[0008] Provided herein are pharmaceutical formulations comprising a recombinant fusion protein comprising an extracellular domain (ECD) of human activin receptor type-IIA (ActRIIa) or a variant thereof linked to a constant domain of an immunoglobulin, such as a human IgG1 Fc domain, and one or more pharmaceutical additives and/or excipients, wherein the formulation is lyophilized.

[0009] In some examples, the ActRIIa protein comprises an amino acid sequence that is at least 70% (e.g., at least 70%,75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to an amino acid sequence that begins at any one of amino acids 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 of SEQ ID NO: 9 and ends 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. In some examples, the ActRIIa protein comprises an amino acid sequence that is at least 70% (e.g., 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: 10. In some examples, the ActRIIa protein comprises an amino acid sequence that is at least 70% (e.g., 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: 11. In some examples, the ActRIIa protein is a fusion protein comprising an ActRIIa extracellular domain and one or more protein domains heterologous to ActRIIa. In some examples, the ActRIIa protein is a fusion protein comprising an Fc domain of an immunoglobulin. In some examples, the Fc domain of the immunoglobulin is an Fc domain of an IgG1 immunoglobulin. In some examples, 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 some examples, 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). In some examples, the ActRIIa fusion 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 examples, the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO: 32. In some examples, the ActRIIa fusion protein consists of the amino acid sequence of SEQ ID NO: 32. In some examples, the ActRIIa fusion protein consists of the amino acid sequence of SEQ ID NO: 41. In some examples, the ActRIIa

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 a human ActRIIa fusion protein, a buffer, a surfactant and a stabilizer, wherein the ActRIIa fusion protein comprisies the amino acid sequence of SEQ ID NO: 32 or SEQ ID NO:41. In some

examples, the ActRIIa fusion protein consists of a variant of the amino acid sequence set forth in SEQ ID NO: 32, wherein the sequence is lacking the C-terminal lysine residue of SEQ ID NO:32. In some examples, the ActRIIa fusion protein variant lacking the C-terminal lysine residue comprises or consists of the amino acid sequence of SEQ ID NO:41. In some examples, the ActRIIa fusion protein is part of a homodimer protein complex. In some examples, the ActRIIa fusion protein is glycosylated. In some examples, the ActRIIa fusion protein has a glycosylation pattern obtainable by expression in a Chinese hamster ovary cell.

[0010] The pharmaceutical formulations described herein comprise an ActRIIa fusion protein and one or more pharmaceutical additives and/or excipients. In certain examples, the pharmaceutical formulations described herein comprise a human ActRIIa fusion protein or a variant thereof, a buffer, a surfactant and a stabilizer.

[0011] In some examples, one or more of the pharmaceutical additives and/or excipients is a buffering agent. In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH above 2. In some examples, the buffering agent is selected to be physiologically compatible and capable of maintaining a reconstituted lyophilized solution described herein at a pH above 2. In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH of the pharmaceutical formulation at a pH of 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6 5.7, 5.8, 5.9 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, or 9.0. In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH of the pharmaceutical formulation between 5-7 (i.e., 5.0-7.0). In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH of the pharmaceutical formulation at a pH of 5.5, 5.6 5.7, 5.8, 5.9 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6 6.7, 6.8, 6.9 or 7.0. In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH of the pharmaceutical formulation between at a pH of 5.5-6.5 (i.e., from 5.5 to 6.5). In some examples, the buffering agent is selected to be physiologically compatible and to maintain a pH of the pharmaceutical formulation of 5.8.

[0012] In some examples, the buffering agent comprises organic acids, succinate, phosphate, acetate, citrate, citric acid, Tris, HEPES, amino acids, or mixtures of amino acids. In certain examples, the buffer is selected from the group consisting of sodium citrate, succinate, and histidine. In some examples, the buffering agent comprises citrate. In certain examples, wherein the buffer is citrate, the citrate buffer comprises tri-sodium citrate

dihydrate and citric acid monohydrate. In some examples, the buffering agent comprises tri-sodium citrate dihydrate. In some examples, the buffering agent comprises citric acid monohydrate. In some examples, the buffering agent comprises tri-sodium citrate dihydrate and citric acid monohydrate. In certain examples, wherein the protein has a negative charge due to the presence of glycans, the buffer is not histidine.

[0013] In some examples, the buffering agent is present in an amount of between 4 mM and 50 mM. In some examples, the buffering agent is present in a concentration of at least 0.1, 0.5, 0.7, 0.8 0.9, 1.0, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, or 500 mM. In some examples, the pharmaceutical formulation comprises at least 10 mM of buffering agent.

[0014] In some examples, the buffering agent is a citrate buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.5. In some examples, the buffering agent is a succinate buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.5. In some examples, the buffering agent is a histidine buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.0. In some examples, the buffering agent is a citrate buffer that maintains a pH of the pharmaceutical formulation at a pH of about 5.8. In some examples, the buffering agent is a succinate buffer that maintains a pH of the pharmaceutical formulation at a pH of about 5.8.

[0015] In some examples, the buffering agent is 10mM of a citrate buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.5. In some examples, the buffering agent is 10mM of a succinate buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.5. In some examples, the buffering agent is 10mM of a histidine buffer that maintains a pH of the pharmaceutical formulation at a pH from about 5.5 to about pH 6.0. In some examples, the buffering agent is 10mM of a citrate buffer that maintains a pH of the pharmaceutical formulation at a pH of about 5.8. In some examples, the buffering agent is 10mM of a succinate buffer that maintains a pH of the pharmaceutical formulation at a pH of about 5.8.

[0016] In some examples, one or more of the pharmaceutical additives and/or excipients is a surfactant. In some examples, the surfactant is selected from the group consisting of: sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride monohydrate, hexadecyltrimethylammonium bromide, CHAPS, CHAPSO, SB3-10, SB3-12,

digitonin, Triton X-100, Triton X-114, TWEEN-20, TWEEN-80, lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, and soy lecithin. In some examples, the surfactant is polysorbate 80 or polysorbate 20. In some examples, the surfactant is polysorbate 80.

[0017] In some examples, the surfactant is present in an amount of 0.05-0.3 mg/mL. In some examples, the pharmaceutical formulation comprises at least 0.001, 0.002, 0.003, 0.004, 0.005, 0.01, 0.02, 0.03, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 0.9, or 1.0% weight/volume of surfactant. In some examples, the pharmaceutical formulation comprises 0.01 to 0.05% weight/volume surfactant. In some examples, the pharmaceutical formulation comprises at least 0.02% weight/volume surfactant. In some examples, the pharmaceutical formulation comprises 0.02% weight/volume surfactant. In some examples, the pharmaceutical formulation comprises 0.02% polysorbate 80 or polysorbate 20.

[0018] In some examples, one or more of the pharmaceutical additives and/or excipients is a stabilizer. In some examples, the stabilizer is selected from the group consisting of: sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, poly-hydroxy compounds, polysaccharides, dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose, and hyaluronic acid. In some examples, the stabilizer is sucrose.

[0019] In some examples, the stabilizer is present in the pharmaceutical formulation at a concentration between 2-16% weight/volume. In some examples, the pharmaceutical formulation comprises between about 8% to about 10% weight/volume stabilizer. In some examples, the pharmaceutical formulation comprises at least 0.005% weight/volume, 0.01% weight/volume, 0.02% weight/volume, 0.03% weight/volume, 0.05% weight/volume, 0.06% weight/volume, 0.07% weight/volume, 0.08% weight/volume, 0.09% weight/volume, 0.1% weight/volume, 0.5% weight/volume, 0.7% weight/volume, 0.8% weight/volume, 0.9% weight/volume, 1.0% weight/volume, 1.2% weight/volume, 1.5% weight/volume, 1.7% weight/volume, 2% weight/volume, 3% weight/volume, 4% weight/volume, 5% weight/volume, 6% weight/volume, 7% weight/volume, 8% weight/volume, 9% weight/volume, 10% weight/volume, 11% weight/volume, 12% weight/volume, 13% weight/volume, 14% weight/volume, 15% weight/volume, 16% weight/volume, 17% weight/volume, 18% weight/volume, 19% weight/volume, or 20% weight/volume stabilizer. In some examples, the stabilizer is present at a concentration of at least 8% weight/volume.

[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 made by lyophilizing the formulation as defined herein. 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 made by reconstituting the lyophilized pharmaceutical formulation as defined herein.

[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 another aspect, there is provided a lyophilized pharmaceutical formulation comprising a human ActRIIa fusion protein, a buffer, a surfactant and a stabilizer, wherein the buffer is selected to be physiologically compatible and to maintain a pH of 5.8 when reconstituted with Sterile Water for Injection and wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41. 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 another aspect, there is provided a lyophilized pharmaceutical formulation comprising 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 another aspect, there is provided a lyophilized pharmaceutical formulation comprising 55.0 mg of a human ActRIIa fusion protein, 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose; wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41. 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 another aspect, there is provided a lyophilized pharmaceutical formulation comprising 72.5 mg of a human ActRIIa fusion protein, 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose; wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41. 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 another aspect, there is provided a reconstituted pharmaceutical formulation comprising 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.

[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

lysine residue (SEQ ID NO: 41) wherein the mixture contains 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, 50%, 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% by weight of SEQ ID NO:32.

[0033] 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) wherein the mixture contains about 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, 50%, 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% by weight of SEQ ID NO:32.

[0034] 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) wherein the mixture contains 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, 50%, 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% by weight of SEQ ID NO:41.

[0035] 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) wherein the mixture contains about 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, 50%, 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% by weight of SEQ ID NO:41.In

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 in the manufacture of a medicament for the treatment.

[0038b] In another aspect, there is provided use of the lyophilized pharmaceutical formulation as defined herein in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH) in a human patient in need thereof, wherein the lyophilized pharmaceutical formulation is to be reconstituted to create a reconstituted formulation, which is to be administered to the patient.

[0038c] In another aspect, there is provided the 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

citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose, wherein the formulation is lyophilized. In some examples, the human ActRIIa fusion protein is a variant of SEQ ID NO: 32 lacking the C-terminal lysine. In some examples, the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:41. In some examples, the human ActRIIa fusion protein is sotatercept.

[0040] In some examples, once reconstituted with Sterile Water, the vial comprises 50 mg/mL of the ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32, 10 mM citrate, 0.2 mg/ml polysorbate 80, and 8% by weight of sucrose. In some examples, the human ActRIIa fusion protein comprises or consists of the amino acid sequence of SEQ ID NO: 41, 10 mM citrate, 0.2 mg/ml polysorbate 80, and 8% by weight of sucrose. In some

examples, once reconstituted with Sterile Water, the vial comprises 50 mg/mL of sotatercept, 10 mM citrate, 0.2 mg/ml polysorbate 80, and 8% by weight of sucrose.

[0041] In some examples, the reconstituted pharmaceutical formulation comprises 50 mg/mL of an ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32, 10 mM citrate, 0.02 mg/ml polysorbate 80, and 80 mg/ml sucrose at pH 5.8. In some examples, the human ActRIIa protein comprises the amino acid sequence of SEQ ID NO: 41, 10 mM citrate, 0.02 mg/ml polysorbate 80, and 80 mg/ml sucrose at pH 5.8. In some examples, the reconstituted pharmaceutical formulation comprises 50 mg/mL of sotatercept, 10 mM citrate, 0.02 mg/ml polysorbate 80, and 80 mg/ml sucrose at pH 5.8.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] **Figure 1** shows components of a kit comprising a lyophilized pharmaceutical formulation comprising an ActRIIa fusion protein and an injection device. A vial (1) holds lyophilized pharmaceutical formulation comprising an ActRIIa fusion protein, reconstituted sterile injectable solution, or sterile injectable solution. A prefilled syringe (2) containing a reconstitution solution is used to reconstitute a lyophilized pharmaceutical formulation comprising an ActRIIa fusion protein from (1) into a sterile injectable solution. A vial adapter (3) couples the vial (1) to the pre-filled syringe (2) via attachment to the vial at one end, and attachment to the pre-filled syringe at an opposite end. A syringe (4) and needle (5) are provided for administration of sterile injectable solution. Swab wipes (6) are provided for sterilization of individual kit components.

[0043] **Figure 2** shows a multiple sequence alignment of various vertebrate ActRIIa proteins and human ActRIIa (SEQ ID NOs: 62-68).

Figures 3A and 3B show the purification of ActRIIa-hFc expressed in CHO cells. The protein purifies as a single, well-defined peak as visualized by sizing column (top panel) and Coomassie stained SDS-PAGE (bottom panel) (left lane: molecular weight standards; right lane: ActRIIa-hFc).

Figures 4A and 4B show the binding of ActRIIa-hFc to activin (top panel) and GDF-11 (bottom bpanel), as measured by Biacore™ assay.

[0044] **Figure 5** shows the effect of pH and buffer on % monomer species by HP-SEC after 6M at 25 °C.

[0045] **Figure 6** shows the effect of pH and buffer on binding activity by Biacore™ after 6M 25 °C stability.

WE CLAIM

1. A pharmaceutical formulation comprising a human ActRIIa fusion protein, a buffer, a surfactant and a stabilizer, wherein the ActRIIa fusion protein comprisies the amino acid sequence of SEQ ID NO: 32 or SEQ ID NO:41.

2. The pharmaceutical formulation of claim 1, wherein the buffer is selected from the group consisting of sodium citrate, succinate, and histidine.

3. The pharmaceutical formulation of claim 1 or 2 wherein the buffer is present in an amount of between 4 mM and 50 mM.

4. The pharmaceutical formulation of claim 1 or 2 wherein the buffer is present in an amount of about 10 mM.

5. The pharmaceutical formulation of claim 1 or 2 wherein the buffer is a citrate buffer at a pH from about 5.5 to about pH 6.5.

6. The pharmaceutical formulation of claim 1 or 2 wherein the buffer is a succinate buffer at a pH from about 5.5 to about pH 6.5.

7. The pharmaceutical formulation of claim 1, or 2 wherein the buffer is a histidine buffer at a pH from about 5.5 to about pH 6.0.

8. The pharmaceutical formulation of claim 1, or 2 wherein the buffer is a citrate buffer at a pH 5.8.

9. The pharmaceutical formulation of claim 1 or 2 wherein the buffer is a succinate buffer at a pH of 5.8.

10. The pharmaceutical formuation of claim 5 or 8, wherein the citrate buffer comprises citric acid monohydrate and tri-sodium citrate dihydrate.

11. The pharmaceutical formulation of any one of claims 1-10, wherein the surfactant is polysorbate 80 or polysorbate 20.

12. The pharmaceutical formulation of claim 11, wherein the surfactant is present in an amount of from about 0.01 to about 0.05 weight/volume.

13. The pharmaceutical formulation of claim 11, wherein the surfactant is present in an amount of about 0.02% weight/volume.

14. The pharmaceutical formulation of any one of claims 1-13, wherein the stabilizer is sucrose.

15. The pharmaceutical formulation of claim 14 wherein sucrose is present in an amount of about 8% to about 10% weight/volume.

16. The pharmaceutical formulation of claim 14 wherein sucrose is present in an amount of about 8% weight/volume.

17. The pharmaceutical formulation of any one of claims 1-16, wherein the human ActRIIa fusion protein is present in an amount of about 75 mg/mL or less.

18. The pharmaceutical formulation of any one of claims 1-16, wherein the human ActRIIa fusion protein is present in an amount of about 50 mg/mL.

19. The pharmaceutical formulation of any one of claims 1-18, wherein the pharmaceutical formulation does not contain a salt.

20. The pharmaceutical formulation of any one of claims 1-19, wherein the ActRIIa fusion protein is sotatercept.

21. The pharmaceutical formulation of any one of claims 1-19, wherein the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO: 32.

22. The pharmaceutical formulation of any one of claims 1-19, wherein the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO: 41.

23. The pharmaceutical formulation of any one of claims 1-19, wherein the formulation comprises a first ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 32 and a second ActRIIa fusion protein comprising the amino acid sequence of SEQ ID NO: 41.

24. A lyophilized pharmaceutical formulation made by lyophilizing the formulation of any one of claims 1-23.

25. The lyophilized pharmaceutical formulation of claim 24, wherein the human ActRIIa fusion protein is provided in an amount of 45 mg/vial or 60 mg/vial.

26. A reconstituted pharmaceutical formulation made by reconstituting the lyophilized pharmaceutical formulation of claim 24.

27. The reconstituted pharmaceutical formulation of claim 26, wherein the lyophilized pharmaceutical formulation is reconstituted with Sterile Water for Injection.

28. The reconstituted pharmaceutical formulation of claim 26, wherein the lyophilized formulation is reconstituted with Sterile Water for Injection to a final protein concentration of approximately 45 mg/mL to 55 mg/mL.

29. The reconstituted pharmaceutical formulation of claim 28, wherein the lyophilized formulation is reconstituted with Sterile Water for Injection to a final protein concentration of approximately 50 mg/mL.

30. The reconstituted pharmaceutical formulation of claim 26, wherein the lyophilized formulation is reconstituted with approximately 0.5 mL to 1.8 mL of Sterile Water for Injection.

31. The reconstituted pharmaceutical formulation of claim 26, wherein the lyophilized formulation is provided in an amount of 45mg/vial, and wherein the formulation is reconstituted with between 0.65 mLto 0.75 mL of Sterile Water for Injection.

32. The reconstituted pharmaceutical formulation of claim 26, wherein 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.

33. A lyophilized pharmaceutical formulation comprising a human ActRIIa fusion protein, a buffer, a surfactant and a stabilizer, wherein the buffer is selected to be physiologically compatible and to maintain a pH of 5.8 when reconstituted with Sterile Water for Injection and wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

34. The lyophilized pharmaceutical formulation of claim 33, wherein the buffer comprises citrate.

35. The lyophilized pharmaceutical formulation of claim 33 or 34, wherein the stabilizer is sucrose.

36. The lyophilized pharmaceutical formulation of any one of claims 33-35, wherein the surfactant is polysorbate 20 or polysorbate 80.

37. The lyophilized pharmaceutical formulation of claim 36, wherein the surfactant is polysorbate 80.

38. A lyophilized pharmaceutical formulation comprising a human ActRIIa fusion protein, citrate, polysorbate 80, and sucrose, wherein the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

39. A lyophilized pharmaceutical formulation comprising 55.0 mg of a human ActRIIa fusion protein, 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, and 88.0 mg sucrose; wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

40. A lyophilized pharmaceutical formulation comprising 72.5 mg of a human ActRIIa fusion protein, 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg

polysorbate 80, and 116.0 mg sucrose; wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

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

42. The pharmaceutical formulation any one of claims 1-41, wherein the pharmaceutical formulation is administered via subcutaneous injection.

43. The pharmaceutical formulation of any one of claims 1-41, wherein the formulation is contained in a glass vial or injection device.

44. Use of a pharmaceutical formulation of any one of claims 1-43 in the manufacture of a medicament for the treatment treating pulmonary arterial hypertension (PAH).

45. Use of the lyophilized pharmaceutical formulation of any one of claims 24, 25, or 33-40 in the manufacture of a medicament for the treatment of pulmonary arterial hypertension (PAH) in a human patient in need thereof, wherein the lyophilized pharmaceutical formulation is to be reconstituted to create a reconstituted formulation, which is to be administered to the patient.

46. The pharmaceutical formulation of any one of claims 1-43, for use in therapy.