

**METHODS FOR TREATING PULMONARY ARTERIAL HYPERTENSION
WITH ACTIVIN RECEPTOR TYPE IIA (ACTRIIA) PROTEINS AND/OR
VARIANTS THEREOF**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 63/607,422, filed December 7, 2023. The foregoing application is incorporated herein by reference.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The contents of the electronic sequence listing (1848179-0002-173-WO1_SL.xml; Size: 36,788 bytes; and Date of Creation: December 5, 2024) are herein incorporated by reference in their entirety

FIELD OF THE INVENTION

[0003] This invention relates to therapies useful for the treatment of pulmonary arterial hypertension. In particular, the invention relates to a method for treating pulmonary arterial hypertension which comprises administering to a patient in need thereof an ActRIIA-Fc fusion protein or a variant thereof, using the dosage regimens specified herein.

BACKGROUND OF THE INVENTION

[0004] Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by elevated blood pressure in the pulmonary arteries, leading to progressive heart failure and reduced life expectancy. Dysregulation of signal transduction involving members of the transforming growth factor β (TGF- β) superfamily, including bone morphogenic protein receptor type II (BMPR-II), activin receptor type IIA (ActRIIA), and the ActRIIA ligands activin A, activin B, growth differentiation factor 8 (GDF8) and GDF11, has been implicated in the underlying disease pathogenesis. An imbalance between anti-proliferation signals mediated by BMPR-II and pro-proliferation signals mediated by ActRIIA and its ligands results in the vascular remodeling of pulmonary arteries.

[0005] Sotatercept, an activin receptor type IIA-Fc fusion protein, can address imbalances in activin/growth differentiation factors and the bone morphogenetic protein signaling. Sotatercept traps activin A to improve cardiopulmonary function in patients with PAH and has demonstrated reverse pulmonary arterial wall and right ventricular remodeling. A phase 3 randomized controlled trial, STELLAR (NCT04576988), demonstrated the clinical benefit of sotatercept as an add-on treatment to stable background therapy for PAH with 6-minute walking distance (6MWD) increased by 40.8 meters and time to clinical worsening reduced by 84% (hazard ratio [HR] 0.16, 95% CI 0.08-0.35). Background therapy was defined as the standard of care therapy for PAH at the time of conduct of STELLAR, including mono-, double-, or triple- therapy of some combination of endothelin receptor antagonist (ERA), phosphodiesterase type-5 (PDE-5) inhibitor, soluble guanylate cyclase (sGC) stimulator, prostaglandin I2 (PGI2) analogue, and PGI2 agonist.

[0006] Throughout STELLAR, sotatercept was dosed based on the patient's individual weight (weight-based dosing). Patients were given an initial dose of 0.3 mg/kg and a second or maintenance dose of 0.7mg/kg. Use of a weight-based dosing regimen places a burden on the administering medical personal to calculate the dose before administering it. Also, sotatercept was available in lyophilized vials containing 45 mg or 65 mg; thus, if the patient did not require the total dose formulated by the administering medical personal, unused sotatercept is wasted.

[0007] Therefore, it is desirable to move away from patient weight-based dosing to patient weight band dosing (dosing based on comparing the patient's weight to a list of pre-determined weight bands and selecting the dose that is pre-selected for the weight band that corresponds to the patient's weight instead of dosing based on each individual's specific weight). Such dosing will preserve safety and efficacy while offering more convenience for patients and medical personal by simplifying dosing, saving time and removing opportunities for error. Also, weight-band dosing can contribute to less drug wastage and reduction in drug substance supply requirements. Also, weight-band dosing could facilitate further patient improvements like the use of an autoinjector by either medical personal or for self-administration.

SUMMARY OF THE INVENTION

[0008] The present disclosure provides therapies useful for the treatment of pulmonary arterial hypertension. In particular, the invention relates to a method for

treating pulmonary arterial hypertension which comprises administering to a patient in need thereof an ActRIIA-Fc fusion protein or a variant thereof, using the dosage regimens specified herein.

In one aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine (e.g. SEQ ID NO:41), wherein the initial dose is 15 mg or a factor of 15 mg and the dose administered to the patient is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial dose, the dose that is pre-selected for the weight band that corresponds to the patient's weight.

[0009] In certain embodiments, the initial dose is 15 mg, 30 mg or 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41.

[0010] In certain embodiments of the dosing regimens described herein the weight band is selected from <50 kg, [50-75) kg, [75-100) kg, [100-125) and >125 kg, wherein the initial dose of the ActRIIA-Fc fusion protein or the ActRIIA-Fc fusion protein variant is selected from one the following:

- (a) 15 mg for a patient weighing less than 50 kg,
- (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,
- (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,
- (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg,

or

- (e) 45 mg for a patient weighing 125 kg or more.

[0011] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof, wherein the initial dose is as described above, wherein the method further comprises administering to the patient a maintenance dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of the ActRIIA-Fc fusion protein consisting of SEQ ID NO:41, wherein the maintenance dose is a factor of 15 and the dose administered to the patient is determined by which weight band the patient's weight falls within.

[0012] In certain embodiments, the maintenance dose is 30 mg, 45 mg, 60 mg, 75 mg or 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a

variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41.

[0013] In certain embodiments of the dosing regimens described herein, the weight band is selected from <50 kg, [50-75) kg, [75-100) kg, [100-125) kg, [125-150) kg or >150 kg, wherein the maintenance dose of the ActRIIA-Fc fusion protein or the ActRIIA-Fc fusion protein variant is selected from one the following:

- (a) 30 mg for a patient weighing less than 50 kg,
- (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,
- (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,
- (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg,
- or
- (e) 90 mg for a patient weighing 125 kg or more.

[0014] In certain embodiments of the dosing regimens described herein, the maintenance dose is administered to the patient every 3 weeks, wherein a first maintenance dose is administered 3 weeks after the initial dose.

[0015] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine (e.g. a human ActRIIA-Fc fusion protein consisting of SEQ ID NO:41) if the patient weighs less than 150 kg.

[0016] In certain embodiments, the patient is administered an initial dose of 15-45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 150 kg.

[0017] In certain embodiments, the patient is administered an initial dose of 10-20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 75 kg.

[0018] In certain embodiments, the patient is administered an initial dose of 20-30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 125 kg.

[0019] In certain embodiments, the patient is administered an initial dose of 30-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 150 kg.

[0020] In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 75 kg.

[0021] In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 50 kg.

[0022] In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [75-100) kg.

[0023] In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [100-125) kg.

[0024] In certain embodiments, wherein the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [125-150) kg.

[0025] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 20-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, if the patient weighs less than 150kg.

[0026] In certain embodiments, the patient is administered a maintenance dose of 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 50kg.

[0027] In certain embodiments, the patient is administered a maintenance dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 75kg.

[0028] In certain embodiments, the patient is administered a maintenance dose of 50-70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 100kg.

[0029] In certain embodiments, the patient is administered a maintenance dose of 70-80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 125kg.

[0030] In certain embodiments, the patient is administered a maintenance dose of 80-90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 150kg.

[0031] In certain embodiments, the patient is administered a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs less than 50kg.

[0032] In certain embodiments, the patient is administered a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [50-75) kg.

[0033] In certain embodiments, the patient is administered a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [75-100) kg.

[0034] In certain embodiments, the patient is administered a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [100-125) kg.

[0035] In certain embodiments, the wherein the patient is administered a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a

variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs between [125-150) kg.

[0036] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, if the patient weighs more than or equal to 125kg.

[0037] In certain embodiments, the patient is administered an initial dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs more than or equal to 150kg.

[0038] In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs more than or equal to 125kg.

[0039] In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs more than or equal to 150kg.

[0040] In certain embodiments, the patient is administered a maintenance dose of 50-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, if the patient weighs more than or equal to 125kg.

[0041] In certain embodiments, the patient is administered a maintenance dose of 75-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs more than or equal to 125kg.

[0042] In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, and the patient weighs more than or equal to 150kg.

[0043] In certain embodiments, the patient is administered the initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32

lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, on Day 1 and a maintenance dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, once every three weeks from Day 1.

[0044] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, on Day 1 if the patient weighs less than 50kg and administering to the patient a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant of SEQ ID NO: 32 lacking the C-terminal lysine, e.g. a variant consisting of SEQ ID NO:41, once every three weeks starting from Day 1 if the patient weighs less than 50kg.

[0045] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising of SEQ ID NO:41 on Day 1 if the patient weighs between [50-75) kg and administering to the patient a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising of SEQ ID NO:41 once every three weeks starting from Day 1 if the patient weighs between [50-75) kg.

[0046] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 on Day 1 if the patient weighs more than or equal to 75 kg and administering to the patient a maintenance dose of between 50-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 once every three weeks starting from Day 1 if the patient weighs more than or equal to 75kg.

[0047] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 on

Day 1 if the patient weighs between [75-100) kg and administering to the patient a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 once every three weeks starting from Day 1 if the patient weighs between [75-100) kg.

[0048] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 on Day 1 if the patient weighs between [100-125) kg and administering to the patient maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 once every three weeks starting from Day 1 if the patient weighs between [100-125) kg.

[0049] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 on Day 1 if the patient weighs more than or equal to 125 kg and administering to the patient a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant ActRIIA-Fc fusion protein comprising SEQ ID NO:41 once every three weeks starting from Day 1 if the patient weighs if the patient weighs more than or equal to 125kg.

[0050] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the initial dose is 15 mg or a factor of 15 mg and the initial dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial dose the dose that is pre-selected for the weight band that corresponds to the patient's weight.

[0051] In certain embodiments, the initial dose is selected from one the following pre-determined weight bands:

[0052] (a) 15 mg for a patient weighing less than 50 kg,

[0053] (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0054] (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0055] (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg,

or

[0056] (e) 45 mg for a patient weighing 125 kg or more.

[0057] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof further comprising administering to the patient a maintenance dose of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the maintenance dose is a factor of 15 mg and the maintenance dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the maintenance dose the dose that is pre-selected for the weight band that corresponds to the patient's weight, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.

[0058] In certain embodiments, the maintenance dose is selected from one the following pre-determined weight bands:

[0059] (a) 30 mg for a patient weighing less than 50 kg,

[0060] (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0061] (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0062] (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg,

or

[0063] (e) 90 mg for a patient weighing 125 kg or more.

[0064] In certain embodiments, the maintenance dose is administered to the patient every 3 weeks.

[0065] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient via subcutaneous injection.

[0066] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

[0067] In certain embodiments, the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

[0068] In certain embodiments, the initial dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

[0069] In certain embodiments, the maintenance dose(s) are each administered in a single injection.

[0070] In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in a single injection.

[0071] In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in two or more injections.

[0072] In certain embodiments, the maintenance dose is administered to the patient every 3 weeks for 72 weeks or less.

[0073] In certain embodiments, the patient is further treated with one or more additional PAH therapies. Additional PAH therapies, include, but are not limited to, phosphodiesterase-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator (sGCS), Endothelin receptor antagonist (ERA), and Prostacyclin-class therapy (prostacyclin = PCY).

[0074] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, wherein the initial dose is selected from the group consisting of:

[0075] (a) 15 mg for a patient weighing less than 50 kg,

[0076] (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0077] (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0078] (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg, and

[0079] (e) 45 mg for a patient weighing 125 kg or more.

[0080] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof further comprising administering to the patient a maintenance dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, approximately 3 weeks after the initial dose, wherein the maintenance dose is selected from the group consisting of:

[0081] (a) 30 mg for a patient weighing less than 50 kg,

[0082] (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0083] (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0084] (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg,
and

[0085] (e) 90 mg for a patient weighing 125 kg or more.

[0086] In certain embodiments, two or more maintenance doses of sotatercept are administered to the patient, with approximately three weeks between each dose.

[0087] In certain embodiments, the initial dose and/or the maintenance dose(s) of sotatercept are administered to the patient via subcutaneous injection.

[0088] In certain embodiments, the initial dose and/or the maintenance dose(s) of sotatercept are administered to the patient with an autoinjector.

[0089] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-50 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the patient weighs less than 150 kg.

[0090] In certain embodiments, the patient is administered an initial dose of 15-45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant.

[0091] In certain embodiments, the patient is administered an initial dose of 10-20 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.

[0092] In certain embodiments, the patient is administered an initial dose of 20-30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 125 kg.

[0093] In certain embodiments, the patient is administered an initial dose of 30-50 mg of a human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.

[0094] In certain embodiments, the patient is administered an initial dose of 15 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.

[0095] In certain embodiments, the patient is administered an initial dose of 15 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50 kg.

[0096] In certain embodiments, the patient is administered an initial dose of 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 75 kg up to, but not including 100 kg.

[0097] In certain embodiments, the patient is administered an initial dose of 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 100 kg up to, but not including 125 kg.

[0098] In certain embodiments, the patient is administered an initial dose of 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 125 kg up to, but not including 150 kg.

[0099] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 20-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.

[0100] In certain embodiments, the patient is administered a maintenance dose of 20-40 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50 kg.

[0101] In certain embodiments, the patient is administered a maintenance dose of 40-50 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.

[0102] In certain embodiments, the patient is administered a maintenance dose of 50-70 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 100 kg.

[0103] In certain embodiments, the patient is administered a maintenance dose of 70-80 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 125 kg.

[0104] In certain embodiments, the patient is administered a maintenance dose of 80-90 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.

[0105] In certain embodiments, the patient is administered a maintenance dose of 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50kg.

[0106] In certain embodiments, the patient is administered a maintenance dose of 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 50 kg up to, but not including 75 kg.

[0107] In certain embodiments, the patient is administered a maintenance dose of 60 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 75 kg, but not including 100 kg.

[0108] In certain embodiments, the patient is administered a maintenance dose of 75 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs 100 kg up to, but not including 125 kg.

[0109] In certain embodiments, the patient is administered a maintenance dose of 75 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs 125 kg up to, but not including 150 kg.

[0110] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the patient weighs more than or equal to 125kg.

[0111] In certain embodiments, the patient is administered an initial dose of 40-50 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.

[0112] In certain embodiments, the patient is administered an initial dose of 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.

[0113] In certain embodiments, the patient is administered an initial dose of 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.

[0114] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient further comprising administering to the patient a maintenance dose of 50-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.

[0115] In certain embodiments, the patient is administered a maintenance dose of 75-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.

[0116] In certain embodiments, the patient is administered a maintenance dose of 90 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.

[0117] In certain embodiments, the patient is administered the initial dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant and the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.

[0118] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs less than 50kg.

[0119] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1 and administering to the patient a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs [50-75) kg.

[0120] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a

sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of between 50-100 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs more than or equal to 75 kg.

[0121] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs between [75-100) kg.

[0122] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs between [100-125) kg.

[0123] In another aspect, the present disclosure provides a method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID

NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs more than or equal to 125kg.

[0124] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 is administered to the patient via subcutaneous injection.

[0125] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 is administered to the patient with an autoinjector.

[0126] In certain embodiments, the maintenance dose of the human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 is administered to the patient with an autoinjector.

[0127] In certain embodiments, the initial dose of the human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 is administered to the patient with an autoinjector.

[0128] In certain embodiments, the maintenance dose(s) are each administered in a single injection

[0129] The summary of the technology described above is non-limiting and other features and advantages of the technology will be apparent from the following detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0130] FIG. 1 shows a multi-sequence alignment of a human ActRIIA extracellular domain compared to various ActRIIA orthologs.

[0131] FIG. 2 shows predicted steady state Cavg following administration of weight-banded and weight-based (0.7 mg/kg) doses

[0132] FIG. 3 shows predicted Cavg (week 1 to week 3) following administration of weight-band based and weight-based (0.3 mg/kg) doses

DETAILED DESCRIPTION OF THE INVENTION

[0133] The present disclosure is directed to therapies useful for the treatment of pulmonary arterial hypertension. In particular, the invention relates to a method for treating pulmonary arterial hypertension which comprises administering to a patient in need thereof an ActRIIA-Fc fusion protein or a variant thereof, based on the weight band the patient falls within.

Definitions

[0134] Listed below are definitions of various terms used herein. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

[0135] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

[0136] As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0137] As used herein, the term “about” in quantitative terms refers to plus or minus 10% of the value it modifies (rounded up to the nearest whole number if the value is not sub-dividable, such as a number of molecules or nucleotides).

[0138] Certain ranges herein are enclosed in brackets or parenthesis. Ranges or numbers enclosed with brackets or a bracket are included in the ranges. Ranges or numbers enclosed with parenthesis or a parenthesis are not included in the ranges. Ranges that are not enclosed by brackets or parenthesis are inclusive of the recited endpoint and independently combinable (for example, the range of “from 50 mg to 500 mg” is inclusive of the endpoints, 50 mg and 500 mg, and all the intermediate values). The endpoints of the ranges and any values disclosed herein are not limited to the precise range or value; they are sufficiently imprecise to include values approximating these ranges and/or values.

[0139] As used herein, the term “comprising” may include the embodiments “consisting of” and “consisting essentially of.” The terms “comprise(s),” “include(s),”

“having,” “has,” “may,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that require the presence of the named ingredients/steps and permit the presence of other ingredients/steps. However, such description should be construed as also describing compositions or processes as “consisting of” and “consisting essentially of” the enumerated components, which allows the presence of only the named components or compounds, along with any acceptable carriers or fluids, and excludes other components or compounds.

[0140] As used herein “weight bands” refer to a range of weights within a series. In certain embodiments, the weight bands used herein begin at 50 kg and are established in increments of 25 kgs. For example, certain weight bands used herein are [50-75) kg, [75-100) kg, and [100-125) kg. Additionally, weight bands can include <50 kg, >125 kg and >150.

[0141] As used herein, a “patient” refers to a mammal capable of having pulmonary arterial hypertension (PAH). In preferred embodiments, the patient is a human. Therapeutic treatment can be performed to reduce the severity or the clinical effects of PAH. Those “in need of treatment” include those patients who have been diagnosed with PAH, are suspected of having PAH, or have clinical symptoms of PAH.

Activin Receptor Type IIA-Fc Fusion Proteins

[0142] ActRIIA Proteins

[0143] In certain embodiments, the present disclosure relates to ActRIIA proteins. As used herein, the term “ActRIIA” refers to a family of activin receptor type IIA (ActRIIA) proteins from any species and variants derived from such ActRIIA proteins by mutagenesis or other modification. Reference to ActRIIA herein is understood to be a reference to any one of the currently identified forms. Members of the ActRIIA family are generally transmembrane proteins, composed of a ligand-binding extracellular domain comprising a cysteine-rich region, a transmembrane domain, and a cytoplasmic domain with predicted serine/threonine kinase activity.

[0144] The term “ActRIIA protein” includes proteins comprising any naturally occurring protein of an ActRIIA family member as well as any variants thereof (including mutants, fragments, fusions, and peptidomimetic forms) that retain a useful activity. Examples of such variant ActRIIA proteins are provided throughout the present disclosure as well as in International Patent Application Publication Nos. WO 2006/012627 and WO 2007/062188, which are incorporated herein by reference in their entirety. Numbering of amino acids for all ActRIIA-related proteins described herein is

based on the numbering of the human ActRIIA precursor protein sequence provided below (SEQ ID NO: 9), unless specifically designated otherwise.

[0145] The canonical human ActRIIA precursor protein sequence is as follows:

1 MGAAAKLAFA VFLISSSGA ILGRSETQEC LFFNANWEKD
RTNQTGVEPC
51 YGDKDKRRHC FATWKNISGS IEIVKQGCWL DDINCYDRTD
CVEKKDSPEV
101 YFCCCEGNMC NEKFSYFPEM EVTQPTSNPV TPKPPYYNIL
LYSLVPLMLI
151 AGIVICAFWV YRHHKMAYPP VLVPTQDPGP PPPSPLLGLK
PLQLLEVkar
201 GRFGCVWKAQ LLNEYVAVKI FPIQDKQSWQ NEYEVYSLPG
MKHENILQFI
251 GAEKRGTSVD VDLWLITAFH EKGSLSDFLK
ANVVSWNELCHIAETMARGL
301 AYLHEDIPGL KDGHKPAISH RDIKSKNVLL KNNLTACIAD
FGLALKFEAG
351 KSAGDTHGQV GTRRYMAPEV LEGAINFQRD AFLRIDMYAM
LVLWELASR
401 CTAADGPVDE YMLPFEEEIG QHPSLEDMQE VVVHKKKRPV
LRDYWQKHAG
451 MAMLCETIEE CWDHDAEARL SAGCVGERIT QMQRLTNIIT
TEDIVTVVTM
501 VTNVDFPPKE SSL (SEQ ID NO: 9)

[0146] The signal peptide is indicated by a single underline; the extracellular domain is indicated in **bold** font; and the potential, endogenous N-linked glycosylation sites are indicated by a double underline.

[0147] The processed (mature) extracellular human ActRIIA protein sequence is as follows:

ILGRSETQECLFFNANWEKDRTNQ**TGVEPC**YGD**DKRRHCFATWKNISGS**IEIVK
QGCW**LD**INCYDRTDC**VEKKDSPEV**YFCCCEGNMCNEKFSYFPEMEVTQPTSNP
VTPKPP (SEQ ID NO: 10)

[0148] The C-terminal “tail” of the extracellular domain is indicated by single underline. The sequence with the “tail” deleted (a Δ15 sequence) is as follows:

ILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVK
QGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNCNEKFSYFPEM (SEQ ID NO:

11)

[0149] The nucleic acid sequence encoding human ActRIIA precursor protein is shown below (SEQ ID NO: 12), as follows nucleotides 159-1700 of Genbank Reference Sequence NM_001616.4. The signal sequence is underlined.

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1      atgggagctg ctgcaaagtt ggcgtttgcc gtctttctta tctcctgttc
51     ttcagggtgct atacttggta gatcagaaac tcaggagtgt cttttcttta
101    atgctaattg ggaaaaagac agaaccaatc aaactggtgt tgaaccgtgt
151    tatggtgaca aagataaacg gcggcattgt ttgctacct ggaagaatat
201    ttctggttcc attgaaatag tgaacaagg ttgttgctg gatgatatca
251    actgctatga caggactgat tgtgtagaaa aaaaagacag ccctgaagta
301    tattttgtt gctgtgaggg caatatgtgt aatgaaaagt ttcttattt
351    tccggagatg gaagtcacac agcccacttc aaatccagt acacctaagc
401    caccctatta caacatcctg ctctattcct tggtgccact tatgttaatt
451    gcgggggattg tcatttgtgc attttgggtg tacaggcatc acaagatggc
501    ctacctcct gtactgttc caactcaaga cccaggacca cccccactt
551    ctccattact aggtttgaaa cactgcagt tattagaagt gaaagcaagg
601    ggaagatttg gttgtgtctg gaaagcccag ttgcttaacg aatatgtggc
651    tgtcaaaata ttccaatac aggacaaaca gtcattggca aatgaatacg
701    aagtctacag ttgcctgga atgaagcatg agaacatatt acagttcatt
751    ggtgcagaaa aacgaggcac cagtgttgat gtggatctt ggctgatcac
801    agcatttcat gaaaagggtt cactatcaga ctttctaag gctaattggg
851    tctcttgga tgaactgtgt catattgcag aaacatggc tagaggattg
901    gcatatttac atgaggatat acctggccta aaagatggc acaaacctgc
951    catatctcac agggacatca aaagtaaaaa tgtgctgttg aaaaacaacc
1001   tgacagcttg cattgctgac ttgggttg ccttaaaatt tgaggctggc
1051   aagtctgcag gcgataccca tggacaggtt ggtaccgga ggtacatggc
1101   tccagaggta ttagagggtg ctataaactt ccaaaggat gcattttga
1151   ggatagatat gtatgcatg ggattagtcc tatgggaact ggcttctgc
1201   tgtactgctg cagatggacc tgtatgaa tacatgttc catttgagga
1251   ggaaattggc cagcatccat ctctgaaga catgcaggaa gtgttgtgc
1301   ataaaaaaaa gaggcctgtt ttaagagatt attggcagaa acatgctgga
1351   atggcaatgc tctgtgaaac cattgaagaa tgttgggatc acgacgcaga

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1401 agccaggta tcagctggat gtgtaggta aagaattacc cagatgcaga
 1451 gactaacaaa tattattacc acagaggaca ttgtaacagt ggtcacatg
 1501 gtgacaaatg ttgactttcc tcccaaagaa tctagtcta (SEQ ID NO: 12)

[0150] The nucleic acid sequence encoding processed soluble (extracellular) human ActRIIA protein is as follows:

1 atacttgga gatcagaaac tcaggagtgt cttttctta atgctaattg
 51 ggaaaaagac agaaccaatc aaactgggtg tgaaccgtgt tatggtgaca
 101 aagataaacg gcggcattgt ttgtctacct ggaagaatat ttctggttcc
 151 attgaaatag tgaacaagg ttgttgctg gatgatata actgctatga
 201 caggactgat tgtgtagaaa aaaaagacag ccctgaagta ttttttgtt
 251 gctgtgaggg caatatgtgt aatgaaaagt ttcttattt tccggagatg
 301 gaagtcacac agcccacttc aatccagtt acacctaage caccc (SEQ ID NO:13)

[0151] ActRIIA is well-conserved among vertebrates, with large stretches of the extracellular domain completely conserved. For example, **FIG. 1** depicts a multi-sequence alignment of a human ActRIIA extracellular domain compared to various ActRIIA orthologs. Many of the ligands that bind to ActRIIA are also highly conserved. Accordingly, from these alignments, it is possible to predict key amino acid positions within the ligand-binding domain that are important for normal ActRIIA-ligand binding activities as well as to predict amino acid positions that are likely to be tolerant to substitution without significantly altering normal ActRIIA-ligand binding activities. Therefore, an active, human ActRIIA variant protein useful in accordance with the presently disclosed methods may include one or more amino acids at corresponding positions from the sequence of another vertebrate ActRIIA, or may include a residue that is similar to that in the human or other vertebrate sequences.

[0152] Without meaning to be limiting, the following examples illustrate this approach to defining an active ActRIIA variant. As illustrated in **FIG. 1**, F13 in the human extracellular domain is Y in *Ovis aries* (SEQ ID NO: 62), *Gallus* (SEQ ID NO: 65), *Bos Taurus* (SEQ ID NO: 66), *Tyto alba* (SEQ ID NO: 67), and *Myotis davidii* (SEQ ID NO: 68) ActRIIA, indicating that aromatic residues are tolerated at this position, including F, W, and Y. Q24 in the human extracellular domain is R in *Bos Taurus* ActRIIA, indicating that charged residues will be tolerated at this position, including D, R, K, H, and E. S95 in the human extracellular domain is F in *Gallus gallus* and *Tyto alba* ActRIIA, indicating that this site may be tolerant of a wide variety of changes, including polar residues, such as E, D, K, R, H, S, T, P, G, Y, and probably

hydrophobic residue such as L, I, or F. E52 in the human extracellular domain is D in *Ovis aries* ActRIIA, indicating that acidic residues are tolerated at this position, including D and E. P29 in the human extracellular domain is relatively poorly conserved, appearing as S in *Ovis aries* ActRIIA and L in *Myotis davidii* ActRIIA, thus essentially any amino acid should be tolerated at this position.

[0153] Moreover, as discussed above, ActRII proteins have been characterized in the art in terms of structural/functional characteristics, particularly with respect to ligand binding (Attisano *et al.* (1992) Cell 68(1):97-108; Greenwald *et al.* (1999) Nature Structural Biology 6(1): 18-22; Allendorph *et al.* (2006) PNAS 103(20: 7643-7648; Thompson *et al.* (2003) The EMBO Journal 22(7): 1555-1566; as well as U.S. Patent Nos: 7,709,605, 7,612,041, and 7,842,663). In addition to the teachings herein, these references provide amply guidance for how to generate ActRII variants that retain one or more desired activities (e.g., ligand-binding activity).

[0154] For example, a defining structural motif known as a three-finger toxin fold is important for ligand binding by type I and type II receptors and is formed by conserved cysteine residues located at varying positions within the extracellular domain of each monomeric receptor (Greenwald *et al.* (1999) Nat Struct Biol 6:18-22; and Hinck (2012) FEBS Lett 586:1860-1870). Accordingly, the core ligand-binding domains of human ActRIIA, as demarcated by the outermost of these conserved cysteines, corresponds to positions 30-110 of SEQ ID NO: 9 (ActRIIA precursor). Therefore, the structurally less-ordered amino acids flanking these cysteine-demarcated core sequences can be truncated by about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 residues at the N-terminus and by about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 residues at the C-terminus without necessarily altering ligand binding. Exemplary ActRIIA extracellular domains truncations include SEQ ID NOs: 10 and 11.

[0155] Accordingly, a general formula for an active portion (e.g., ligand binding) of ActRIIA is a protein that comprises, consists essentially of, or consists of amino acids 30-110 of SEQ ID NO: 9. Therefore ActRIIA proteins may, for example, comprise, consist essentially of, or consist of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a portion of ActRIIA beginning at a residue corresponding to any one of amino acids 21-30 (e.g., beginning at any one of amino acids 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) of SEQ ID NO: 9 and ending at a position corresponding to

any one amino acids 110-135 (*e.g.*, ending at any one of amino acids 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, or 135) of SEQ ID NO: 9. Other examples include constructs that begin at a position selected from 21-30 (*e.g.*, beginning at any one of amino acids 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30), 22-30 (*e.g.*, beginning at any one of amino acids 22, 23, 24, 25, 26, 27, 28, 29, or 30), 23-30 (*e.g.*, beginning at any one of amino acids 23, 24, 25, 26, 27, 28, 29, or 30), 24-30 (*e.g.*, beginning at any one of amino acids 24, 25, 26, 27, 28, 29, or 30) of SEQ ID NO: 9, and end at a position selected from 111-135 (*e.g.*, ending at any one of amino acids 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 or 135), 112-135 (*e.g.*, ending at any one of amino acids 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 or 135), 113-135 (*e.g.*, ending at any one of amino acids 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 or 135), 120-135 (*e.g.*, ending at any one of amino acids 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134 or 135), 130-135 (*e.g.*, ending at any one of amino acids 130, 131, 132, 133, 134 or 135), 111-134 (*e.g.*, ending at any one of amino acids 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, or 134), 111-133 (*e.g.*, ending at any one of amino acids 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, or 133), 111-132 (*e.g.*, ending at any one of amino acids 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, or 132), or 111-131 (*e.g.*, ending at any one of amino acids 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, or 131) of SEQ ID NO: 9.

[0156] Variants within these ranges are also contemplated, particularly those comprising, consisting essentially of, or consisting of an amino acid sequence that has at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the corresponding portion of SEQ ID NO: 9 or SEQ ID NO: 10. Thus, in some embodiments, an ActRIIA protein may comprise, consist essentially of, or consist of a protein that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 30-110 of SEQ ID NO: 9 or SEQ ID NO: 10. Optionally, ActRIIA proteins comprise a protein that is at least 70%, 75%, 80%, 85%,

86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 30-110 of SEQ ID NO: 9, and comprising no more than 1, 2, 5, 10 or 15 conservative amino acid changes in the ligand-binding pocket. Optionally, ActRIIA proteins comprise a protein that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 10, and comprising no more than 1, 2, 5, 10 or 15 conservative amino acid changes in the ligand-binding pocket.

[0157] In certain embodiments, the ActRIIA proteins described herein are soluble (*e.g.*, an extracellular domain of ActRIIA). In some embodiments, ActRIIA proteins inhibit (*e.g.*, Smad signaling) of one or more GDF/BMP ligands (*e.g.*, GDF11, GDF8, activin (activin A, activin B, activin AB, activin C, activin E) BMP6, GDF3, BMP15, and/or BMP10). In some embodiments, ActRIIA proteins bind to one or more GDF/BMP ligands (*e.g.*, GDF11, GDF8, activin (activin A, activin B, activin AB, activin C, activin E) BMP6, GDF3, BMP15, and/or BMP10).

[0158] In some embodiments, the ActRIIA protein is a fusion protein comprising an ActRIIA domain and one or more protein domains heterologous to ActRIIA. In some embodiments, the ActRIIA protein is a fusion protein comprising an Fc domain of an immunoglobulin. In some embodiments, the Fc domain of the immunoglobulin is an Fc domain of an IgG1 immunoglobulin.

[0159] An example of a native amino acid sequence that may be used for the Fc portion of human IgG1 (G1Fc) is shown below (SEQ ID NO: 1). Dotted underline indicates the hinge region, and solid underline indicates positions with naturally occurring variants. In part, the disclosure provides polypeptides comprising, consisting essential of, or consisting of amino acid sequences with 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 1. Naturally occurring variants in G1Fc would include E134D and M136L according to the numbering system used in SEQ ID NO: 1 (see Uniprot P01857).

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1  THTCPPCPPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE
51 VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD
   WLNGKEYKCK
101 VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSREEMTKNQ VSLTCLVKGF
151 YPSDIAVEWE SNGQPENNYK TTPVLDSDG SFFLYSKLTV
   DKSRWQQGNV

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201 FSCSVMHEAL HNHYTQKSLS LSPGK (SEQ ID NO: 1)

[0160] Optionally, the IgG1 Fc domain has one or more mutations at residues such as Asp-265, lysine 322, and Asn-434. In certain cases, the mutant IgG1 Fc domain having one or more of these mutations (*e.g.*, Asp-265 mutation) has reduced ability of binding to the Fc γ receptor relative to a wild-type Fc domain. In other cases, the mutant Fc domain having one or more of these mutations (*e.g.*, Asn-434 mutation) has increased ability of binding to the MHC class I-related Fc-receptor (FcRN) relative to a wild-type IgG1 Fc domain.

[0161] An example of a native amino acid sequence that may be used for the Fc portion of human IgG2 (G2Fc) is shown below (SEQ ID NO: 6). Dotted underline indicates the hinge region and double underline indicates positions where there are data base conflicts in the sequence (according to UniProt P01859). In part, the disclosure provides polypeptides comprising, consisting essential of, or consisting of amino acid sequences with 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 6.

1 VECPCPAPP VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ

51 FNWYVDGVEV HNAKTKPREE QFNSTFRVVS VLTVVHQDWL

NGKEYKCKVS

101 NKGLPAPIEK TISKTKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP

151 SDIAVEWESN GQPENNYKTT PPMLDSDGSF FLYSKLTVDK

SRWQQGNVFS

201 CSVMHEALHN HYTQKSLSLS PGK (SEQ ID NO: 6)

[0162] Two examples of amino acid sequences that may be used for the Fc portion of human IgG3 (G3Fc) are shown below. The hinge region in G3Fc can be up to four times as long as in other Fc chains and contains three identical 15-residue segments preceded by a similar 17-residue segment. The first G3Fc sequence shown below (SEQ ID NO: 3) contains a short hinge region consisting of a single 15-residue segment, whereas the second G3Fc sequence (SEQ ID NO: 4) contains a full-length hinge region. In each case, dotted underline indicates the hinge region, and solid underline indicates positions with naturally occurring variants according to UniProt P01859. In part, the disclosure provides polypeptides comprising, consisting essential of, or consisting of amino acid sequences with 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 3 and 4.

1 EPKSCDTPPP CPRCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
 51 VSHEDPEVQF KQYVDGVEVH NAKTKPREEQ YNSTFRVVS
LTVLHQDWLN
 101 GKEYKCKVSN KALPAIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL
 151 TCLVKGFYPS DIAVEWESSG QPENNYNTTP PMLDSDGSFF LYSKLTVDKS
 201 RWQQGNIFSC SVMHEALHNR ETQKSLSLSP GK (SEQ ID NO: 3)

1 ELKTPLGDTT HTCPRCPEPK SCDTPPPCPR CPEPKSCDTP PPCPRCPEPK
 51 SCDTPPPCPR CPAPELLGGP SVFLFPPKPK DTLMISRTPE
 101 EDPEVQFKWY VDGVEVHNAK TKPREEQYNS TFRVVSVLTV
LHQDWLNGKE
 151 YKCKVSNKAL PAIEKTISK TKGQPREPQV YTLPPSREEM TKNQVSLTCL
 201 VKGFYPSDIA VEWESSGQPE NNYNTTPML DSDGSFFLYS KLTVDKSRWQ
 251 QGNIFSCSVM HEALHNRETQ KSLSLSPGK (SEQ ID NO: 4)

[0163] Naturally occurring variants in G3Fc (for example, see Uniprot P01860) include E68Q, P76L, E79Q, Y81F, D97N, N100D, T124A, S169N, S169del, F221Y when converted to the numbering system used in SEQ ID NO: 3, and the present disclosure provides fusion proteins comprising G3Fc domains containing one or more of these variations. In addition, the human immunoglobulin IgG3 gene (*IGHG3*) shows a structural polymorphism characterized by different hinge lengths [see Uniprot P01859]. Specifically, variant WIS is lacking most of the V region and all of the CH1 region. It has an extra interchain disulfide bond at position 7 in addition to the 11 normally present in the hinge region. Variant ZUC lacks most of the V region, all of the CH1 region, and part of the hinge. Variant OMM may represent an allelic form or another gamma chain subclass. The present disclosure provides additional fusion proteins comprising G3Fc domains containing one or more of these variants.

[0164] An example of a native amino acid sequence that may be used for the Fc portion of human IgG4 (G4Fc) is shown below (SEQ ID NO: 5). Dotted underline indicates the hinge region. In part, the disclosure provides polypeptides comprising, consisting essential of, or consisting of amino acid sequences with 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 5.

1 ESKYGPPCPS CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ

51 EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV
 LHQDWLNGKE
 101 YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL
 151 VKGFYPSDIA VEWESNGQPE NNYKTTPPV L DSDGSFFLYS RLTVDKSRWQ
 201 EGNVFSCSVM HEALHNHYTQ KSLSLSLGK (SEQ ID NO: 5)

[0165] Various methods are known in the art that increase desired pairing of Fc-containing fusion polypeptide chains in a single cell line to produce a preferred asymmetric fusion protein at acceptable yields [Klein et al (2012) mAbs 4:653-663; and Spiess et al (2015) Molecular Immunology 67(2A): 95-106]. Methods to obtain desired pairing of Fc-containing chains include, but are not limited to, charge-based pairing (electrostatic steering), “knobs-into-holes” steric pairing, SEEDbody pairing, and leucine zipper-based pairing [Ridgway et al (1996) Protein Eng 9:617-621; Merchant et al (1998) Nat Biotech 16:677-681; Davis et al (2010) Protein Eng Des Sel 23:195-202; Gunasekaran et al (2010); 285:19637-19646; Wranik et al (2012) J Biol Chem 287:43331-43339; US5932448; WO 1993/011162; WO 2009/089004, and WO 2011/034605].

[0166] It is understood that different elements of the fusion proteins (*e.g.*, immunoglobulin Fc fusion proteins) may be arranged in any manner that is consistent with desired functionality. For example, an ActRIIA polypeptide domain may be placed C-terminal to a heterologous domain, or alternatively, a heterologous domain may be placed C-terminal to an ActRII polypeptide domain. The ActRIIA polypeptide domain and the heterologous domain need not be adjacent in a fusion protein, and additional domains or amino acid sequences may be included C- or N-terminal to either domain or between the domains.

[0167] In some embodiments, the ActRIIA fusion protein further comprises a linker domain positioned between the ActRIIA protein domain and the one or more heterologous domains (*e.g.*, an Fc immunoglobulin domain). In other embodiments, the fusion protein further comprises a linker domain positioned between the protein domain and the Fc domain of the immunoglobulin. In certain embodiments, the linker domain is a polyglycine linker. In certain embodiments, the protein is glycosylated. In some embodiments, the linker domain is selected from the group consisting of: TGGG (SEQ ID NO: 23), TGGGG (SEQ ID NO: 21), SGGGG (SEQ ID NO: 22), GGGGS (SEQ ID NO: 25), GGG (SEQ ID NO: 19), GGGG (SEQ ID NO: 20), and SGGG (SEQ ID NO: 24).

[0168] In certain embodiments, the ActRIIA fusion protein comprises an ActRIIA protein linked to an Fc region by a linker domain. In certain embodiments, the ActRIIA fusion protein comprises an ActRIIA protein comprising SEQ ID NO: 10 linked to an Fc region of SEQ ID NO: 1 by a linker domain of SEQ ID NO: 23, wherein the linked and Fc region and linker are linked at the C-terminus of the ActRIIA protein.

[0169] In some embodiments, the ActRIIA protein comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32. In some embodiments, the ActRIIA protein comprises the amino acid sequence of SEQ ID NO: 32. In some embodiments, the ActRIIA protein consists of the amino acid sequence of SEQ ID NO: 32. SEQ ID NO: 32 is also known as sotatercept. In some embodiments, the ActRIIA protein is part of a homodimer protein complex. In some embodiments, the ActRIIA protein is glycosylated. In some embodiments, the ActRIIA protein has a glycosylation pattern obtainable by expression in a Chinese hamster ovary cell.

[0170] In some alternative embodiments, the ActRII protein (*e.g.*, SEQ ID NO: 32) lacks the C-terminal lysine. In some embodiments, the ActRII protein lacking the C-terminal lysine is SEQ ID NO: 41. In some embodiments, the formulation comprises a mixture of SEQ ID NO:32 and SEQ ID NO:41.

[0171] In some embodiments, ActRIIA proteins comprise, consist, or consist essentially of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of any one of SEQ ID NOs: 9, 10, 11, 32, 36, 39 and 41.

Dosing Regimens

[0172] Currently sotatercept (SEQ ID NO: 32) is dosed based on the individual weight of the patient. Each patient is administered an initial dose of 0.3 mg/kg according to the table below:

Table 1

Patient Weight Range (kg)	Injection Volume (mL)	Kit Type
30.0 - 40.8	0.2	1 x 45 mg vial
40.9 - 57.4	0.3	
57.5 - 74.1	0.4	
74.2 - 90.8	0.5	
90.9 - 107.4	0.6	
107.5 - 124.1	0.7	
124.2 - 140.8	0.8	
140.9 - 157.4	0.9	
157.5 - 174.1	1.0	1 x 60 mg vial
174.2 - 180.0	1.1	

[0173] Following the initial dose, every three weeks the patient is administered a maintenance dose of 0.7 mg/kg according to the table below:

Table 2

Patient Weight Range (kg)	Injection Volume (mL)	Kit Type
30.0 - 40.8	0.2	1 x 45 mg vial
40.9 - 57.4	0.3	
57.5 - 74.1	0.4	
74.2 - 90.8	0.5	
90.9 - 107.4	0.6	
107.5 - 124.1	0.7	
124.2 - 140.8	0.8	
140.9 - 157.4	0.9	
157.5 - 174.1	1.0	1 x 60 mg vial
174.2 - 180.0	1.1	

[0174] The present invention eliminates the need for medical personnel to calculate the amount of an ActRIIA fusion protein or variant thereof, such as sotatercept, to be administered to the patient based on the patient's individual weight

and reduces the amount of waste by allowing full doses to be used instead of only possible using a portion of the current 45 mg and 60 mg vials.

[0175] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, on Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, administered to a patient as an initial dose is a factor of 15. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as an initial dose is 15 mg, 30 mg or 45 mg.

[0176] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1, and a maintenance dose at least every three weeks after Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as a maintenance dose is a factor of 15. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as an initial dose is 15 mg, 30 mg or 45 mg. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as maintenance dose is 30 mg, 45 mg, 60 mg, 75 mg or 90 mg.

[0177] Described herein are methods for treating pulmonary arterial hypertension in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the initial dose is 15 mg or a factor of 15 mg and the initial dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial dose the dose that is pre-selected for the weight band that corresponds to the patient's weight.

[0178] In certain embodiments, the initial dose is selected from one the following pre-determined weight bands:

[0179] (a) 15 mg for a patient weighing less than 50 kg,

[0180] (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0181] (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0182] (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg,

or

[0183] (e) 45 mg for a patient weighing 125 kg or more.

[0184] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, wherein the initial dose is selected from the group consisting of:

[0185] (a) 15 mg for a patient weighing less than 50 kg,

[0186] (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0187] (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0188] (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg,

and

[0189] (e) 45 mg for a patient weighing 125 kg or more.

[0190] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, wherein the initial dose is selected from the group consisting of:

[0191] (a) 15 mg for a patient weighing less than 50 kg,

[0192] (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,

[0193] (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,

[0194] (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg,

and

[0195] (e) 45 mg for a patient weighing 125 kg or more.

[0196] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof further comprising administering to the patient a maintenance dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, approximately 3 weeks after the initial dose, wherein the maintenance dose is selected from the group consisting of:

[0197] (a) 30 mg for a patient weighing less than 50 kg,

[0198] (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,
[0199] (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,
[0200] (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg,
and

[0201] (e) 90 mg for a patient weighing 125 kg or more.

[0202] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as an initial dose is a factor of 12. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as an initial dose is 12 mg, 24 mg or 36 mg.

[0203] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1, and a maintenance dose at least every three weeks after Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as a maintenance dose is a factor of 12. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as maintenance dose is 12 mg, 24 mg, 36 mg, 48 mg, 60 mg, 72 mg, 84 mg or 96 mg.

[0204] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant comprising SEQ ID NO: 32 lacking the C-terminal lysine administered to a patient as an initial dose is a factor of 10. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant

comprising SEQ ID NO:41 administered to a patient as an initial dose is 10 mg, 20 mg or 30 mg.

[0205] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1, and a maintenance dose at least every three weeks after Day 1, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as a maintenance dose is a factor of 10. In certain embodiments, the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 administered to a patient as maintenance dose is 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg or 90 mg.

[0206] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 15-45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 12 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 24 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion

protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

[0207] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of 12 mg of a human ActRIIA-Fc fusion protein comprising

SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [50-75) kg.

[0208] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of 12 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [35-50) kg.

[0209] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 24 mg of a human ActRIIA-Fc fusion protein comprising

SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [100-125) kg.

[0210] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 24 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant

comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [75-100) kg.

[0211] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less

than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [125-150) kg.

[0212] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg.

[0213] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 10-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs

less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 15-45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 12 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 24 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about

45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a variant comprising SEQ ID NO: 32 lacking the C-terminal lysine if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

[0214] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 10-20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of about 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of about 12 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of about 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered an initial dose of about 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [50-75) kg.

[0215] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 10-20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of about 10 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is

administered an initial dose of about 12 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of about 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of about 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [35-50) kg.

[0216] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 20-30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 24 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not

including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [100-125) kg.

[0217] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 24 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an

ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [75-100) kg.

Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 30-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered an initial dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [125-150) kg.

[0218] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of about 30-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose

of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered an initial dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg.

[0219] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1 and a maintenance dose at least every three weeks after Day 1, wherein the maintenance dose is 20-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 30-90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered an initial dose of 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered maintenance dose of 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 55 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 65 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of 75 mg of a

human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 96 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

[0220] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered a maintenance dose of 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered a maintenance dose of 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain

embodiments, the patient is administered a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [35-50) kg.

[0221] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered maintenance dose of 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered a maintenance dose of 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [50-75) kg.

Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 50-70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 55 mg of a human ActRIIA-Fc fusion protein

comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 65 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [75-100) kg.

[0222] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 70-80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an

ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [100-125) kg.

[0223] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 80-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 96 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human

ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [125-150) kg.

[0224] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of 80-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg.

[0225] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 on Day 1 and a maintenance dose at least every three weeks after Day 1, wherein the maintenance dose is about 20-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc

fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 30-90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 35 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 36 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered an initial dose of about 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered maintenance dose of about 48 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 55 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered maintenance dose of about 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 65 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

In certain embodiments, the patient is administered a maintenance dose of about 70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 96 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than 150 kg.

[0226] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 20-40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32,

or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered a maintenance dose of about 20 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered a maintenance dose of about 25 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered a maintenance dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 50 kg. In certain embodiments, the patient is administered an initial dose of about 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [35-50) kg.

[0227] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 40-50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered maintenance dose of about 40 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered maintenance dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered a maintenance dose of about 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 75 kg. In certain embodiments, the patient is administered a maintenance dose of about 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [50-75) kg.

[0228] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 50-70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 50 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 55 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 65 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered maintenance dose of about 70 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 100 kg. In certain embodiments, the patient is administered a maintenance dose of about 60 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [75-100] kg.

[0229] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 70-80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 70 mg of a human ActRIIA-Fc fusion protein

comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 72 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 125 kg. In certain embodiments, the patient is administered a maintenance dose of about 75 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [100-125) kg.

[0230] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 80-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is

administered a maintenance dose of about 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 96 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs less than (but not including) 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs between [125-150) kg.

[0231] Described herein are methods for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient a maintenance dose of about 80-100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 80 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 84 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 85 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 95 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about

100 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg. In certain embodiments, the patient is administered a maintenance dose of about 90 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 if the patient weighs greater than 150 kg.

[0232] In certain embodiments, the maintenance dose is administered to a patient at least three weeks after the initial dose. In certain embodiments, two or more maintenance doses are administered to the patient, with approximately three weeks between each dose. In other embodiments, the maintenance dose is administered to a patient three, four, five, six, seven, eight, nine or ten weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient three weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient four weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient five weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient six weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient seven weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient eight weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient nine weeks after the initial dose. In other embodiments, the maintenance dose is administered to a patient ten weeks after the initial dose.

[0233] In certain embodiments, the methods for treating pulmonary arterial hypertension which comprises administering to a patient in need thereof an ActRIIA-Fc fusion protein or a variant thereof, such as a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, include the dosage regimens represented in Table 3 below:

Table 3

Body Weight (kg)	Initial Dose (mg)	Maintenance Dose (mg)
<50	15	30
[50-75)	15	45
[75-100)	30	60
[100-125)	30	75
[125, 150] or >=125	45	90

* In the table above and throughout the application, if a number is enclosed by a bracket the number is included in the range and if a number is adjacent to a parenthesis, the number is not included in the band.

[0234] As shown in Table 3, weight bands beginning at 50 kg are established in increments of 25 kgs. Each weight band is associated with an initial dose and maintenance doses each having a factor of 15. Patients weighing less than 50 kg are administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 and maintenance doses of 30 mg. Patients weighing [50-75) kg are administered an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 and a maintenance doses of 45 mg. Patients weighing [75-100) kg are administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 and maintenance doses of 60 mg. Patients weighing [100-125) kg are administered an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 and maintenance doses of 75 mg. Patients weighing 125 kg or more are administered an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 and maintenance doses of 90 mg.

[0235] In any of the methods described herein, in certain embodiments, the maintenance dose is administered to the patient every 3 weeks for 72 weeks or less. In other embodiments, the maintenance dose is administered to the patient every 3 weeks for 72 weeks or more.

[0236] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA protein or the human ActRIIA protein variant is administered to the patient via subcutaneous injection.

[0237] In certain embodiments, the initial dose and/or the maintenance dose of the human ActRIIA protein or the human ActRIIA protein variant is administered to the patient with an autoinjector. In certain embodiments, the maintenance dose of the human ActRIIA protein or the human ActRIIA protein variant is administered to the patient with an autoinjector. In certain embodiments, the initial dose of the human ActRIIA protein or the human ActRIIA protein variant is administered to the patient with an autoinjector. In certain embodiments, the maintenance dose(s) are each administered in a single injection.

[0238] In certain embodiments, the auto injector contains 15 mg, 30 mg, 45 mg, 60 mg, 75 mg, or 90 mg of sotatercept. In certain embodiments, the auto injector contains 15 mg, 30 mg, 45 mg, 60 mg, 75 mg, or 90 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41. In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in a single injection. In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in two or more injections. An example of a suitable autoinjector is the Molly® autoinjector, currently on the market.

[0239] Described herein are methods of administering an ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 with an autoinjector, comprising administering to the patient an initial dose of the ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or the human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the initial dose is 15 mg or a factor of 15 mg and the initial dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial

dose, the dose that is pre-selected for the weight band that corresponds to the patient's weight.

[0240] Described herein are methods of administering an ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 with an autoinjector, comprising administering to the patient, in a first autoinjector, an initial dose of the ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or the human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the initial dose is 15 mg or a factor of 15 mg and the initial dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial dose, the dose that is pre-selected for the weight band that corresponds to the patient's weight.

[0241] Described herein are methods of administering an ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 with an autoinjector, comprising administering to the patient a maintenance dose of the ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or the human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the maintenance dose is a factor of 15 mg and the maintenance dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting, as the maintenance dose the dose that is pre-selected for the weight band that corresponds to the patient's weight, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.

[0242] Described herein are methods of administering an ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 with an autoinjector, comprising administering to the patient, in a second autoinjector, a maintenance dose of the ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or the human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the maintenance dose is a factor of 15 mg and the maintenance dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting, as the maintenance dose the dose that is pre-selected for the weight band that corresponds to the patient's weight, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.

[0243] In certain embodiments, the auto injector contains an initial dose of 15 mg, 30 mg, 45 mg, 60 mg, 75 mg, or 90 mg of sotatercept. In certain embodiments, the auto injector contains a maintenance dose of 15 mg, 30 mg, 45 mg, 60 mg, 75 mg, or 90 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41. In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in a single injection. In certain embodiments, the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg, which is administered to the patient in two or more injections. An example of a suitable autoinjector is the Molly® autoinjector, currently on the market. In certain embodiments, the autoinjector delivers a dose volume of 1.8 mL. In certain embodiments, the autoinjector is used to deliver the dose to the thigh, arm or abdomen. In certain embodiments, the dose is delivered in 2-3 seconds. In certain embodiments the autoinjector comprises a 27 gauge needle. In certain embodiment, the needle length can be 6mm.

METHODS, USES AND MEDICAMENTS

[0244] Described herein are methods of treating pulmonary arterial hypertension (PAH) comprising administering to a patient in need thereof an ActRII polypeptide according to the dosing regimens described herein. In some embodiments, the disclosure contemplates methods of treating, preventing, or reducing the progression rate and/or severity of pulmonary arterial hypertension, comprising administering to a patient in need thereof an ActRII polypeptide according to the dosing regimens described herein.

[0245] In some embodiments, the administration of an ActRII polypeptide according to the dosing regimens described herein results in a change of one or more hemodynamic or functional parameters (*e.g.*, a reduction in pulmonary vascular resistance (PVR); an increase in 6-minute walk distance (6MWD); a decrease of the N-terminal pro B-type natriuretic peptide (NT-proBNP) levels; a prevention or delay in pulmonary hypertension Functional Class progression as recognized by the World Health Organization (WHO); a promotion or increase in pulmonary hypertension Functional Class regression as recognized by the WHO; an improvement in right ventricular function; and an improvement in pulmonary artery pressure).

[0246] In one aspect, the invention provides a method of treating PAH in a patient in need thereof comprising administering a human ActRIIA-Fc fusion protein comprising

SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 according to the dosing regimens described herein. In one aspect, the invention provides a method of treating PAH in a patient in need thereof comprising administering to the patient a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, wherein the amount of a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41 is determined upon which weight-band the patient falls within.

[0247] A pulmonary arterial hypertension condition treated by methods describe herein, can comprise any one or more of the conditions recognized according to the World Health Organization (WHO). See, *e.g.*, Simonneau (2019) Eur Respir J: 53:1801913.

Table 4: Clinical Classification of Pulmonary Arterial Hypertension

Group 1: Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced PAH
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome

[0248] The clinical purpose of the classification of PAH is to categorize clinical conditions associated with PAH into specific subgroups according to their pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and treatment strategy. This clinical classification may be updated when new data are available on the above features or when additional clinical entities are considered.

[0249] As used herein, the term “pulmonary hemodynamic parameter” refers to any parameter used to describe or evaluate the blood flow through the heart and pulmonary vasculature. Examples of pulmonary hemodynamic parameters include, but are not limited to, mean pulmonary artery pressure (mPAP), diastolic pulmonary artery pressure (dPAP) [also known as pulmonary artery diastolic pressure (PADP)], systolic pulmonary artery pressure (sPAP) [also known as pulmonary artery systolic pressure (PASP)], mean right atrial pressure (mRAP), pulmonary capillary wedge pressure (PCWP) [also known as pulmonary artery wedge pressure (PAWP)], pulmonary vascular resistance (PVR) and cardiac output (CO).

[0250] Many of the pulmonary hemodynamic parameters described above are interrelated. For example, PVR is related to mPAP, PCWP and CO according to the following equation:

[0251] $PVR = (mPAP - PCWP) / CO$ [Woods Units]

[0252] The PVR measures the resistance to flow imposed by the pulmonary vasculature without the influence of the left-sided filling pressure. PVR can also be measured according to the following equations:

[0253] $PVR = TPG \times 80 / CO$ [unit: dynes-sec-cm⁻⁵] OR $PVR = (mPAP - PCWP) \times 80 / CO$ [unit: dynes-sec-cm⁻⁵]

[0254] In some embodiments, the total peripheral resistance (TPR) can be measured using the following equation:

[0255] $TPR = mPAP / CO$.

[0256] According to some embodiments, a pre-capillary pulmonary arterial contribution to PH may be reflected by an elevated PVR. In some embodiments, the normal PVR is 20-130 dynes-sec-cm⁻⁵ or 0.5-1.1 Wood units. According to some embodiments, an elevated PVR may refer to a PVR above 2 Wood units, above 2.5 Wood units, above 3 Wood units or above 3.5 Wood units.

[0257] As yet another example, mPAP is related to dPAP and sPAP according to the following equation: $mPAP = (2/3)dPAP + (1/3)sPAP$

[0258] Furthermore, dPAP and sPAP can be used to calculate the pulse pressure (mmHg) using the following equation: pulse pressure=sPAP-dPAP

[0259] Pulse pressure can be used to calculate the pulmonary artery compliance using the following equation: pulmonary artery compliance (mL.mmHg⁻¹) = stroke volume/pulse pressure

[0260] In some embodiments, the pulmonary hemodynamic parameters are measured directly, such as during a right heart catheterization. In other embodiments, the pulmonary hemodynamic parameters are estimated and/or evaluated through other techniques such as magnetic resonance imaging (MRI) or echocardiography.

[0261] Exemplary pulmonary hemodynamic parameters include mPAP, PAWP, and PVR. The one or more pulmonary hemodynamic parameters may be measured by any appropriate procedures, such as by utilizing a right heart catheterization or echocardiography. Various hemodynamic characteristics of PH and PAH are shown in Table 5.

[0262] Table 5. Hemodynamic Characteristics of Pulmonary Hypertension (PH) and PAH

	Hemodynamic Characteristics
Pulmonary Hypertension	mPAP >20 mmHg
Pulmonary arterial hypertension	mPAP >20 mmHg
	PAWP ≤15 mmHg
	PVR ≥3 Wood units

[0263] The clinical classification or hemodynamic characteristics of PAH described herein, and the associated diagnostic parameters may be updated or varied based on the availability of new or existing sources of data or when additional clinical entities are considered.

[0264] Also described herein are methods of treating pulmonary arterial hypertension (PAH) comprising administering to a patient in need thereof an ActRII polypeptide according to the dosing regimens described herein, wherein the patient is already on a PAH treatment (background therapy). In some embodiments, the disclosure contemplates methods of treating, preventing, or reducing the progression rate and/or severity of pulmonary arterial hypertension, comprising administering to a patient in need thereof an ActRII polypeptide according to the dosing regimens described herein, wherein the patient is already on a PAH treatment (background therapy).

[0265] In certain embodiments, the dosing regimens described herein are administered to a patient already receiving what is defined at the time of the STELLAR trial, the standard of care for treating PAH and is considered on a background therapy.

Background therapy defined as the standard of care therapy for PAH at the time of conduct of STELLAR, includes mono-, double-, or triple- therapy of some combination of endothelin receptor antagonist (ERA), phosphodiesterase type-5 (PDE-5) inhibitor, soluble guanylate cyclase (sGC) stimulator, prostaglandin I₂ (PGI₂) analogue, and PGI₂ agonist.

[0266] In certain embodiments, the dosing regimens described herein are administered to a patient, wherein the patient is further treated with one or more PAH therapies. In certain embodiments, the one or more PAH therapies, are selected from the group consisting of phosphodiesterase-5 inhibitor (PDE-5i), soluble guanylate cyclase stimulator (sGCS), Endothelin receptor antagonist (ERA), and Prostacyclin-class therapy (prostacyclin = PCY).

Pharmaceutical Formulations

[0267] In some embodiments of the methods described herein, the ActRIIA proteins described herein are administered as a pharmaceutical composition comprising an ActRIIA protein and one or more pharmaceutical additives and/or excipients. In some embodiments, the pharmaceutical formulations are lyophilized. In some embodiments, the formulations are reconstituted from a lyophilized formulation. In other embodiments, the pharmaceutical formulations are liquid formulations. In other embodiments, the pharmaceutical formulations are stable liquid formulations.

[0268] In one embodiment of the pharmaceutical formulations provided herein, comprises 15, 30, 45, 60, 75 or 90 mg of an ActRIIA protein; citric acid monohydrate, tri-sodium citrate dehydrate, polysorbate 80, and sucrose.

[0269] In certain embodiments the dose is administered parenterally. In some embodiments, the dose is administered via subcutaneous injection. In some embodiments, the dose is administered via intradermal injection. In some embodiments, the dose is administered via intramuscular injection. In some embodiments, the dose is administered via intravenous injection. In some embodiments, the dose is self-administered.

[0270] In some embodiments, the lyophilized pharmaceutical formulation comprises a protein that comprises, consists essentially of, or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 9 or SEQ ID NO: 32. In certain such embodiments, the protein comprises an amino acid sequence that is least 90%, 95%, or 99% identical to SEQ ID NO: 9 or SEQ ID NO: 32, wherein the protein binds to activin and/or GDF11. In certain embodiments, the protein comprises the amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 32. In other embodiments, the protein consists of the amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 32.

[0271] In some embodiments, the lyophilized pharmaceutical formulation comprises a protein that comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32. In certain embodiments, the protein consists essentially of the amino acid sequence of SEQ ID NO: 32. In other embodiments, the protein consists of the amino acid sequence of SEQ ID NO: 32. In other embodiments, the protein consists of a variant of SEQ ID NO:32 lacking the C-terminal lysine residue (i.e. SEQ ID NO:41).

[0272] In certain embodiments, the protein is part of a homodimer protein complex.

[0273] In certain embodiments, the protein is glycosylated.

[0274] In certain embodiments, the pH range of the liquid pharmaceutical formulation or reconstituted lyophilized pharmaceutical formulation comprising an ActRIIA-Fc fusion protein is from 5 to 7. In some embodiments, the pharmaceutical formulation comprising an ActRIIA-Fc fusion protein further comprises a buffering agent. In some embodiments, the buffering agent is added in an amount of at least 10 mM. In some embodiments, the buffering agent is added in an amount in the range of between about 10 mM to about 200 mM. In some embodiments, the buffering agent comprises citrate.

[0275] In some embodiments, the pharmaceutical formulation further comprises a surfactant. In some embodiments, the surfactant comprises a polysorbate. In some embodiments, the surfactant comprises polysorbate 20 or polysorbate 80. In some embodiments, the surfactant comprises polysorbate 80.

[0276] In some embodiments, the pharmaceutical formulation further comprises a lyoprotectant. In some embodiments, the lyoprotectant comprises a sugar, such as a disaccharide (*e.g.*, sucrose). In some embodiments, the lyoprotectant comprises sucrose, trehalose, mannitol, polyvinylpyrrolidone (PVP), dextrose, and/or glycine. In some embodiments, the lyoprotectant comprises sucrose. In some embodiments, the lyophilized pharmaceutical formulation comprises the lyoprotectant and protein in a weight ratio of at least 1:1 protein to lyoprotectant. In some embodiments, the

lyophilized pharmaceutical formulation comprises the lyoprotectant and protein in a weight ratio of from 1:1 to 1:10 protein to lyoprotectant. In some embodiments, the lyophilized pharmaceutical formulation comprises the lyoprotectant and protein in a weight ratio of 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10 protein to lyoprotectant. In some embodiments, the pharmaceutical formulation comprises the lyoprotectant and protein in a weight ratio of 1:6 protein to lyoprotectant. In certain embodiments of the foregoing, the lyophilized pharmaceutical formulation comprises lyoprotectant in an amount sufficient to stabilize the protein.

[0277] In certain embodiments of the methods described herein, the ActRIIA-Fc fusion proteins described herein are administered as liquid pharmaceutical formulations comprising a human ActRIIA-Fc fusion protein, or a variant, a buffer, a surfactant, a stabilizing agent, and optionally one or more antioxidants. In certain embodiments, the pharmaceutical formulations described herein, comprise a human ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, a buffer, a surfactant, a stabilizing agent, and optionally one or more antioxidants.

[0278] In certain embodiments of the methods described herein, the ActRIIA-Fc fusion proteins described herein are administered as liquid pharmaceutical formulations comprising ActRIIA-Fc fusion protein comprising SEQ ID NO: 32, or an ActRIIA-Fc fusion protein variant comprising SEQ ID NO:41, a buffer, a surfactant, a stabilizing agent, and optionally one or more antioxidants, wherein the buffer is not histidine.

Kits

[0279] The present disclosure provides a kit comprising a pharmaceutical formulation provided herein and an injection device. In certain embodiments of the kits disclosed herein, the injection device comprises a syringe. In certain such embodiments, the syringe is pre-filled with a stable liquid formulation.

[0280] In certain embodiments of the kits disclosed herein, the kit further comprises an injectable device for use in administering the sterile injectable solution parenterally. In some embodiments, the sterile injectable solution is administered via subcutaneous injection. In some embodiments, the sterile injectable solution is administered via intradermal injection. In some embodiments, the sterile injectable solution is administered via intramuscular injection. In some embodiments, the sterile injectable solution is administered via intravenous injection.

[0281] In certain embodiments of the kits disclosed herein, the kit further comprises an autoinjector for use in administering the sterile injectable solution. In some embodiments, the sterile injectable solution is self-administered. In some embodiments, the sterile injectable solution comprises a therapeutically effective dose.

Example 1: Analysis of Sotatercept Clinical Trial Data to Establish Weight Band

[0282] An integrated population pharmacokinetic model was developed using data from two Phase 1 studies in healthy participants, two Phase 2 studies (SPECTRA and PULSAR) and one Phase 3 study (STELLAR) in participants with pulmonary arterial hypertension (PAH), as described in Ait-Oudhia S, Jaworowicz D, Hu Z, Bihorel S, Hu S, Balasubrahmanyam B, Mistry B, de Oliveira Pena J, Wenning L, Gheyas F. Population pharmacokinetic modeling of sotatercept in healthy participants and patients with pulmonary arterial hypertension. CPT Pharmacometrics Syst Pharmacol. 2024 Aug;13(8):1380-1393. doi: 10.1002/psp4.13166. Epub 2024 May 29. PMID: 38812074; PMCID: PMC11330185. The relationships between sotatercept exposure and efficacy (e.g., 6MWD, PVR) and safety (e.g., hemoglobin) endpoints were assessed, and it was determined that the average steady-state concentration of sotatercept over a dosing interval (C_{avg}) was related to the assessed endpoints. It is therefore expected that similar sotatercept C_{avg} values will result in a similar safety and efficacy profile.

[0283] The population pharmacokinetic model was used to predict the average steady-state sotatercept C_{avg} for both weight-based and weight-banded dosing. A total of 250 sets of simulations were conducted incorporating parameter uncertainty (fixed effects parameters only) and inter-individual variability based on the population pharmacokinetic model. For each set of simulations, a virtual population of 2000 PAH patients was generated by sampling with replacement from PAH participants (n = 286) who received sotatercept treatment in STELLAR (n=162), PULSAR (n=103), and SPECTRA (n=21) (body weight range 39.6 to 136.4 kg across all three studies). For each virtual patient, C_{avg} values were calculated as area under the concentration-time curve (AUC) divided by the dosing interval of three weeks. For each set of simulations, the 5th, 25th, 50th, 75th, and 95th percentiles of C_{avg} values for the 2000 virtual patients were calculated. The median of these percentiles over the 250 sets of simulations were reported for each weight band and dose combination. For maintenance doses (e.g., 0.7 mg/kg for the weight-based dosing scheme), steady state C_{avg} values

were calculated; for initial doses (e.g., 0.3 mg/kg for the weight-based dosing scheme), Cavg values over week 1 to week 3 were calculated.

[0284] Five weight bands ranging from <50 kg to ≥ 125 kg as well as corresponding doses (total of 6 dose strengths for initial and maintenance doses) were selected after exploring numerous weight band and dose combinations. Selection of weight bands and corresponding doses were based on striking a balance among the following considerations: a) comparable distribution of Cavg overall and for each weight band; b) convenience to patients and health care providers; and c) practically reasonable number of weight bands and dose strengths. Fewer than the proposed number of weight bands/dose strengths would be more convenient but would lead to larger exposure differences.

[0285] The distributions of predicted Cavg for weight-banded dosing and weight-based dosing are presented in FIG. 2 and Table 6 for maintenance doses and in FIG. 3 and Table 7 for initial doses. The central tendency (median) and the spread of the Cavg in the proposed weight-banded dosing are similar to weight-based dosing for both maintenance and initial doses.

[0286] For maintenance doses, the median Cavg values in the proposed weight-banded dosing are comparable overall (within 1% of the median Cavg for weight-based dosing) and across individual weight bands (within 10% of the median Cavg for weight-based dosing) FIG.2 and Table 6. Efficacy and safety of sotatercept are driven primarily by maintenance doses and given the similar predicted exposures, efficacy and safety are expected to be comparable between weight-banded and weight-based dosing.

[0287] For initial doses, the median Cavg in the proposed weight-banded dosing is similar overall (within 9% of the median Cavg for weight-based dosing) and across individual weight bands (within 20% of the median Cavg for weight-based dosing) FIG. 3 and Table 7. The slightly lower exposure in some weight bands for the initial dose is not expected to impact efficacy. Similarly, the slightly higher exposure in some weight bands is not expected to impact safety since the exposure with initial dose administration (0.3 mg/kg) is several fold lower compared to the steady state exposure for the maintenance dose (0.7 mg/kg Q3W).

[0288] In general, the simulation results demonstrate that the proposed weight-banded doses (initial and maintenance) of sotatercept are expected to provide comparable exposures to weight-based dosing.

[0289] Table 6: Predicted steady state Cavg following administration of weight-banded and weight-based (0.7 mg/kg) doses

Body Weight (kg)	Weight-based dosing (Q3W)		Proposed Weight-Banded Dose (Q3W)		Ratio of median Cavg (weight band/weight based)
	Dose (mg/kg)	Cavg (ng/mL)*	Dose (mg)	Cavg (ng/mL)*	
<50	0.7	7831 [4249 - 13375]	30	7349 [3960 - 12615]	0.94
≥50 – <75	0.7	8205 [4395 - 14267]	45	8437 [4435 - 14962]	1.03
≥75 – <100	0.7	8680 [4664 - 15067]	60	8812 [4683 – 15541]	1.02
≥100 – <125	0.7	9005 [4883 - 15542]	75	8766 [4770 - 15097]	0.97
≥125	0.7	9490 [5267 - 16003]	90	9124 [5066 - 15485]	0.96
All Weights	0.7	8379 [4476 - 14640]	Overall	8491 [4468 - 15076]	1.01
* Median [5 th percentile – 95 th percentile] are presented					

[0290] Table 7: Predicted Cavg (week 1 to week 3) following administration of weight-band based and weight-based (0.3 mg/kg) doses

Body Weight (kg)	Weight-based dosing		Proposed Weight-Banded Dose		Ratio of median Cavg (weight band/weight based)
	Dose (mg/kg)	Cavg (ng/mL)*	Dose (mg)	Cavg (ng/mL)*	
<50	0.3	1346 [772 - 2132]	15	1469 [836 - 2339]	1.09
≥50 – <75	0.3	1478 [837 - 2308]	15	1180 [662 - 1892]	0.80
≥75 – <100	0.3	1597 [914 - 2475]	30	1890 [1072 - 2975]	1.18
≥100 – <125	0.3	1688 [975 - 2570]	30	1534 [890 - 2366]	0.91
≥125	0.3	1757 [1034 - 2665]	45	1976 [1161 - 3016]	1.12
Overall	0.3	1519 [854 - 2393]	Overall	1388 [728 - 2562]	0.91
* Median [5 th percentile – 95 th percentile] are presented					

[0291] The disclosed subject matter is not to be limited in scope by the specific embodiments and examples described herein. Indeed, various modifications of the disclosure in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[0292] All references (*e.g.*, publications or patents or patent applications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual reference (*e.g.*, publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Other embodiments are within the following claims.

Table 6: Sequences		
SEQ ID NO:	Description	Sequence
1	AA a native amino acid sequence that may be used for the Fc portion of human IgG1 (G1Fc)	THTCPPCPAP ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLS LSPGK
3	AA a G3Fc sequence containing a short hinge region consisting of a single 15-residue segment	EPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRTQKSLSLSPGK
4	AA Fc portion of human IgG3 (G3Fc).	ELKTPGLDTHHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRTQKSLSLSPGK
6	AA a native amino acid sequence that may be used for the Fc portion of human IgG2 (G2Fc)	VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
9	AA canonical human ActRIIA precursor protein sequence	MGAAAKLAFA VFLISCSSGAILGRSETQECLFFNANWEKD RTNQTGVEPCYGDGDKRRHCFATWKNISGSIEIVKQGCW LDDINCYDRDTCVEKKDSPEVYFCCCEGNMCNEKFSYFPEM EVTQPTSNPVTTPKPPYYNILLVSLVPLMLIAGIVICAFWV YRHHKMAYPPVLVPTQDPGPPPPSPLLGLKPLQLLEVKA RGRFGCVWKAQLLNEYVAVKIFPIQDKQSWQNEYEVYS

		LPGMKHENILQFIGAEKRGTSVDVDLWLITAFHEKGSLSDFLKANVVSWNELCHIAETMARGLAYLHEDIPGLKDGHKPAISHRDIKSKNVLLKNNLTACIADFGLALKFEAGKSAGDTHGQVGTRRYMAPEVLEGAINFQRDAFLRIDMYAMGLVLWELASRCTAADGPVDEYMLPFEEEIGQHPSLEDMQEVVVHKKKRPVLRDYWQKHAGMAMLCETIEECWDHDAEARLSAGCVGERITQMQRLTNIIT TEDIVTVVTMTNVDFPPKESSL
10	AA processed (mature) extracellular human ActRIIA polypeptide sequence	ILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPP
11	AA processed (mature) extracellular human ActRIIA polypeptide sequence with the “tail” deleted (a Δ15 sequence)	ILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEM
12	NT nucleic acid sequence encoding human ActRIIA precursor protein	atgggagctg ctgcaaagtt ggcgtttgcc gtctttctta tctcctgttc ttcagggtgct atacttggtg gatcagaaac tcaggagtgt cttttcttta atgctaattg ggaaaaagac agaaccaatc aaactggtgt tgaaccgtgt tatggtgaca aagataaacg gcggcattgt tttgctacct ggaagaatat ttctggttcc attgaaatag tgaacaagg ttgttggtctg gatgatatac actgctatga caggactgat tgtgtagaaa aaaaagacag ccctgaagta tatttttggt gctgtgaggg caatatgtgt aatgaaaagt tttcttattt tccggagatg gaagtcacac agcccacttc aaatccagtt acacctaagc caccctatta caacatcctg ctctattcct tggtgccact tatgttaatt gcggggattg tcatttggtg attttggtg tacaggcatc acaagatggc ctaccctcct gtacttggtc caactcaaga cccaggacca ccccccactt ctccattact aggtttgaaa cactgcagt tattagaagt gaaagcaagg ggaagatttg gttgtgtctg gaaagcccag ttgcttaacg aatatgtggc tgtcaaaata tttccaatac aggacaaaca gtcatggcaa aatgaatacg aagtctacag tttgcctgga atgaagcatg agaacatatt acagttcatt ggtgcagaaa aacgaggcac cagtgttgat gtggatcttt ggctgatcac agcatttcat gaaaagggtt cactatcaga ctttcttaag

		gctaattgtgg tctcttggaa tgaactgtgt catattgcag aaaccatggc tagaggattg gcatattttac atgaggatat acctggccta aaagatggcc acaaacctgc catatctcac agggacatca aaagtaaaaa tgtgctgttg aaaaacaacc tgacagcttg cattgctgac tttgggttgg ccttaaaatt tgaggctggc aagtctgcag gcgataccca tggacagggt ggtacccgga ggtacatggc tccagaggta ttagagggtg ctataaactt ccaaagggat gcatttttga ggatagatat gtatgccatg ggattagtcc tatgggaact ggcttctcgc tgtactgctg cagatggacc tgtagatgaa tacatgttgc catttgagga ggaaattggc cagcatccat ctcttgaaga catgcaggaa gttgttgtgc ataaaaaaaa gaggcctgtt ttaagagatt attggcagaa acatgctgga atggcaatgc tctgtgaaac cattgaagaa tgttgggac acgacgcaga agccaggtta tcagctggat gtgtaggatga aagaattacc cagatgcaga gactaacaaa tattattacc acagaggaca ttgtaacagt ggtcacaatg gtgacaaatg ttgactttcc tcccaaagaa tctagtcta
13	NT nucleic acid sequence encoding processed soluble (extracellular) human ActRIIA	atacttggta gatcagaaac tcaggagtgt cttttcttta atgctaattg ggaaaaagac agaaccaatc aaactgggtg tgaaccgtgt tatggtgaca aagataaacg gcggcattgt tttgctacct ggaagaatat ttctggttcc attgaaatag tgaaacaagg ttgttggtg gatgatatca actgctatga caggactgat tgtgtagaaa aaaaagacag ccctgaagta tatttttgtt gctgtgaggg caatatgtgt aatgaaaagt tttcttattt tccggagatg gaagtcacac agcccacttc aaatccagtt acacctaagc caccc
19	AA linker	GGG
20	AA linker	GGGG
21	AA linker	TGGGG
22	AA linker	SGGGG
23	AA linker	TGGG
24	AA linker	SGGG
25	AA linker	GGGGS
32	AA ActRII-hFc	ILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRH CFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPE VYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVT PKPTGG GTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPVPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV

		EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
41	AA ActRII-hFc lacking C- terminal lysine	ILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRH CFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPE VYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPTGG GTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPVPPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG
62	AA <i>Ovis aries</i> ActRIIA extracellular domain	ILGRSETQECLFYNNANWERDRTNRTGVESCYGDKDKRR HCFATWXNISGSIDIVKQGCWLDDINCYDRTDCIEKKDSP EVYFCCCEGNMCNERFSYFPEMEVTQPTSNPVTPKPP
65	AA <i>Gallus gallus</i> ActRIIA extracellular domain	ILGRSETQECLYYNANWEKDKTNRSGIEPCYGDKDKRRH CFATWXNISGSIEIVKQGCWLDDINCYDRNDICIEKKDSPE VFFCCCEGNMCNERFFYFPEMEVTQPTSNPVTPKPP
66	AA <i>Bos Taurus</i> ActRIIA extracellular domain	ILGRSETQECLFYNNANWERDRTNRTGVESCYGDKDKHR HCFATWXNISGSIEIVKQGCWLDDINCYDKTDCIEKKDSP EVYFCCCEGNMCNERFSYFPEMEVTQPTSNPVTPKPP
67	AA <i>Tyto alba</i> ActRIIA extracellular domain	ILGRSETQECLYYNANWEKDKTNRSGIEPCYGDKDKRRH CFATWXNISGSIEIVKQGCWLDDINCYDRNDICIEKKDSPE VFFCCCEGNMCNERFFYFPEMEVTQPTSNPVTPKPP
68	AA <i>Myotis davidii</i> ActRIIA extracellular domain	ILGRSETQECIFYNNANWERDKNRTGVELCYGDKDKRRH CFATWXNISGSIEIVKQGCWLDDINCYDRTDCIEKKDSPE VYFCCCEGNMCNERFSYFPEMEVTQPTSNPVTPKPP

WHAT IS CLAIMED IS:

1. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant consisting of a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the initial dose is 15 mg or a factor of 15 mg and the initial dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting as the initial dose, the dose that is pre-selected for the weight band that corresponds to the patient's weight.
2. The method of claim 1, wherein the initial dose is selected from one the following pre-determined weight bands:
 - (a) 15 mg for a patient weighing less than 50 kg,
 - (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,
 - (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,
 - (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg, or
 - (e) 45 mg for a patient weighing 125 kg or more.
3. The method of claim 2, further comprising administering to the patient a maintenance dose of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the maintenance dose is a factor of 15 mg and the maintenance dose is determined by comparing the patient's weight to a list of pre-determined weight bands and selecting, as the maintenance dose the dose that is pre-selected for the weight band that corresponds to the patient's weight, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.
4. The method of claim 3, wherein the maintenance dose is selected from one the following pre-determined weight bands:
 - (a) 30 mg for a patient weighing less than 50 kg,
 - (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,
 - (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,
 - (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg, or

- (e) 90 mg for a patient weighing 125 kg or more.
5. The method of claim 4, wherein the maintenance dose is administered to the patient every 3 weeks.
6. The method of any one of claims 3-5, wherein the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient via subcutaneous injection.
7. The method of any one of claims 3-6, wherein the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.
8. The method of claim 7, wherein the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.
9. The method of claim 7 or 8, wherein the initial dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.
10. The method of any one of claims 3-9, wherein the maintenance dose(s) are each administered in a single injection.
11. The method of any one of claims 3-9, wherein the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg is administered to the patient in a single injection.
12. The method of any one of claims 3-9, wherein the patient weighs 125 kg or more, wherein the maintenance dose of 90 mg is administered to the patient in two or more injections.
13. The method of any one of claims 3-12, wherein the maintenance dose is administered to the patient every 3 weeks for 72 weeks or less.

14. The method of any one of claims 3-13, wherein the maintenance dose is administered to the patient every 3 weeks for 72 weeks or more.

15. The method of any one of claims 1-14, wherein the patient is treated with one or more additional PAH therapies.

16. The method of any claim 15, wherein the one or more additional PAH therapies are selected from the group consisting of a phosphodiesterase-5 inhibitor (PDE-5i), a soluble guanylate cyclase stimulator (sGCS), an endothelin receptor antagonist (ERA), and a prostacyclin-class therapy.

17. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, wherein the initial dose is selected from the group consisting of:

- (a) 15 mg for a patient weighing less than 50 kg,
- (b) 15 mg for a patient weighing from 50 kg up to, but not including 75 kg,
- (c) 30 mg for a patient weighing from 75 kg up to, but not including 100 kg,
- (d) 30 mg for a patient weighing from 100 kg up to, but not including 125 kg, and
- (e) 45 mg for a patient weighing 125 kg or more.

18. The method of claim 17, further comprising administering to the patient a maintenance dose of sotatercept or a sotatercept variant lacking the C-terminal lysine, approximately 3 weeks after the initial dose, wherein the maintenance dose is selected from the group consisting of:

- (a) 30 mg for a patient weighing less than 50 kg,
- (b) 45 mg for a patient weighing from 50 kg up to, but not including 75 kg,
- (c) 60 mg for a patient weighing from 75 kg up to, but not including 100 kg,
- (d) 75 mg for a patient weighing from 100 kg up to, but not including 125 kg, and
- (e) 90 mg for a patient weighing 125 kg or more.

19. The method of claim 18, wherein two or more maintenance doses are administered to the patient, with approximately three weeks between each dose.

20. The method of any one of claims 17-19, wherein the initial dose and/or the maintenance dose(s) are administered to the patient via subcutaneous injection.
21. The method of any one of claims 17-20, wherein the initial dose and/or the maintenance dose(s) are administered to the patient with an autoinjector.
22. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 10-50 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant consisting of a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the patient weighs less than 150 kg.
23. The method of claim 22, wherein the patient is administered 15-45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant.
24. The method of claim 22, wherein the patient is administered 10-20 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.
25. The method of claim 22, wherein the patient is administered 20-30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 125 kg.
26. The method of claim 22, wherein the patient is administered 30-50 mg of a human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.
27. The method of claim 22, wherein the patient is administered 15 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.
28. The method of claim 22, wherein the patient is administered 15 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50 kg.

29. The method of claim 22, wherein the patient is administered 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 75 kg up to, but not including 100 kg.
30. The method of claim 22, wherein the patient is administered 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 100 kg up to, but not including 125 kg.
31. The method of claim 22, wherein the patient is administered 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 125 kg up to, but not including 150 kg.
32. The method of any one of claims 22 to 32, further comprising administering to the patient a maintenance dose of 20-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.
33. The method of claim 32, wherein the patient is administered 20-40 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50 kg.
34. The method of claim 32, wherein the patient is administered 40-50 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 75 kg.
35. The method of claim 32, wherein the patient is administered 50-70 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 100 kg.
36. The method of claim 32, wherein the patient is administered 70-80 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 125 kg.

37. The method of claim 32, wherein the patient is administered 80-90 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 150 kg.

38. The method of claim 32, wherein the patient is administered 30 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs less than 50kg.

39. The method of claim 32, wherein the patient is administered 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 50 kg up to, but not including 75 kg.

40. The method of claim 32, wherein the patient is administered 60 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs from 75 kg, but not including 100 kg.

41. The method of claim 32, wherein the patient is administered 75 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs 100 kg up to, but not including 125 kg.

42. The method of claim 32, wherein the patient is administered 75 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs 125 kg up to, but not including 150 kg.

43. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 40-50 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41, wherein the patient weighs more than or equal to 125kg.

44. The method of claim 43, wherein the patient is administered 40-50 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.

45. The method of claim 43, wherein the patient is administered 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.
46. The method of claim 43, wherein the patient is administered 45 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.
47. The method of claim 43, further comprising administering to the patient a maintenance dose of 50-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.
48. The method of claim 47, wherein the patient is administered 75-100 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 125kg.
49. The method of claim 47, wherein the patient is administered 90 mg of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the patient weighs more than or equal to 150kg.
50. The method of any one of claims 47-49, wherein the patient is administered the initial dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant and the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant, wherein the maintenance dose is administered to the patient approximately 3 weeks after the initial dose.
51. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth

in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs less than 50kg.

52. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 15 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1 and administering to the patient a maintenance dose of 45 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs [50-75) kg.

53. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of between 50-100 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs more than or equal to 75 kg.

54. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 60 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs between [75-100) kg.

55. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 30 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 75 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs between [100-125) kg.

56. A method for treating pulmonary arterial hypertension in a patient in need thereof comprising administering to the patient an initial dose of 45 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 on Day 1, and administering to the patient a maintenance dose of 90 mg of a human ActRIIA-Fc fusion protein comprising a sequence of amino acids as set forth in SEQ ID NO: 32, or a human ActRIIA-Fc fusion protein variant comprising a sequence of amino acids as set forth in SEQ ID NO: 41 once every three weeks starting from Day 1, wherein the patient weighs more than or equal to 125kg.

57. The method of any one of claims 50-56, wherein the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient via subcutaneous injection.

58. The method of any one of claims 50-56, wherein the initial dose and/or the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

59. The method of claim 50-56, wherein the maintenance dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

60. The method of claim 50-56, wherein the initial dose of the human ActRIIA-Fc fusion protein or the human ActRIIA-Fc fusion protein variant is administered to the patient with an autoinjector.

61. The method of any one of claims 50-56, wherein the maintenance dose(s) are each administered in a single injection.