fusion protein consists of the amino acid sequence of SEQ ID NO: 32 or 41. In an aspect, there is provided a pharmaceutical formulation comprising 50-75 mg/mL of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO:41, 4-50 mM citrate buffer, 0.01-0.05% weight/volume (w/v) polysorbate 80, and 8-10% (w/v) sucrose, and wherein the pharmaceutical formulation has a pH of 5.5-6.5. In some

[0020] In certain examples, the pharmaceutical formulations described herein do not contain a salt.

[0021] Also described herein are lyophilized pharmaceutical formulations made by lyophilizing the liquid formulations described herein. In another aspect, there is provided a lyophilized pharmaceutical formulation comprising 15-100 mg of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.1-1.0 mg of citric acid monohydrate, 1.0-5.0 mg tri-sodium citrate dihydrate, 0.1-1.0 mg polysorbate 80, and 50-150 mg sucrose. Also described herein are pharmaceutical formulations, wherein the formulation is reconstituted from a lyophilized formulation. In another aspect, there is provided a reconstituted pharmaceutical formulation comprising a lyophilized pharmaceutical formulation and water, wherein the lyophilized pharmaceutical formulation comprises 15-100 mg of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.1-1.0 mg of citric acid monohydrate, 1.0-5.0 mg tri-sodium citrate dihydrate, 0.1-1.0 mg polysorbate 80, and 50-150 mg sucrose.

[0022] In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection to a final protein concentration of 10-100 mg/mL. In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection to a final protein concentration of 45-55 mg/mL. In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection to a final protein concentration of approximately 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 45 mg/mL, 46 mg/mL, 47 mg/mL, 48 mg/mL, 49 mg/mL, 50 mg/mL, 51 mg/mL, 52 mg/mL, 53 mg/mL, 54 mg/mL, 55 mg/mL, 60 mg/mL, 65 mg/mL, 70 mg/mL, 75 mg/mL mg/mL, 80 mg/mL, 85 mg/mL, 90 mg/mL, 95 mg/mL or 100 mg/mL. In certain examples, the human ActRIIa fusion protein is present in an amount of about 75 mg/mL or less. In certain examples, the human ActRIIa fusion protein is present in an amount of about 50 mg/mL.

[0023] In some examples, the protein is provided in a lyophilized pharmaceutical formulation in a vial. In some examples, the lyophilized formulation comprises an ActRIIa fusion protein as defined herein in an amount of 45 mg/vial or 60 mg/vial.

[0024] In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation is

reconstituted with Sterile Water for Injection to a final protein concentration of approximately 45 mg/mL, 46 mg/mL, 47 mg/mL, 48 mg/mL, 49 mg/mL, 50 mg/mL, 51 mg/mL, 52 mg/mL, 53 mg/mL, 54 mg/mL, or 55 mg/mL. In some examples, the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection to a final protein concentration of approximately 50 mg/mL.

[0025] In certain embodimens, the lyophilized formulation is reconstituted with approximately 0.5 mL to 1.8 mL of Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation is reconstituted with approximately 0.5 mL, 0.56 mL, 0.58 mL, 0.6 mL, 0.62 mL, 0.64 mL, 0.66 mL, 0.68 mL, 0.70 mL, 0.72 mL, 0.74 mL, 0.76 mL, 0.78 mL, 0.8 mL, 0.8 2mL, 0.84 mL, 0.86 mL, 0.88 mL, 0.9 mL, 0.9 2 mL, 0.94 mL, 0.96 mL, 0.98 mL, 1 mL, 1.1 mL, 1.15 mL, 1.2 mL, 1.25 mL, 1.3 mL, 1.35 mL, 1.4 mL, 1.45 mL, 1.5 mL, 1.55 mL, 1.6 mL, 1.65 mL, 1.7 mL, 1.75 mL, or 1.8 mL of Sterile Water for Injection. In some examples,

the lyophilized pharmaceutical formulation comprises an ActRIIa fusion protein that is provided in an amount of 45 mg/vial, and the formulation is reconstituted with 0.9 mL, 0.95 mL, 1 mL or 1.1 mL of Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation comprises an ActRIIa fusion protein that is provided in an amount of 45 mg/vial, and the formulation is reconstituted with 1.1 mL of Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation comprises an ActRIIa fusion protein that is provided in an amount of 60 mg/vial, and wherein the formulation is reconstituted with 0.90 mL, 0.95 mL, 1.00 mL, 1.05 mL, 1.10 mL, 1.15 mL, 1.20 mL, 1.25 mL, 1.30 mL, 1.35 mL, 1.40 mL, 1.45 mL or 1.50 mL of Sterile Water for Injection. In some examples, the lyophilized pharmaceutical formulation comprises an ActRIIa fusion protein that is provided in an amount of 60 mg/vial, and wherein the formulation is reconstituted with 1.30 mL of Sterile Water for Injection.

[0026] In certain examples, the lyophilized formulation is provided in an amount of 45mg/vial, and wherein the formulation is reconstituted with between 0.65 mL to 0.75 mL of Sterile Water for Injection. In certain examples, the lyophilized formulation is provided in an amount of 60 mg/vial, and wherein the formulation is reconstituted with between 0.65 mL to 1.75 mL of Sterile Water for Injection.

[0027] In certain examples, the lyophilized pharmaceutical formulation comprises a human ActRIIa fusion protein of SEQ ID NO: 32 or a variant of SEQ ID NO:32 lacking the C-terminal lysine (SEQ ID NO: 41), a buffer, a surfactant and a stabilizer, wherein the buffering agent is selected to be physiologically compatible and to maintain a pH of 5.8 when reconstituted with Sterile Water for Injection. In certain examples, the buffering agent comprises citrate. In certain, the stabilizer is sucrose. In certain examples, the surfactant is polysorbate 20 or polysorbate 80. In certain examples, the surfactant is polysorbate 80. In certain examples, the lyophilized pharmaceutical formulation comprises sotatercept, a buffer, a surfactant and a stabilizer, wherein the buffering agent is selected to be physiologically compatible and to maintain a pH of 5.8 when reconstituted with Sterile Water for Injection.

[0028] In certain examples, the lyophilized pharmaceutical formulation comprises a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 or comprising the amino acid sequence of SEQ ID NO: 41, citrate, polysorbate 80, and sucrose. In some examples, the human ActRIIa fusion protein consists of the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized formulation comprises a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and a human ActRIIa fusion

protein comprising the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized pharmaceutical formulation comprises sotatercept.

[0029] In certain examples, the lyophilized pharmaceutical formulation comprises 55.0 mg of a human ActRIIa fusion protein comprising the amino acid sequence ofof SEQ ID NO: 32 or a variant of SEQ ID NO:32 lacking the C-terminal lysine residue (e.g., comprising the amino acid sequence of SEQ ID NO: 41), 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose. In some examples, the human ActRIIa fusion protein consists of the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized formulation comprises a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized pharmaceutical formulation comprises sotatercept.

[0030] In certain examples, the lyophilized pharmaceutical formulation comprises a human ActRIIa fusion protein of 72.5 mg of SEQ ID NO: 32 or a variant of SEQ ID NO:32 lacking the C-terminal lysine residue (SEQ ID NO: 41), 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose In some examples, the human ActRIIa fusion protein consists of the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized formulation comprises a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO:41. In some examples, the lyophilized pharmaceutical formulation comprises sotatercept.

[0031] In certain examples, the reconstituted pharmaceutical formulation comprises 50 mg/mL of a human ActRIIa protein comprising the amino acid sequence of SEQ ID NO: 32 or a human ActRIIa protein comprising the amino acid sequence of SEQ ID NO:41, 10 mM citrate, 0.2 mg/ml polysorbate 80, and 80 mg/ml sucrose at pH 5.8. In some examples, the human ActRIIa fusion protein

consists of the amino acid sequence of SEQ ID NO:41. In some examples, the reconstituted formulation comprises a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and a human ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO:41. In some examples, the reconstituted pharmaceutical formulation comprises sotatercept. In an aspect, there is provided a reconstituted pharmaceutical formulation comprising a lyophilized pharmaceutical formulation and water, wherein the reconstituted pharmaceutical formulation comprises 50 mg/mL of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 10 mM citrate, 0.2 mg/mL polysorbate 80, and 80 mg/mL sucrose at pH 5.8.

[0032] In certain examples, the pharmaceutical formulations described herein contain a mixture of SEQ ID NO: 32 and a variant of SEQ ID NO:32 lacking the C-terminal lysine residue (SEQ ID NO: 41). In certain examples, the pharmaceutical formulations described herein contain a mixture of SEQ ID NO: 32 and a variant of SEQ ID NO:32 lacking the C-terminal

certain examples, the pharmaceutical formulations described herein contain 100% of SEQ ID NO: 32 by weight. In certain examples, the pharmaceutical formulations described herein contain 100% of SEQ ID NO: 41 by weight.

[0036] In some examples, the pharmaceutical formulation is administered parenterally (e.g., by intravenous infusion). In some examples, the pharmaceutical formulation is administered via subcutaneous injection. In certain examples, the formulation is contained in a glass vial or injection device.

[0037] Also described herein are methods of treating pulmonary arterial hypertension (PAH), comprising administering to a patient in need thereof a pharmaceutical formulation described herein.

[0038] Also described herein are uses of a pharmaceutical formulation for the treatment of pulmonary arterial hypertension (PAH), comprising administering to a patient in need thereof the pharmaceutical formulation described herein.

[0038a] In another aspect, there is provided use of a pharmaceutical formulation as defined herein, or a reconstituted pharmaceutical formulation as defined herein, in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH).

[0038b] In another aspect, there is provided use of a lyophilized pharmaceutical formulation as defined herein in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH).

[0038c] In another aspect, there is provided the pharmaceutical formulation as defined herein, or a reconstituted pharmaceutical formulation as defined herein, for use in therapy.

[0039] In some examples, the disclosure provides a lyophilized pharmaceutical formulation for the treatment of pulmonary arterial hypertension in a subject in need thereof comprising a human ActRIIa fusion protein of SEQ ID NO: 32, citrate, polysorbate 80, and sucrose, wherein the formulation is lyophilized. In some examples, the vial comprises a lyophilized pharmaceutical formulation comprising a human ActRIIa fusion protein of SEQ ID NO: 32, citric acid monohydrate, tri-sodium citrate dihydrate, polysorbate 80, and sucrose, wherein the formulation is lyophilized. In some examples, the vial comprises a lyophilized pharmaceutical formulation comprising 55 mg of the protein (i.e., ActRIIa fusion protein), 0.48 mg of citric acid monohydrate, 2.56 mg of tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose, wherein the formulation is lyophilized. In some examples, the vial comprises a lyophilized pharmaceutical formulation comprising 72.5 mg ActRIIa fusion protein, 0.64 mg citric acid monohydrate, 3.37 mg tri-sodium

WE CLAIM

1. A pharmaceutical formulation comprising 50-75 mg/mL of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO:41, 4-50 mM citrate buffer, 0.01-0.05% weight/volume (w/v) polysorbate 80, and 8-10% (w/v) sucrose, and wherein the pharmaceutical formulation has a pH of 5.5-6.5.

2. The pharmaceutical formulation of claim 1, wherein the pharmaceutical formulation comprises 50 mg/mL of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO:41,10 mM citrate buffer, 0.02% (w/v) polysorbate 80, and 8% (w/v) sucrose.

3. The pharmaceutical formulation of claim 1, wherein the pharmaceutical formulation has a pH of 5.8.

4. A lyophilized pharmaceutical formulation comprising 15-100 mg of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.1-1.0 mg of citric acid monohydrate, 1.0-5.0 mg tri-sodium citrate dihydrate, 0.1-1.0 mg polysorbate 80, and 50-150 mg sucrose.

5. The lyophilized pharmaceutical formulation of claim 4, wherein the lyophilized pharmaceutical formulation comprises 40 mg to 75 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41.

6. The lyophilized pharmaceutical formulation of claim 5, wherein the lyophilized pharmaceutical formulation comprises 45 mg or 60 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41.

7. The lyophilized pharmaceutical formulation of claim 4, wherein the lyophilized pharmaceutical formulation comprises 55 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose.

8. The lyophilized pharmaceutical formulation of claim 4, wherein the lyophilized pharmaceutical formulation comprises 72.5 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose.

9. The lyophilized pharmaceutical formulation of any one of claims 4-8, wherein the lyophilized pharmaceutical formulation is contained in a vial.

10. A reconstituted pharmaceutical formulation comprising a lyophilized pharmaceutical formulation and water, wherein the lyophilized pharmaceutical formulation comprises 15-100 mg of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.1-1.0 mg of citric acid monohydrate, 1.0-5.0 mg tri-sodium citrate dihydrate, 0.1-1.0 mg polysorbate 80, and 50-150 mg sucrose.

11. The reconstituted pharmaceutical formulation of claim 10, wherein the lyophilized pharmaceutical formulation comprises 40 mg to 75 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41.

12. The reconstituted pharmaceutical formulation of claim 11, wherein the lyophilized pharmaceutical formulation comprises 45 mg or 60 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41.

13. The reconstituted pharmaceutical formulation of claim 10, wherein the lyophilized pharmaceutical formulation comprises 55 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose.

14. The reconstituted pharmaceutical formulation of claim 10, wherein the lyophilized pharmaceutical formulation comprises 72.5 mg of the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose.

15. The reconstituted pharmaceutical formulation of claim 10, wherein the water is Sterile Water for Injection.

16. The reconstituted pharmaceutical formulation of claim 15, wherein the volume of the Sterile Water for Injection ranges from 0.8 mL to 1.5 mL.

17. The reconstituted pharmaceutical formulation of claim 16, wherein the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41 is provided in an amount of 45mg, and wherein the volume of the Sterile Water for Injection is 0.9 mL.

18. The reconstituted pharmaceutical formulation of claim 16, wherein the combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41 is provided in an amount of 60 mg, and wherein the volume of the Sterile Water for Injection is 1.2 mL.

19. A reconstituted pharmaceutical formulation comprising a lyophilized pharmaceutical formulation and water, wherein the reconstituted pharmaceutical formulation comprises 50 mg/mL of a combination of the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and the human ActRIIa-Fc fusion protein comprising the amino acid sequence of SEQ ID NO: 41, 10 mM citrate, 0.2 mg/mL polysorbate 80, and 80 mg/mL sucrose at pH 5.8.

20. The reconstituted pharmaceutical formulation of claim 19, wherein the reconstituted pharmaceutical formulation is suitable for subcutaneous administration.

21. The reconstituted pharmaceutical formulation of claim 19, wherein the reconstituted pharmaceutical formulation is contained in a vial or an injection device.

22. Use of a pharmaceutical formulation of any one of claims 1-3, or a reconstituted pharmaceutical formulation of any one of claims 10-21, in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH).

23. Use of a lyophilized pharmaceutical formulation of any one of claims 4-8 in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH).

24. The pharmaceutical formulation of any one of claims 1-3, or a reconstituted pharmaceutical formulation of any one of claims 10-21, for use in therapy.