ACTRII PROTEINS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/223,265, filed July 19, 2021, the content of which is hereby incorporated by reference in its entirety.

FIELD

The present application describes a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII polypeptide. The application also relates to a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII polypeptide, wherein the polypeptide comprises an amino acid sequence that is at least 90% identical to an amino acid sequence corresponding to residues 30-110 of SEQ ID NO: 1.

BACKGROUND

Telangiectasia refers to a condition in which widened venules (tiny blood vessels) cause threadlike red lines or patterns on the skin. These patterns, or telangiectases, are thought to be caused by the release or activation of vasoactive substances under a multitude of conditions. While telangiectases are often benign, they may be caused by a serious illness such as hereditary hemorrhagic telangiectasia (HHT). In patients with HHT, telangiectases may appear in vital organs, such as the liver. The rupture of these telangiectases may result in life-threatening hemorrhaging.

Telangiectasia may manifest as a side effect upon the administration of certain drugs, such as an ALK-1 receptor fusion protein (dalantercept), an endoglin-neutralizing antibody (TRC105), and certain ActRII polypeptides (Garber K. Nat Biotechnol. 2016;34(5):458-461).

There is a high, unmet need for effective therapies for reducing the risk of telangiectasia in patients receiving one or more ActRII polypeptides for treatment of an underlying disease. Accordingly, it is an object of the present disclosure to provide methods for risk of telangiectasia in patients receiving an ActRII polypeptide.

SUMMARY

In one aspect, the present disclosure refers to use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein (i) one

or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for a period of 24 weeks; and (ii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, one or more doses of the ActRIIA fusion protein is to be administered to the patient in an amount that is reduced by at least half of the amount of the dose of (i); wherein the ActRIIA fusion protein comprises (a) an ActRIIA polypeptide comprising the amino acid sequence of SEQ ID NO: 2; (b) an Fc domain of an immunoglobulin; (c) a linker domain positioned between the ActRIIA polypeptide domain and the Fc domain of the immunoglobulin.

In another aspect, the present disclosure refers to use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein (i) one or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for 24 weeks; (ii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, skipping a dose, wherein the patient is not treated for 6 weeks after step (i); and (iii) resuming the administration of one or more doses of the ActRIIA fusion protein to the patient in an amount of 0.3 mg/kg once every 3 weeks for at least 24 weeks; wherein the ActRIIA fusion protein comprises (a) an ActRIIA polypeptide comprising the amino acid sequence of SEQ ID NO: 2; (b) an Fc domain of an immunoglobulin; (c) a linker domain positioned between the ActRIIA polypeptide domain and the Fc domain of the immunoglobulin.

In another aspect, the present disclosure refers to use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein (i) one or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for a period of 24 weeks or less; (ii) after step (i), one or more doses of the ActRIIA fusion protein is to be administered to the patient in an amount of 0.7 mg/kg once every 3 weeks as long as the patient does not show one or more symptoms or risk factors for developing telangiectasia; and (iii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, while receiving the dose of step (ii), one or more doses of the ActRIIA fusion protein is to be administered in lieu of the dose of step (ii), wherein the dose is to be administered in an amount of 0.3 mg/kg once every 3 weeks until symptoms improve; wherein the ActRIIA fusion protein comprises the amino acid sequence of SEQ ID NO: 2, thereby treating or preventing telangiectasia.

In certain examples, the disclosure provides a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII

polypeptide, wherein the method comprises administering the ActRII polypeptide on a dosing regimen comprising: (i) administering a first dose of ActRII polypeptide to a patient in an amount of 0.3 mg/kg; and (ii) administering a second dose of ActRII polypeptide to the patient in an amount of 0.7 mg/kg; wherein a third dose is initiated if the patient shows symptoms or comprises risk factors for developing telangiectasia, thereby decreasing the risk of telangiectasia. In certain examples, the disclosure provides a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII polypeptide, wherein the polypeptide comprises an amino acid sequence that is at least 90% identical to an amino acid sequence corresponding to residues 30-110 of SEQ ID NO: 1, wherein the method comprises administering the ActRII polypeptide on a dosing regimen comprising: (i) administering a first dose of ActRII polypeptide to a patient in an amount of 0.3 mg/kg; and (ii) administering a second dose of ActRII polypeptide to the patient in an amount of 0.7 mg/kg; wherein a third dose is initiated if the patient shows symptoms or comprises risk factors for developing telangiectasia, thereby decreasing the risk of telangiectasia. In some examples, the third dose comprises administering a dose of ActRII polypeptide to the patient in an amount of 0.3 mg/kg. In some examples, the third dose comprises withholding treatment of the ActRII polypeptide for a period of at least 2-6 weeks. In some examples, the third dose comprises withholding treatment of the ActRII polypeptide for a period of at least 3 weeks. In some examples, the first dose is administered to the patient for at least 3 weeks. In some examples, the second dose is administered for at least 21 weeks. In some examples, the second dose is administered for at least 45 weeks.

In certain examples, the disclosure provides a method of reducing a risk of telangiesctasia when treating a patient with an ActRII polypeptide, wherein the method comprises administering an ActRII polypeptide on a dosing regimen comprising: (i) administering one or more first doses of the ActRII polypeptide to a patient in an amount of 0.3 mg/kg one every 3 weeks for a period of 24 weeks; wherein if the patient shows one or more symptoms or risk factors for developing telangiectasia administering one or more second doses of the ActRII polypeptide to the patient in an amount that is reduced by at least half of the amount of the first dose.

In certain examples, the disclosure provides a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII polypeptide wherein the method comprises administering the ActRII polypeptide on a dosing

regimen comprising: (i) administering ActRII polypeptide to a patient in an amount of 0.3 mg/kg every 3 weeks; wherein if the patient shows symptoms or comprises risk factors for developing telangiectasia, administering ActRII polypeptide to a patient in an amount of 0.3 mg/kg every 6 weeks thereby decreasing the risk of telangiectasia. In certain examples, the disclosure provides a method of decreasing a risk of telangiectasia in a patient receiving a therapeutically effective amount of an ActRII polypeptide, wherein the polypeptide comprises an amino acid sequence that is at least 90% identical to an amino acid sequence corresponding to residues 30-110 of SEQ ID NO: 1, wherein the method comprises administering the ActRII polypeptide on a dosing regimen comprising: (i) administering the ActRII polypeptide to a patient in an amount of 0.3 mg/kg every 3 weeks; wherein if the patient shows symptoms or comprises risk factors for developing telangiectasia, administering ActRII polypeptide to a patient in an amount of 0.3 mg/kg every 6 weeks thereby decreasing the risk of telangiectasia. In some examples, the therapeutically effective amount of the ActRII polypeptide is 0.7 mg/kg every 3 weeks.

In certain examples, the disclosure provides a method of treating pulmonary arterial hypertension, wherein the method comprises administering to a patient in need thereof an ActRII polypeptide on a dosing regimen comprising: (i) administering a first dose of the ActRII polypeptide to the patient in an amount of 0.3 mg/kg; and (ii) administering a second dose of the ActRII polypeptide to the patient in an amount of 0.7 mg/kg once every 3 weeks for as long as the patient needs treatment; wherein the polypeptide comprises an amino acid sequence that is at least 90% identical to an amino acid sequence corresponding to residues 30-110 of SEQ ID NO: 1.

In some examples, the symptoms of telangiectasia are selected from the group consisting of pain, itching, threadlike red marks on the skin, mucocutaneous telangiectases, gastrointestinal bleeding, lesions on the skin, epistaxis, gingival bleeding, arteriovenous malformations, internal telangiectases, and red spots on the skin. In some examples, the symptoms of telangiectasia comprise lesions on the skin. In some examples, the symptoms of telangiectasia comprise gingival bleeding. In some examples, the symptoms of telangiectasia comprise epistaxis. In some examples, the symptoms of telangiectasia comprise arteriovenous malformations. In some examples, the symptoms of telangiectasia comprises internal telangiectases. In some examples, the arteriovenous malformations or internal telangiectases occur in internal organs (*e.g.*, brain, liver, lungs, spleen, urinary tract, and spine). In some examples, the risk factors for developing

telangiectasia are selected from the group consisting of: low BMP9 levels; low BMP10 levels; low VEGF levels; hereditary hemorrhagic telangiectasia (HHT); and connective tissue disease (CTD).

In some examples, the decreasing the risk comprises alleviating or improving the severity telangiectasia. In some examples, the decreasing the risk comprises preventing the progression of telangiectasia. In some examples, the third dose comprises withholding treatment of the ActRII polypeptide until the telangiectasia improves to ≤ Grade 1. In some examples, the method improves the severity of telangiectasia from Grade 2 to Grade 1. In some examples, the method improves the severity of telangiectasia from Grade 3 to Grade 2. In some examples, the method improves the severity of telangiectasia from Grade 3 to Grade 1. In some examples, the method prevents progression of the telangiectasia from Grade 1 to Grade 2. In some examples, the method prevents progression of the telangiectasia from Grade 2 to Grade 3. In some examples, the patient is receiving the ActRII polypeptide for the treatment of PH. In some examples, the patient is receiving the ActRII polypeptide for the treatment of PAH.

In some examples, the polypeptide comprises an amino acid sequence that is at least 95% identical to an amino acid sequence corresponding to residues 30-110 of SEQ ID NO: 1. In some examples, the polypeptide comprises an amino acid sequence that is at least 90% identical to an amino acid sequence corresponding to residues 21-135 of SEQ ID NO: 1. In some examples, the polypeptide comprises an amino acid sequence that is at least 95% identical to an amino acid sequence corresponding to residues 21-135 of SEQ ID NO: 1. In some examples, the ActRII polypeptide 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: 2. In some examples, the ActRII polypeptide 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: 3. In some examples, the ActRII polypeptide is a fusion protein further 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 Fc fusion protein further comprises a linker domain positioned between the ActRII polypeptide domain and the Fc domain of the immunoglobulin. In some examples, the linker domain is selected from the

group consisting of: TGGG (SEQ ID NO: 20), TGGGG (SEQ ID NO: 18), SGGGG (SEQ ID NO: 19), GGGGS (SEQ ID NO: 22), GGG (SEQ ID NO: 16), GGGG (SEQ ID NO: 17), and SGGG (SEQ ID NO: 21). In some examples, the ActRII polypeptide 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: 23. In some examples, the ActRII polypeptide 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: 40.

In some examples, the polypeptide is lyophilized. In some examples, the polypeptide is soluble. In some examples, the polypeptide is administered to the patient using subcutaneous injection. In some examples, the polypeptide is administered to the patient on a schedule selected from the group consisting of: every week, every 2 weeks, every 3 weeks, and every 4 weeks. In some examples, the polypeptide is administered to the patient every 3 weeks. In some examples, the polypeptide is administered to the patient every 4 weeks. In some examples, the polypeptide is part of a homodimer protein complex. In some examples, the polypeptide is glycosylated. In some examples, the polypeptide has a glycosylation pattern obtainable by expression in a Chinese hamster ovary cell. In some examples, the ActRII polypeptide binds to one or more ligands selected from the group consisting of: activin A, activin B, and GDF11. In some examples, the ActRII polypeptide binds to activin and/or GDF11. In some examples, the ActRII polypeptide further binds to one or more ligands selected from the group consisting of: BMP10, GDF8, and BMP6.

In some examples, the method further comprises administering to the patient an additional active agent and/or supportive therapy. In some examples, the additional active agent and/or supportive therapy is selected from the group consisting of: beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), diuretic agents, lipid-lowering medications, endothelin blockers, PDE5 inhibitors, prostacyclins, or a left ventricular assist device (LVAD). In some examples, the additional active agent and/or supportive therapy is selected from the group consisting of: prostacyclin and derivatives thereof (*e.g.*, epoprostenol, treprostinil, and iloprost); prostacyclin receptor agonists (*e.g.*, selexipag); endothelin receptor antagonists (*e.g.*, thelin,

ambrisentan, macitentan, and bosentan); calcium channel blockers (*e.g.*, amlodipine, diltiazem, and nifedipine; anticoagulants (*e.g.*, warfarin); diuretics; oxygen therapy; atrial septostomy; pulmonary thromboendarterectomy; phosphodiesterase type 5 inhibitors (*e.g.*, sildenafil and tadalafil); activators of soluble guanylate cyclase (*e.g.*, cinaciguat and riociguat); ASK-1 inhibitors (*e.g.*, CIIA; SCH79797; GS-4997; MSC2032964A; 3H-naphtho[1,2,3-de]quiniline-2,7-diones, NQDI-1; 2-thioxo-thiazolidines, 5-bromo-3-(4-oxo-2-thioxo-thiazolidine-5-ylidene)-1,3-dihydro-indol-2-one); NF-κB antagonists (*e.g.*, dh404, CDDO-epoxide; 2.2-difluoropropionamide; C28 imidazole (CDDO-Im); 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO); 3-Acetyloleanolic Acid; 3-Triflouroacetyloleanolic Acid; 28-Methyl-3-acetyloleanane; 28-Methyl-3-trifluoroacetyloleanane; 28-Methyloxyoleanolic Acid; SZC014; SCZ015; SZC017; PEGylated derivatives of oleanolic acid; 3-O-(beta-D-glucopyranosyl) oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[a-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid; 3-O-[alpha-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 28-O-β-D-glucopyranosyl-oleanolic acid; 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS1); oleanolic acid 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS2); methyl 3,11-dioxoolean-12-en-28-olate (DIOXOL); $ZCVI_4$-2; Benzyl 3-dehydr-oxy-1,2,5-oxadiazolo[3',4':2,3]oleanolate); a left ventricular assist device (LVAD), or lung and/or heart transplantation. In some examples, the patient has been treated with one or more agents selected from the group consisting of: phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin receptor agonist, and endothelin receptor antagonists. In some examples, the one or more agents is selected from the group consisting of: bosentan, sildenafil, beraprost, macitentan, selexipag, epoprostenol, treprostinil, iloprost, ambrisentan, and tadalafil. In some examples, the method further comprises administration of one or more agents selected from the group consisting of: phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin receptor agonist, and endothelin receptor antagonists. In some examples, the one or more agents is selected from the group consisting of: bosentan, sildenafil, beraprost, macitentan, selexipag, epoprostenol, treprostinil, iloprost, ambrisentan, and tadalafil. In some examples, the patient has been treated with one or more

vasodilators prior to administration of the polypeptide. In some examples, the method further comprises administration of one or more vasodilators. In some examples, the one or more vasodilators is selected from the group consisting of prostacyclin, epoprostenol, and sildenafil. In some examples, the vasodilator is prostacyclin. In some examples, the patient has been receiving one or more therapies for PAH. In some examples, the one or more therapies for PAH is selected from the group consisting of: prostacyclin and derivatives thereof (*e.g.*, epoprostenol, treprostinil, and iloprost); prostacyclin receptor agonists (*e.g.*, selexipag); endothelin receptor antagonists (*e.g.*, thelin, ambrisentan, macitentan, and bosentan); calcium channel blockers (*e.g.*, amlodipine, diltiazem, and nifedipine; anticoagulants (*e.g.*, warfarin); diuretics; oxygen therapy; atrial septostomy; pulmonary thromboendarterectomy; phosphodiesterase type 5 inhibitors (*e.g.*, sildenafil and tadalafil); activators of soluble guanylate cyclase (*e.g.*, cinaciguat and riociguat); ASK-1 inhibitors (*e.g.*, CIIA; SCH79797; GS-4997; MSC2032964A; 3H-naphtho[1,2,3-de]quiniline-2,7-diones, NQDI-1; 2-thioxo-thiazolidines, 5-bromo-3-(4-oxo-2-thioxo-thiazolidine-5-ylidene)-1,3-dihydro-indol-2-one); NF-κB antagonists (*e.g.*, dh404, CDDO-epoxide; 2.2-difluoropropionamide; C28 imidazole (CDDO-Im); 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO); 3-Acetyloleanolic Acid; 3-Triflouroacetyloleanolic Acid; 28-Methyl-3-acetyloleanane; 28-Methyl-3-trifluoroacetyloleanane; 28-Methyloxyoleanolic Acid; SZC014; SCZ015; SZC017; PEGylated derivatives of oleanolic acid; 3-O-(beta-D-glucopyranosyl) oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[a-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid; 3-O-[alpha-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 28-O-β-D-glucopyranosyl-oleanolic acid; 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS1); oleanolic acid 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS2); methyl 3,11-dioxoolean-12-en-28-olate (DIOXOL); ZCVI$_4$-2; Benzyl 3-dehydr-oxy-1,2,5-oxadiazolo[3',4':2,3]oleanolate); a left ventricular assist device (LVAD), or lung and/or heart transplantation.

WE CLAIM:

1. Use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein

(i) one or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for a period of 24 weeks; and

(ii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, one or more doses of the ActRIIA fusion protein is to be administered to the patient in an amount that is reduced by at least half of the amount of the dose of (i);

wherein the ActRIIA fusion protein comprises

(a) an ActRIIA polypeptide comprising the amino acid sequence of SEQ ID NO: 2;

(b) an Fc domain of an immunoglobulin;

(c) a linker domain positioned between the ActRIIA polypeptide domain and the Fc domain of the immunoglobulin.

2. Use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein

(i) one or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for 24 weeks;

(ii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, skipping a dose, wherein the patient is not treated for 6 weeks after step (i); and

(iii) resuming the administration of one or more doses of the ActRIIA fusion protein to the patient in an amount of 0.3 mg/kg once every 3 weeks for at least 24 weeks;

wherein the ActRIIA fusion protein comprises

(a) an ActRIIA polypeptide comprising the amino acid sequence of SEQ ID NO: 2;

(b) an Fc domain of an immunoglobulin;

(c) a linker domain positioned between the ActRIIA polypeptide domain and the Fc domain of the immunoglobulin.

3. Use of an ActRIIA fusion protein in the manufacture of a medicament for the treatment or prevention of telangiectasia, wherein

(i) one or more doses of the ActRIIA fusion protein is to be administered to a patient in an amount of 0.3 mg/kg once every 3 weeks for a period of 24 weeks or less;

(ii) after step (i), one or more doses of the ActRIIA fusion protein is to be administered to the patient in an amount of 0.7 mg/kg once every 3 weeks as long as the patient does not show one or more symptoms or risk factors for developing telangiectasia; and

(iii) if the patient shows one or more symptoms or risk factors for developing telangiectasia, while receiving the dose of step (ii), one or more doses of the ActRIIA fusion protein is to be administered in lieu of the dose of step (ii), wherein the dose is to be administered in an amount of 0.3 mg/kg once every 3 weeks until symptoms improve;

wherein the ActRIIA fusion protein comprises the amino acid sequence of SEQ ID NO: 2, thereby treating or preventing telangiectasia.

4. The use of claim 3, wherein step (iii) comprises administration of one or more doses of ActRIIA fusion protein to the patient in an amount of 0.3 mg/kg once every 3 weeks for at least 24 weeks.

5. The use of claim 3, wherein the patient is not treated with the ActRIIA fusion protein for a period of at least 2-6 weeks between step (ii) and step (iii).

6. The use of claim 3 or claim 5, wherein the patient is not treated with the ActRIIA fusion protein for a period of at least 3 weeks between step (ii) and step (iii).

7. The use of any one of claims 3-6, wherein, step (i) comprises administration of the dose to the patient for at least 3 weeks.

8. The use of any one of claims 3-7, wherein step (ii) comprises administration of the dose to the patient for at least 21 weeks.

9. The use of any one of claims 3-7, wherein step (ii) comprises administration of the second dose to the patient for at least 45 weeks.

10. The use of any one of claims 1-9, wherein the one or more symptoms of telangiectasia are selected from the group consisting of pain, itching, threadlike red marks on the skin,

mucocutaneous telangiectases, gastrointestinal bleeding, lesions on the skin, epistaxis, gingival bleeding, arteriovenous malformations, internal telangiectases, and red spots on the skin.

11. The use of any one of claims 1-10, wherein the risk factors for developing telangiectasia are selected from the group consisting of:

i. low BMP9 levels;
ii. low BMP10 levels;
iii. low VEGF levels;
iv. hereditary hemorrhagic telangiectasia (HHT); and
v. connective tissue disease (CTD).

12. The use of any one of claims 1-10, wherein the medicament alleviates or improves the severity of telangiectasia in the patient.

13. The use of any one of claims 1-12, wherein the medicament prevents the progression of telangiectasia in the patient.

14. The use of claim 2 or claim 3, wherein the step (iii) comprises withholding administration of the ActRIIA fusion protein until the telangiectasia improves to ≤ Grade 1.

15. The use of any one of claims 1-14, wherein the patient is to be administered the medicament for the treatment of pulmonary hypertension.

16. The use of any one of claims 1-15, wherein the patient is to be administered the medicament for the treatment of pulmonary arterial hypertension.

17. The use of any one of claims 1-16, wherein the Fc domain of the immunoglobulin is an Fc domain of an IgG1 immunoglobulin.

18. The use of any one of claims 1-17, wherein the linker domain is selected from the group consisting of: TGGG (SEQ ID NO: 20), TGGGG (SEQ ID NO: 18), SGGGG (SEQ ID NO: 19), GGGGS (SEQ ID NO: 22), GGG (SEQ ID NO: 16), GGGG (SEQ ID NO: 17), and SGGG (SEQ ID NO: 21).

19. The use of any one of claims 1-18, wherein the ActRIIA fusion protein comprises the amino acid sequence of SEQ ID NO: 23.

20. The use of any one of claims 1-18, wherein the ActRIIA fusion protein comprises the amino acid sequence of SEQ ID NO: 40.

21. The use of any one of claims 1-20, wherein the ActRIIA fusion protein is reconstituted following lyophilization.

22. The use of any one of claims 1-21, wherein the ActRIIA fusion protein is soluble.

23. The use of any one of claims 1-22, wherein the ActRIIA fusion protein is to be administered to the patient using subcutaneous injection.

24. The use of any one of claims 1-23, wherein the ActRIIA fusion protein is part of a homodimer protein complex.

25. The use of any one of claims 1-24, wherein the ActRIIA fusion protein is glycosylated.

26. The use of any one of claims 1-25, wherein the ActRIIA fusion protein binds to one or more ligands comprising activin A, activin B, and/or GDF11.

27. The use of claim 26, wherein the ActRIIA fusion protein further binds to one or more of: BMP10, GDF8, and BMP6.

28. The use of any one of claims 1-27, wherein the patient is to be administered an additional active agent and/or supportive therapy.

29. The use of claim 28, wherein the additional active agent and/or supportive therapy comprises beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), diuretic agents, lipid-lowering medications, endothelin blockers, PDE5 inhibitors, prostacyclins, and/or a left ventricular assist device (LVAD).

30. The use of claim 29, wherein the additional active agent and/or supportive therapy further comprises prostacyclin and derivatives thereof (*e.g.*, epoprostenol, treprostinil, and iloprost); prostacyclin receptor agonists (*e.g.*, selexipag); endothelin receptor antagonists (*e.g.*, thelin, ambrisentan, macitentan, and bosentan); calcium channel blockers (*e.g.*, amlodipine, diltiazem, and nifedipine; anticoagulants (*e.g.*, warfarin); diuretics; oxygen therapy; atrial septostomy; pulmonary thromboendarterectomy; phosphodiesterase type 5 inhibitors (*e.g.*, sildenafil and tadalafil); activators of soluble guanylate cyclase (*e.g.*,

cinaciguat and riociguat); ASK-1 inhibitors (*e.g.*, CIIA; SCH79797; GS-4997; MSC2032964A; 3H-naphtho[1,2,3-de]quiniline-2,7-diones, NQDI-1; 2-thioxo-thiazolidines, 5-bromo-3-(4-oxo-2-thioxo-thiazolidine-5-ylidene)-1,3-dihydro-indol-2-one); NF-κB antagonists (*e.g.*, dh404, CDDO-epoxide; 2.2-difluoropropionamide; C28 imidazole (CDDO-Im); 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO); 3-Acetyloleanolic Acid; 3-Triflouroacetyloleanolic Acid; 28-Methyl-3-acetyloleanane; 28-Methyl-3-trifluoroacetyloleanane; 28-Methyloxyoleanolic Acid; SZC014; SCZ015; SZC017; PEGylated derivatives of oleanolic acid; 3-O-(beta-D-glucopyranosyl) oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid; 3-O-[beta-D-glucopyranosyl-(1-->3)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[beta-D-glucopyranosyl-(1-->2)-beta-D-glucopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 3-O-[a-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid; 3-O-[alpha-L-rhamnopyranosyl-(1-->3)-beta-D-glucuronopyranosyl] oleanolic acid 28-O-beta-D-glucopyranosyl ester; 28-O-β-D-glucopyranosyl-oleanolic acid; 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS1); oleanolic acid 3-O-β-D-glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS2); methyl 3,11-dioxoolean-12-en-28-olate (DIOXOL); ZCVI$_4$-2; Benzyl 3-dehydr-oxy-1,2,5-oxadiazolo[3',4':2,3]oleanolate); a left ventricular assist device (LVAD), lung transplantation and/or heart transplantation.

31. The use of any one of claims 1-30, wherein the patient has been administered with one or more agents selected from the group consisting of: phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin receptor agonist, and endothelin receptor antagonists.

32. The use of claim 31, wherein the one or more agents is selected from the group consisting of: bosentan, sildenafil, beraprost, macitentan, selexipag, epoprostenol, treprostinil, iloprost, ambrisentan, and tadalafil.

33. The use of any one of claim 1-32, wherein the patient has been administered one or more therapies for PAH.