of claim 150, wherein the effective amount produces a udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient of between about 5110 and about 8290 nghr/ml.

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160. The method of claim 159, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

161. The method of claim 159, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

162. The method of any one of claims 150-161, wherein the SVHD patient is a Fontan patient, who has undergone Fontan surgery.

163. The method of any one of claims 150-161, wherein the SVHD patient has undergone Norwood surgery.

164. The method of any one of claims 150-161, wherein the SVHD patient has undergone Bi-lateral Glenn surgery.

165. A pharmaceutical composition for oral administration for treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle, wherein the SVHD patient is in need of treatment to improve ventricular performance of the single functioning ventricle as measured by myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at ventilatory anaerobic threshold (VAT), exercise capacity as measured by oxygen consumption at maximal effort or max VO_2, work rate at VAT, ventilatory equivalents of carbon dioxide (VE/VCO_2), diastolic blood pressure at rest and/or oxygen saturation (%) at rest, said pharmaceutical composition comprising

an effective amount of udenafil or a pharmaceutically acceptable salt thereof, whereby, when said oral pharmaceutical composition is orally administered to the SVHD patient daily, the effective amount of udenafil produces in the SVHD patient a udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient of between 300 and 700 ng/ml and at least one or more of the following in the SVHD patient is improved:

(a) ventricular performance of the SVHD's patient's single functioning ventricle as measured by MPI;
(b) exercise capacity as measured by oxygen consumption at VAT;
(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;
(d) work rate at VAT;
(e) VE/VCO_2 at VAT;
(f) diastolic blood pressure at rest; and
(g) oxygen saturation (%) at rest.

166. The oral pharmaceutical composition of claim 165, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about 500 ng/ml.

167, The oral pharmaceutical composition of claim 166, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml.

168. The oral pharmaceutical composition of claim 166, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

169. The oral pharmaceutical composition of claim 165, wherein the effective amount further produces a udenafil T_{max} pharmacokinetic blood plasma profile in the SVHD patient of between about 1 hour and 1.6 hours.

170. The oral pharmaceutical composition of claim 169, wherein the udenafil T_{max} is about 1.3 hr.

171. The oral pharmaceutical composition of claim 170, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

172. The oral pharmaceutical composition of claim 170, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

173. The oral pharmaceutical composition of claim 165, wherein the effective amount produces a udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient of between about 2550 and about 4150 nghr/ml.

174. The oral pharmaceutical composition of claim 173, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about 3350 nghr/ml.

175. The oral pharmaceutical composition of claim 174, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

176. The oral pharmaceutical composition of claim 174, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

177. The oral pharmaceutical composition of claim 165, wherein the effective amount produces a udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient of between about 5110 and about 8290 nghr/ml.

178. The oral pharmaceutical composition of claim 177, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about 6701 nghr/ml.

179. The oral pharmaceutical composition of claim 178, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

180. The oral pharmaceutical composition of claim 178, wherein the udenafil AUC_{0-24} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

181. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is a Fontan patient, who has undergone Fontan surgery.

182. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient has undergone Norwood surgery.

183. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient has undergone Bi-lateral Glenn surgery.

184. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is at least 6 years of age.

185. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is at least 8 years of age.

186. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is at least 10 years of age.

187. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is at least 12 years of age.

188. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is an adolescent.

189. The oral pharmaceutical composition of any one of claims 165-180, wherein the SVHD patient is an adult.

190. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is at least 6 years of age.

191. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is at least 8 years of age.

192. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is at least 10 years of age.

193. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is at least 12 years of age.

194. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is an adolescent.

195. The oral pharmaceutical composition of claim 181, wherein the SVHD patient is an adult.

196. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is at least 6 years of age.

197. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is at least 8 years of age.

198. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is at least 10 years of age.

199. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is at least 12 years of age.

200. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is an adolescent.

201. The oral pharmaceutical composition of claim 182, wherein the SVHD patient is an adult.

202. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is at least 6 years of age.

203. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is at least 8 years of age.

204. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is at least 10 years of age.

205. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is at least 12 years of age.

206. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is an adolescent.

207. The oral pharmaceutical composition of claim 183, wherein the SVHD patient is an adult.

208. The method of treating a single ventricular heart disease (SVHD) patient who has undergone Fontan surgery (Fontan patient), to maintain, produce a minimal decrease in, or increase ventricular performance comprising administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the patient.

209. The method of claim 208, wherein said method comprises minimizing or producing no decrease in ventricular performance over time.

210. The method of claim 208, wherein the PDE5 inhibitor is preferably udenafil or a pharmaceutically acceptable salt thereof.

211. The method of any one of claims 1 to 19, wherein said method improves the Fontan patient's myocardial performance index (MPI).

212. A pharmaceutical composition for oral administration for treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle for improving the SVHD patient's myocardial performance index (MPI), wherein the SVHD patient is in need of treatment with the oral pharmaceutical composition to improve the SVHD patient's MPI, said pharmaceutical composition comprising:

an effective amount of udenafil or a pharmaceutically acceptable salt thereof, whereby, when said oral pharmaceutical composition is orally administered to the SVHD patient daily to improve the SVHD patient's MPI, the effective amount of udenafil produces in the SVHD patient a udenafil pharmacokinetic plasma profile, wherein the udenafil pharmacokinetic plasma profile is selected from a group of udenafil pharmacokinetic plasma profiles consisting of a C_{max} between 300 and 700 ng/ml, a T_{max} between 1 and 1.6 hr, an AUC_{τ} between 2550 and 4150 nghr/ml or more, and an AUC_{0-24} between 5110 and 8290 nghr/ml, individually, collectively or in any combination thereof .

213. The oral pharmaceutical composition of claim 212, wherein the C_{max} is about 500 ng/ml.

2140. The oral pharmaceutical composition of claim 213, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml.

215. The oral pharmaceutical composition of claim 213, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

216. The pharmaceutical composition of claim 2128, wherein the T_{max} is about 1.3 hr.

273. The oral pharmaceutical composition of claim 216, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

218. The oral pharmaceutical composition of claim 216, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

219. The oral pharmaceutical composition of claim 212, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is 3350 nghr/ml.

220. The oral pharmaceutical composition of claim 219, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

221. The oral pharmaceutical composition of claim 219, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

222. The pharmaceutical composition of claim 212, wherein the AUC_{0-24} is about 6701 nghr/ml.

223. The oral pharmaceutical composition of claim 222, wherein the udenafil AUC_τ pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

224. The oral pharmaceutical composition of claim 222, wherein the udenafil AUC_τ pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

225. The oral pharmaceutical composition of anyone of claims 212-224, wherein the SVHD patient is a Fontan patient, who had Fontan surgery.

226. A method of treating a single ventricular heart disease (SVHD) patient who has undergone Fontan surgery (Fontan patient), to improve ventricular performance, maintain ventricular performance, or decrease the rate of decline of ventricular performance, comprising administering, preferably daily, an effective amount of an effective PDE5 inhibitor to the patient.

227. A method of treating a single ventricular heart disease (SVHD) patient who has undergone Fontan surgery (Fontan patient), comprising:

administering daily an effective amount of udenafil or a pharmaceutically acceptable salt thereof to the Fontan patient, to improve the SVHD patient's:

(a) ventricular performance of the SVHD patient's single ventricle as measured by MPI;

(b) exercise capacity as measured by oxygen consumption at anaerobic threshold (VAT);

(c) exercise capacity as measured by oxygen consumption at maximal effort or max VO_2;

(d) work rate at VAT;

(e) ventilatory equivalents of carbon dioxide (VE/VCO_2) at VAT;

(f) diastolic blood pressure at rest; and/or

(g) oxygen saturation (%) at rest; including (a) through (g) each individually, collectively or in any combination.

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228. A pharmaceutical composition for oral administration for treating a single ventricular heart disease (SVHD) patient who has a single functioning ventricle for improving certain markers of the SVHD patient's, wherein the markers include myocardial performance index (MPI), exercise capacity as measured by oxygen consumption at anaerobic threshold (VAT), work rate at VAT and VE/VCO_2 at VAT, wherein the SVHD patient is in need of treatment with the oral pharmaceutical composition to improve the SVHD patient's markers, said pharmaceutical composition comprising:

an effective amount of udenafil or a pharmaceutically acceptable salt thereof, whereby, when said oral pharmaceutical composition is orally administered to the SVHD patient daily to improve the SVHD patient's markers, the effective amount of udenafil produces in the SVHD patient a udenafil pharmacokinetic plasma profile, wherein the udenafil pharmacokinetic plasma profile is selected from a group of udenafil pharmacokinetic plasma profiles consisting of a C_{max} between 300 and 700 ng/ml, a T_{max} between 1 and 1.6 hr, an AUC_{τ} between 2550 and 4150 nghr/ml or more, and an AUC_{0-24} between 5110 and 8290 nghr/ml, individually, collectively or in any combination thereof .

229. The oral pharmaceutical composition of claim 228, wherein the C_{max} is about 500 ng/ml.

230. The oral pharmaceutical composition of claim 229, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 500 ng/ml.

231. The oral pharmaceutical composition of claim 229, wherein the udenafil C_{max} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 500 ng/ml.

232. The pharmaceutical composition of claim 228, wherein the T_{max} is about 1.3 hr.

233. The oral pharmaceutical composition of claim 232, wherein the udenafil T_{max} is about -20 to about +25% of about 1.3 hr.

234. The oral pharmaceutical composition of claim 232, wherein the udenafil T_{max} is about -20 to about +20% of about 1.3 hr.

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235. The oral pharmaceutical composition of claim 228, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is 3350 nghr/ml.

236. The oral pharmaceutical composition of claim 235, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 3350 nghr/ml.

237. The oral pharmaceutical composition of claim 235, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 3350 nghr/ml.

238. The pharmaceutical composition of claim 228, wherein the AUC_{0-24} is about 6701 nghr/ml.

239. The oral pharmaceutical composition of claim 238, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +25% of about 6701 nghr/ml.

240. The oral pharmaceutical composition of claim 238, wherein the udenafil AUC_{τ} pharmacokinetic blood plasma profile in the SVHD patient is about -20 to about +20% of about 6701 nghr/ml.

241. The oral pharmaceutical composition of any one of claims 228-240, wherein the SVHD patient is a Fontan patient, who had Fontan surgery.

242. The oral pharmaceutical composition of any one of claims 228-240, wherein the markers of the SVHD patient further includes exercise capacity as measured by oxygen consumption at maximal effort or max VO_2.

243. The oral pharmaceutical composition of any one of claims 228-240, wherein the markers of the SVHD patient further includes exercise capacity as measured by oxygen

consumption at maximal effort or max VO_2, and wherein the SVHD patient is a Fontan patient, who had Fontan surgery.

244. The oral pharmaceutical composition of any one of claims 228-240, wherein the markers of the SVHD patient further includes MPI.

245. The oral pharmaceutical composition of any one of claims 228-240, wherein the markers of the SVHD patient further includes MPI, and wherein the SVHD patient is a Fontan patient, who had Fontan surgery.

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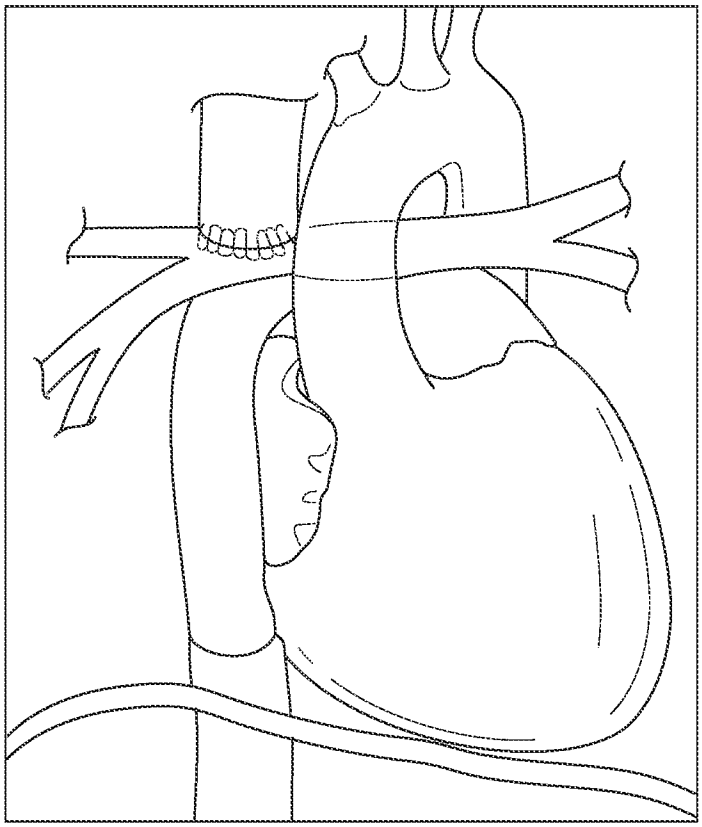
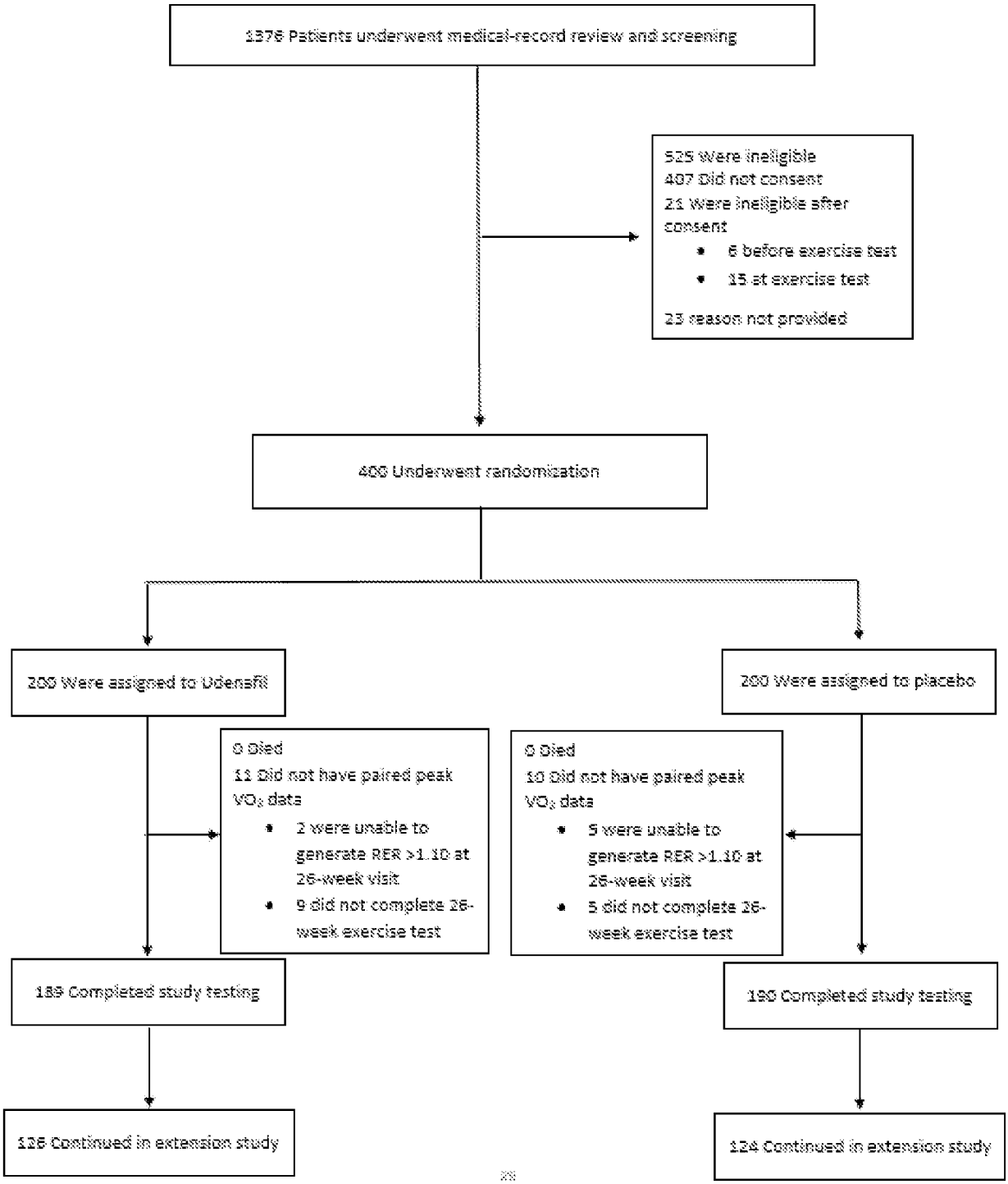


FIG. 1A

FIG. 1B


1378 Patients underwent medical-record review and screening
525 Were ineligible
407 Did not consent
21 Were ineligible after consent
• 6 before exercise test
• 15 at exercise test
23 reason not provided
400 Underwent randomization
200 Were assigned to Udenafil
200 Were assigned to placebo
0 Died
12 Did not have paired peak VO_2 data
• 2 were unable to generate RER >1.10 at 26-week visit
• 9 did not complete 26-week exercise test
0 Died
10 Did not have paired peak VO_2 data
• 5 were unable to generate RER >1.10 at 26-week visit
• 5 did not complete 26-week exercise test
188 Completed study testing
190 Completed study testing
126 Continued in extension study
124 Continued in extension study

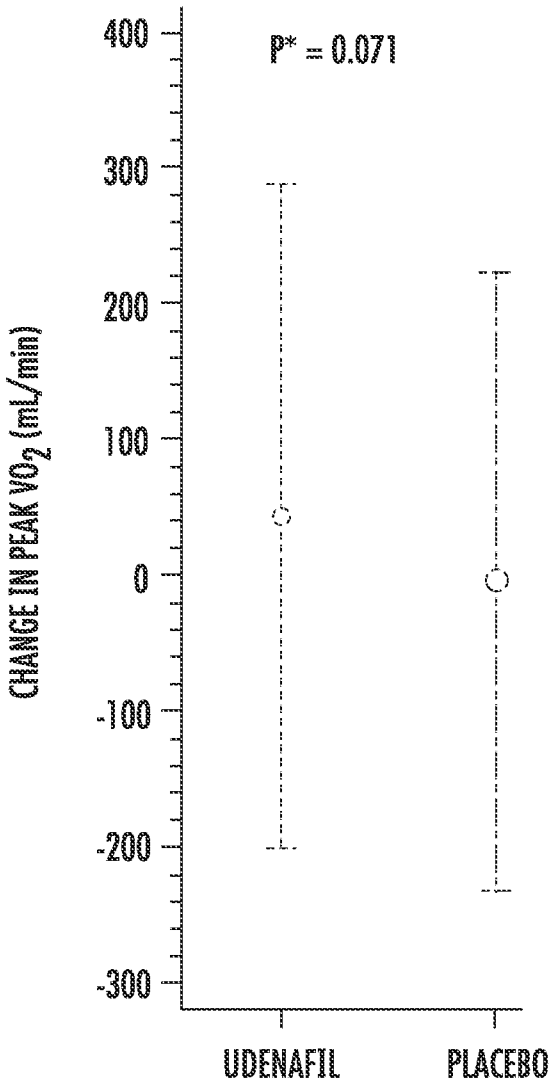

P* = 0.071
400
300
200
100
0
-100
-200
-300
CHANGE IN PEAK VO_2 (mL/min)
UDENAFIL
PLACEBO

FIG. 2A

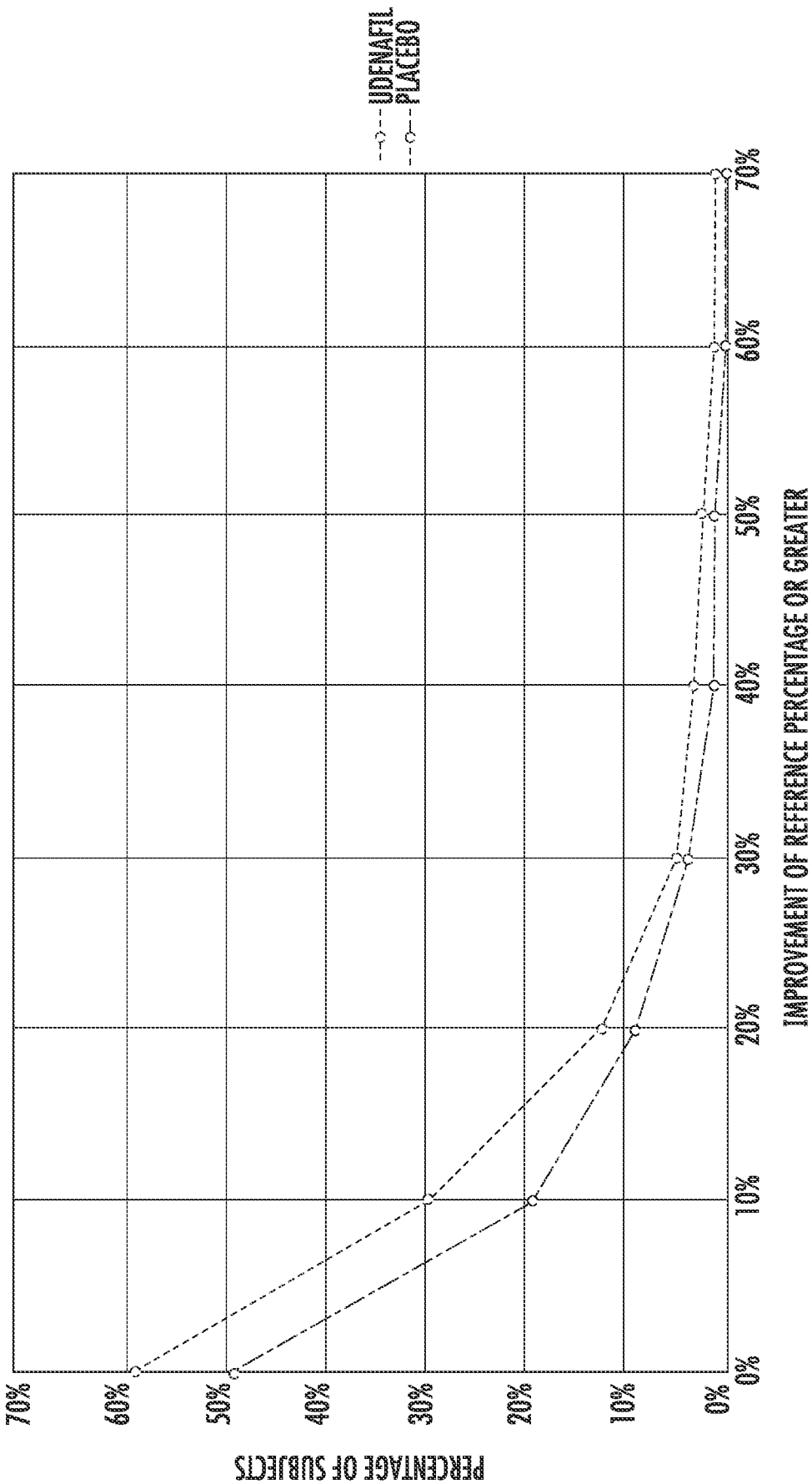

UDENAFIL
PLACEBO
PERCENTAGE OF SUBJECTS
0%
10%
20%
30%
40%
50%
60%
70%
IMPROVEMENT OF REFERENCE PERCENTAGE OR GREATER

FIG. 2B

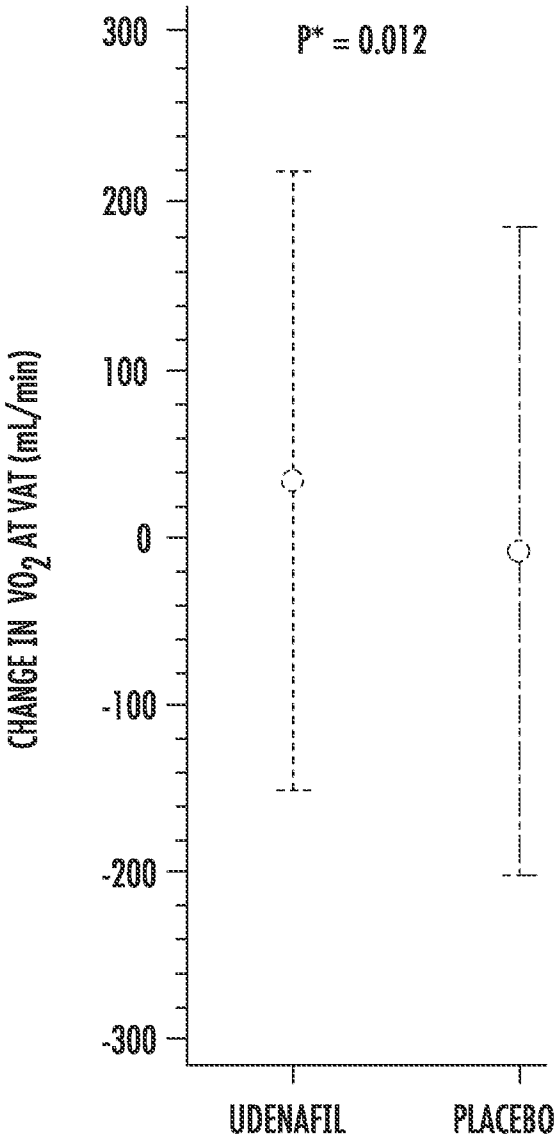

P* = 0.012
300
200
100
0
-100
-200
-300
CHANGE IN VO_2 AT VAT (mL/min)
UDENAFIL
PLACEBO

FIG. 3A

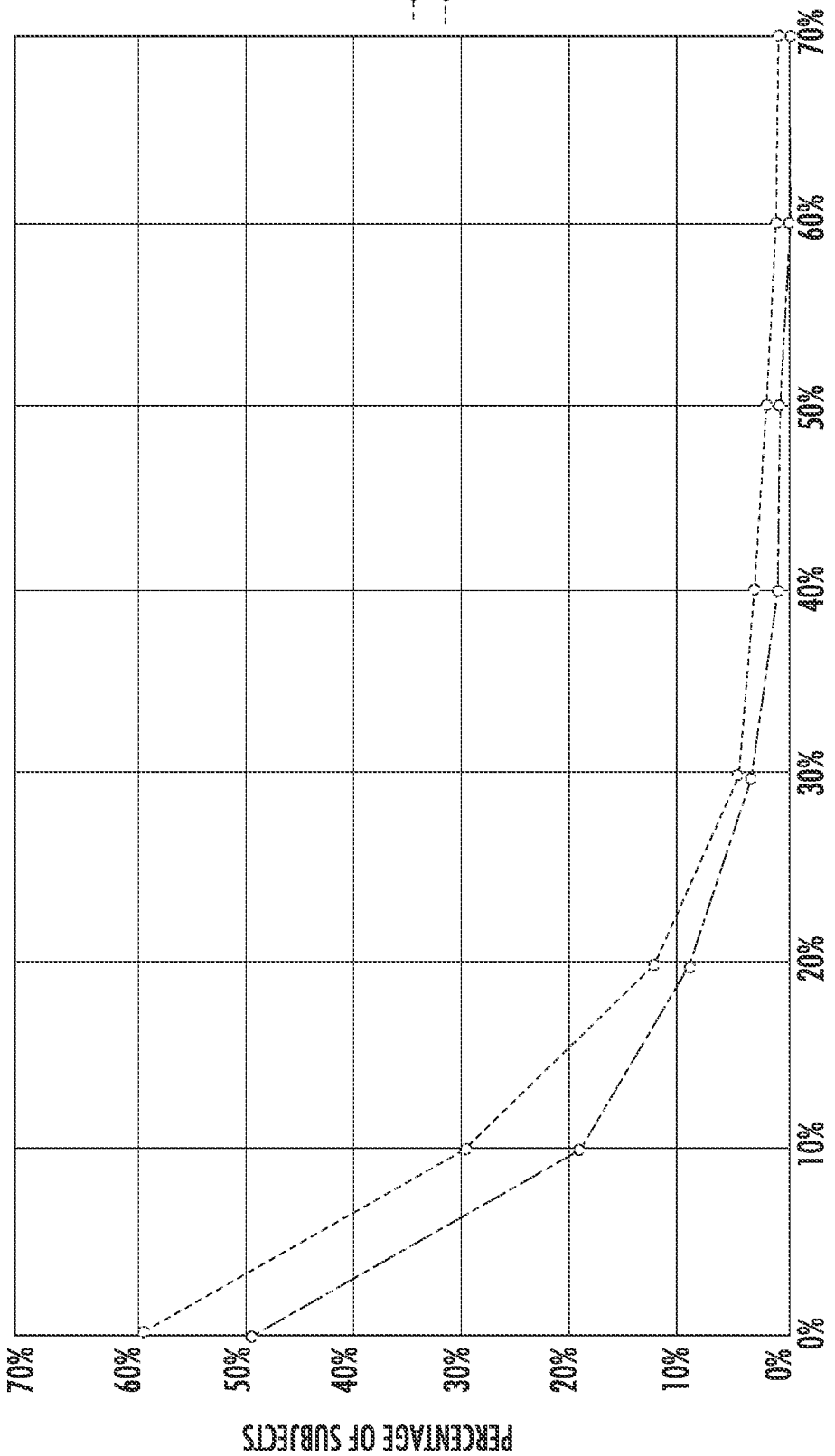

UDENAFIL
PLACEBO
PERCENTAGE OF SUBJECTS
0%
10%
20%
30%
40%
50%
60%
70%
IMPROVEMENT OF REFERENCE PERCENTAGE OR GREATER
0%
10%
20%
30%
40%
50%
60%
70%

FIG. 3B

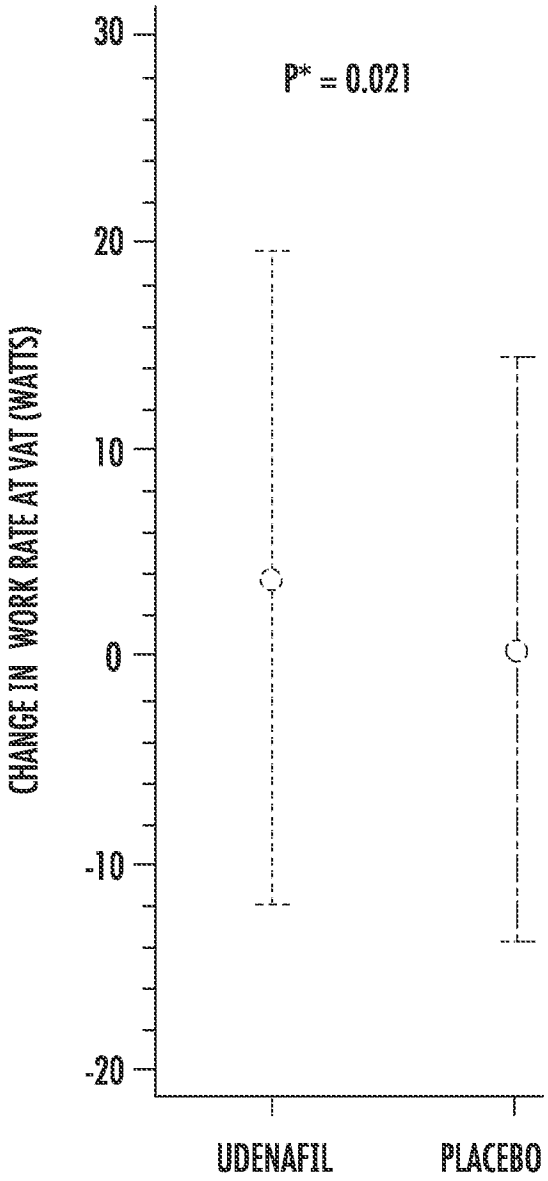

30
20
10
0
-10
-20
P* = 0.021
CHANGE IN WORK RATE AT VAT (WATTS)
UDENAFIL
PLACEBO

FIG. 4A

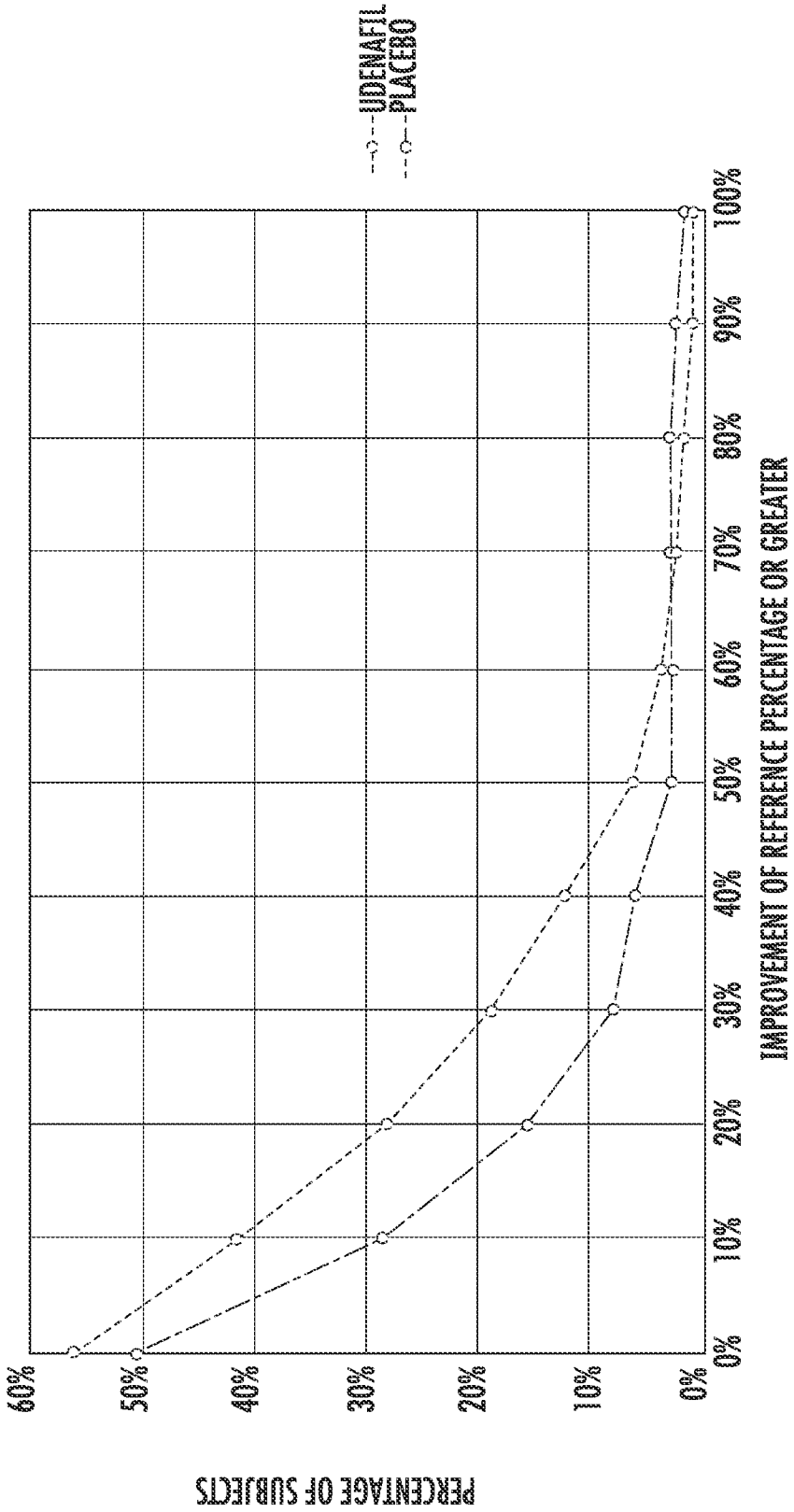

UDENAFIL
PLACEBO
PERCENTAGE OF SUBJECTS
60%
50%
40%
30%
20%
10%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
IMPROVEMENT OF REFERENCE PERCENTAGE OR GREATER

FIG. 4B

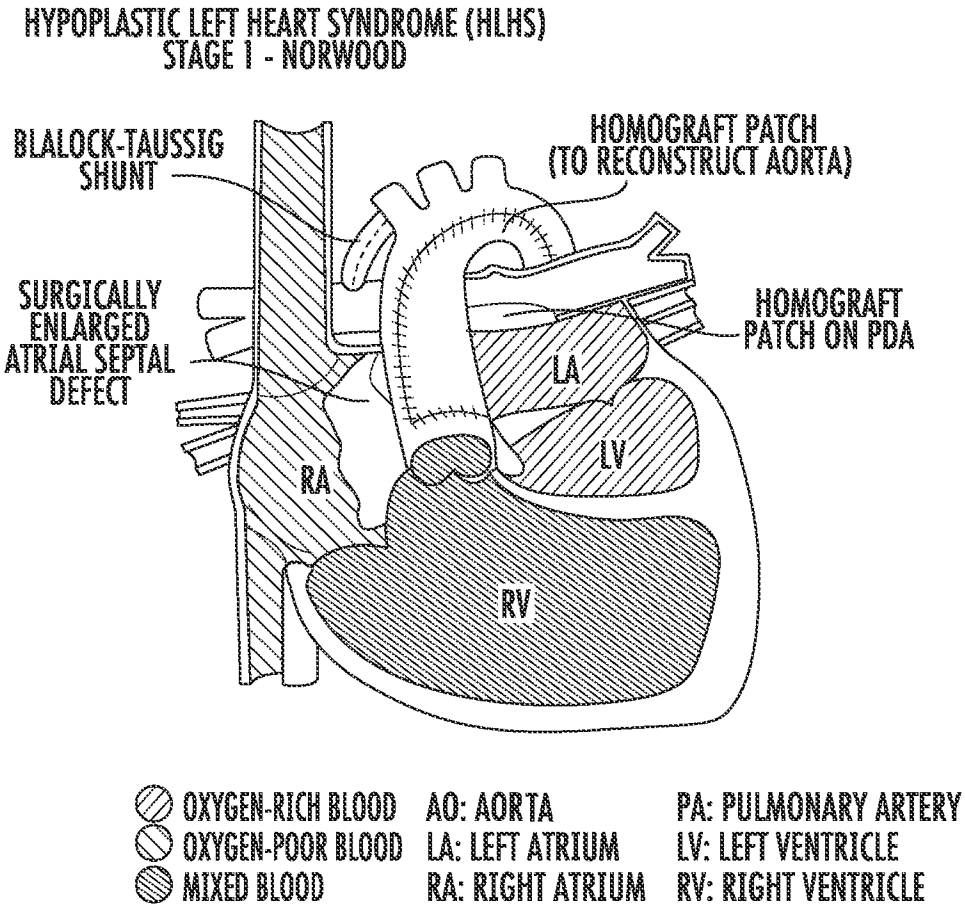

HYPOPLASTIC LEFT HEART SYNDROME (HLHS)
STAGE I - NORWOOD
BLALOCK-TAUSSIG SHUNT
HOMOGRAFT PATCH (TO RECONSTRUCT AORTA)
SURGICALLY ENLARGED ATRIAL SEPTAL DEFECT
HOMOGRAFT PATCH ON PDA
LA
LV
RA
RV
OXYGEN-RICH BLOOD
OXYGEN-POOR BLOOD
MIXED BLOOD
AO: AORTA
LA: LEFT ATRIUM
RA: RIGHT ATRIUM
PA: PULMONARY ARTERY
LV: LEFT VENTRICLE
RV: RIGHT VENTRICLE

FIG. 5

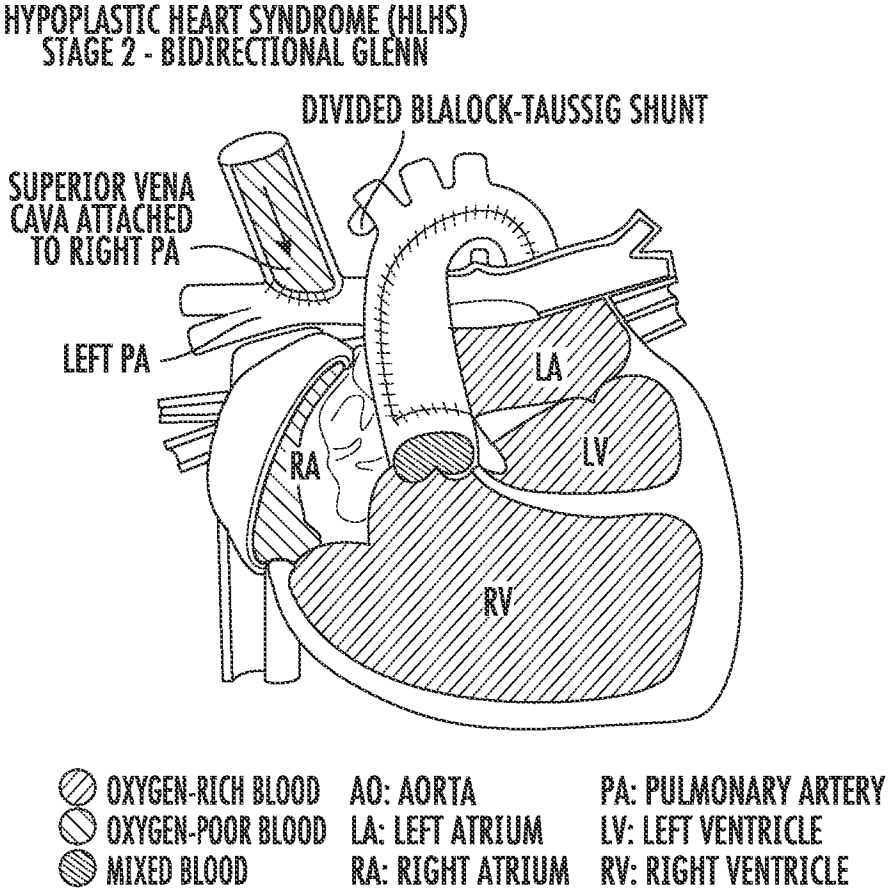

HYPOPLASTIC HEART SYNDROME (HLHS)
STAGE 2 - BIDIRECTIONAL GLENN
DIVIDED BLALOCK-TAUSSIG SHUNT
SUPERIOR VENA CAVA ATTACHED TO RIGHT PA
LEFT PA
LA
LV
RA
RV
OXYGEN-RICH BLOOD
OXYGEN-POOR BLOOD
MIXED BLOOD
AO: AORTA
LA: LEFT ATRIUM
RA: RIGHT ATRIUM
PA: PULMONARY ARTERY
LV: LEFT VENTRICLE
RV: RIGHT VENTRICLE

FIG. 6

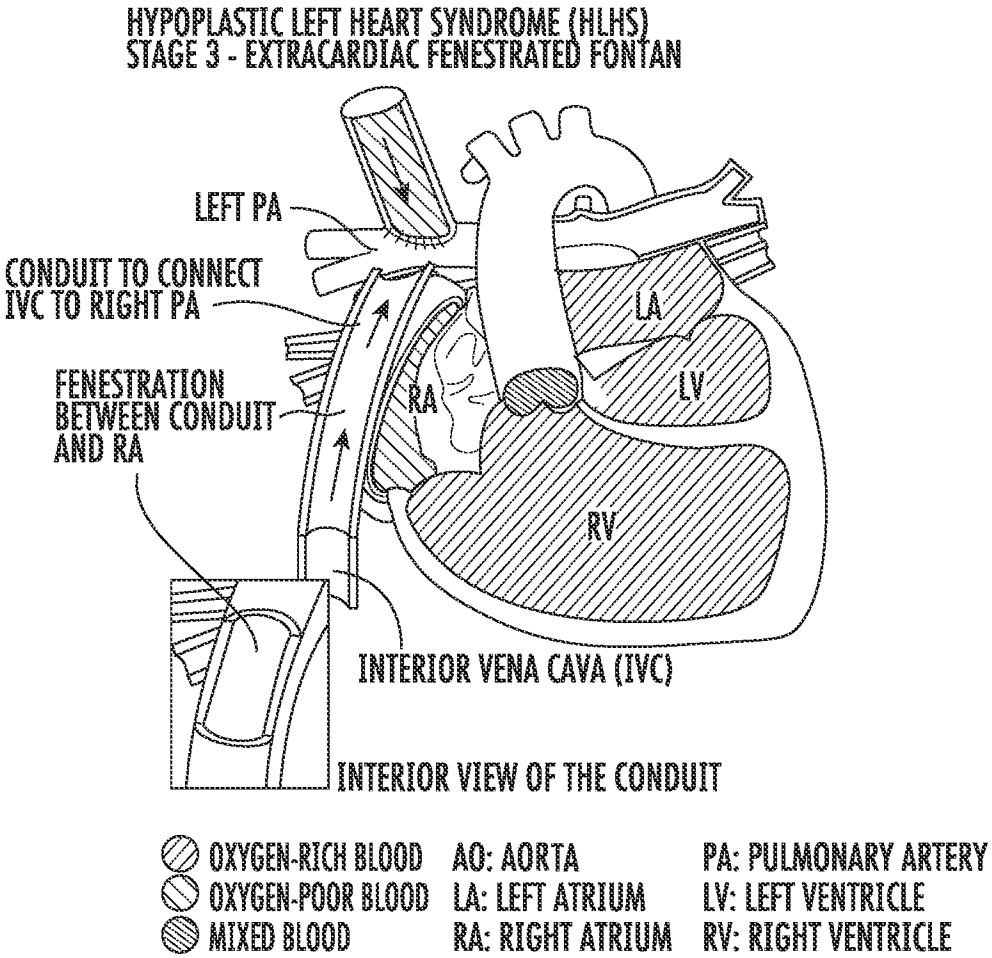

HYPOPLASTIC LEFT HEART SYNDROME (HLHS)
STAGE 3 - EXTRACARDIAC FENESTRATED FONTAN
LEFT PA
CONDUIT TO CONNECT IVC TO RIGHT PA
FENESTRATION BETWEEN CONDUIT AND RA
LA
LV
RA
RV
INTERIOR VENA CAVA (IVC)
INTERIOR VIEW OF THE CONDUIT
OXYGEN-RICH BLOOD
OXYGEN-POOR BLOOD
MIXED BLOOD
AO: AORTA
LA: LEFT ATRIUM
RA: RIGHT ATRIUM
PA: PULMONARY ARTERY
LV: LEFT VENTRICLE
RV: RIGHT VENTRICLE

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/32493

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/519, 31/522; A61P 9/00 (2020.01)

CPC - A61K 31/519, 31/522; A61P 9/00

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

B. FIELDS SEARCHED

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

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

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.
X	US 2019/0030037 A1 (MEZZION PHARMA CO., LRD. et al.) 31 January 2019 (31.01.2019) paragraphs [0022], [0030], [0074]-[0075], [0079], [0089], [0092], [0096], [0101]	1-25, 36-37, 54-62, 77-81, 88-89
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Y		82, 83, 90, 91
Y	US 2008/0021368 A1 (DASI, LP et al.) 24 January 2008 (24.01.2008) paragraphs [0033]-[0037]	82, 83, 90, 91
A	US 2005/0272741 A1 (RYCHIK, J et al.) 08 December 2005 (08.12.2005) see entire document	1-25, 36-37, 54-62, 77-83, 88-91

☐ 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
"D" document cited by the applicant in the international application
"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
08 September 2020 (08.09.2020)	25 SEP 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/32493

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.: 26-35, 38-53, 84-87 and 92-245
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:

Regarding claims 26-35, 38-53, 84-87 and 92-245, see form ISA/224 mailed on 09 July 2020 (09.07.2020). PCT Article 6 states that the claims shall be clear and concise. Claims 26-35, 38-53, 84-87 and 92-245 do not meet this requirement, even assuming for the sake of argument that the individual claims are clear and concise in themselves, because the lack of clarity of the claims as a whole arises from the lack of conciseness.

3. ☒ Claims Nos.: 63-76
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:

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.:

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.