CLAIMS

1. Use of an activin receptor type II (ActRII) signaling inhibitor in the manufacture of a medicament for the treatment of beta-thalassemia in a subject in need thereof, wherein said medicament comprises an initial dose of about 0.8 mg/kg or about 1.0 mg/kg of the ActRII signaling inhibitor that is first to be administered to the subject, and a subsequent dose of the ActRII signaling inhibitor that is to be administered to the subject once every 21 days, such that the beta-thalassemia is treated,

wherein said medicament is to be administered subcutaneously in the upper arm, abdomen, or thigh of the subject,

wherein the subject has a β^0/β^0 genotype,

wherein the subject has prior splenectomy,

wherein the ActRII signaling inhibitor is a polypeptide comprising: ~~an amino acid sequence selected from the group consisting of:~~

~~(a) an amino acid sequence that is at least 90% identical to SEQ ID NO:25;~~

~~(a) an amino acid sequence that is at least 95% identical to SEQ ID NO:25;~~

~~(a) an amino acid sequence that is at least 98% identical to SEQ ID NO:25; and~~

~~an amino acid sequence of SEQ ID NO:25~~

(i) a fragment of the extracellular domain of ActRIIB, wherein the fragment consists of the amino acid sequence of SEQ ID NO:23;

(ii) a linker; and

(iii) an Fc of an IgG.

2. The use of the ActRII signaling inhibitor of claim 1, wherein the subject has hereditary persistence of fetal hemoglobin.

3. The use of the ActRII signaling inhibitor of claim 1, wherein the subject has alpha-thalassemia.

~~4. The use of the ActRII signaling inhibitor of any of claims 1 to 3, wherein the beta-thalassemia is transfusion-dependent beta-thalassemia.~~

~~5~~4. The use of the ActRII signaling inhibitor of any of claims 1 to ~~4~~3, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered based on the difference between a first measurement of hemoglobin concentration and a second measurement of hemoglobin concentration as follows:

i) when the second measurement of hemoglobin concentration is less than or equal to 12.5 g/dL, then a) the second measurement of hemoglobin concentration is less than or equal to 1.5 g/dL greater than the first measurement of hemoglobin concentration; and b) the subsequent dose is equal to the initial dose;

ii) when the second measurement of hemoglobin concentration is less than or equal to 12.5 g/dL, then a) the second measurement of hemoglobin concentration is greater than 1.5 g/dL greater than the first measurement of hemoglobin concentration; and b) the subsequent dose is approximately 25% less than the initial dose;

iii) when the second measurement of hemoglobin concentration is (i) greater than 12.5 g/dL and less than or equal to 14 g/dL; and (ii) less than or equal to 1.5 g/dL greater than the first measurement of hemoglobin concentration, then a) the subsequent dose is equal to the initial dose; and b) a dose delay of up to twelve weeks is implemented until a third measurement of hemoglobin concentration is determined to be less than or equal to 12.5 g/dL;

iv) when the second measurement of hemoglobin concentration is (i) greater than 12.5 g/dL and less than or equal to 14 g/dL, and (ii) greater than 1.5 g/dL greater than the first measurement of hemoglobin concentration, then a) the subsequent dose is approximately 25% less than the initial dose; and b) a dose delay of up to twelve weeks is implemented until a third measurement of hemoglobin concentration is determined to be (i) less than or equal to 12.5 g/dL, and (ii) the change

between the first measurement of hemoglobin concentration and the third measurement of hemoglobin concentration is less than or equal to 1.5 g/dL; and

v) when the second measurement of hemoglobin concentration is greater than 14 g/dL; then, a) the subsequent dose is approximately 25% less than the initial dose; and b) a dose delay of up to twelve weeks is implemented until a third measurement of hemoglobin concentration is determined to be less than 12.5 g/dL.

~~6. The use of the ActRII signaling inhibitor of any of claims 1 to 4, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered based on the difference between a first measurement of hematocrit and a second measurement of hematocrit.~~

~~7. The use of the ActRII signaling inhibitor of any of claims 1 to 4, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered based on the difference between a first measurement of fetal hemoglobin concentration and a second measurement of fetal hemoglobin concentration.~~

~~8. The use of the ActRII signaling inhibitor of any of claims 1 to 4, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered to the subject after the administration of the initial dose has been discontinued, wherein the initial dose is discontinued after a second measurement of hemoglobin concentration, hematocrit, or fetal hemoglobin concentration has been taken for a period of time after a first measurement.~~

~~9~~5. The use of the ActRII signaling inhibitor of ~~any of claims 5 to 8~~ claim 4, wherein the first measurement of hemoglobin concentration~~, hematocrit, or fetal hemoglobin concentration~~ is taken prior to the administration with the initial dose of the ActRII signaling inhibitor.

~~10~~6. The use of the ActRII signaling inhibitor of ~~any of claims 5 to 8~~claim 4, wherein the first measurement of hemoglobin concentration, hematocrit, or fetal hemoglobin concentration is taken immediately after the initial dose of the ActRII signaling inhibitor has been administered to the subject or within at most 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 1 week thereof.

~~11~~7. The use of the ActRII signaling inhibitor of ~~any one of claims 5 to 10~~ claim 5 or claim 6, wherein the second measurement of hemoglobin~~, hematocrit, or fetal hemoglobin~~ concentration is taken approximately 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months after the initial dose of the ActRII signaling inhibitor has been administered to the subject.

~~12. The use of the ActRII signaling inhibitor of claim 8, wherein the administration of the initial dose is discontinued within 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks of after the second measurement has been taken.~~

~~13. The use of the ActRII signaling inhibitor of any one of claims 5 to 12, wherein the subsequent dose of the ActRII signaling inhibitor is about 0.3 mg/kg, about 0.45 mg/kg, about 0.6 mg/kg, about 1.0 mg/kg, or about 1.25 mg/kg.~~

~~14. The use of the ActRII signaling inhibitor of any one of claims 5, 8, 11, or 12, wherein~~

~~(a) the second measurement of hemoglobin concentration is less than or equal to 12.5 g/dL;~~

~~(a) the second measurement of hemoglobin concentration is less than or equal to 1.5 g/dL greater than the first measurement of hemoglobin concentration; and~~

~~(a) the subsequent dose is equal to the initial dose.~~

15. The use of the ActRII signaling inhibitor of any one of claims 5, 8, 11, or 12, wherein

(a) the second measurement of hemoglobin concentration is less than or equal to 12.5 g/dL;

(a) the second measurement of hemoglobin concentration is greater than 1.5 g/dL greater than the first measurement of hemoglobin concentration; and

(a) the subsequent dose is approximately 25% less than the initial dose.

16. The use of the ActRII signaling inhibitor of any one of claims 5, 8, 11, or 12, wherein

(a) the second measurement of hemoglobin concentration is (i) greater than 12.5 g/dL and less than or equal to 14 g/dL; and (ii) less than or equal to 1.5 g/dL greater than the first measurement of hemoglobin concentration;

(a) the subsequent dose is equal to the initial dose; and

(a) a second period of time consists of a dose delay of up to twelve weeks until a third measurement of hemoglobin concentration is less than or equal to 12.5 g/dL is taken.

17. The use of the ActRII signaling inhibitor of any one of claims 5, 8, 11, or 12, wherein

(a) the second measurement of hemoglobin concentration is (i) greater than 12.5 g/dL and less than or equal to 14 g/dL, and (ii) greater than 1.5 g/dL greater than the first measurement of hemoglobin concentration;

(b) the subsequent dose is approximately 25% less than the initial dose; and

(c) a dose delay of up to twelve weeks until a third measurement of hemoglobin concentration is determined to be (i) less than or equal to 12.5 g/dL, and (ii) the change between the first measurement of hemoglobin concentration and the third measurement of hemoglobin concentration is less than or equal to 1.5 g/dL.

~~18. The use of the ActRII signaling inhibitor of any one of claims 5, 8, 11, or 12, wherein~~

~~(a) the second measurement of hemoglobin concentration is greater than 14 g/dL;~~

~~(b) the subsequent dose is approximately 25% less than the initial dose; and~~

~~(c) a second period of time consists of a dose delay of up to twelve weeks until a third measurement of hemoglobin concentration is less than 12.5 g/dL is taken.~~

~~19~~8. The use of an ActRII signaling inhibitor of any one of the preceding claims, wherein administration of the medicament to the subject increases fetal hemoglobin levels in the subject.

~~20. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the ActRII signaling inhibitor is a polypeptide comprising: (i) a fragment of the extracellular domain of ActRIIB, wherein the fragment consists of the amino acid sequence of SEQ ID NO:23; (ii) a linker; and (iii) an Fc of an IgG.~~

~~21~~9. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the ActRII signaling inhibitor is a polypeptide comprising the amino acid sequence of SEQ ID NO:25.

~~22~~10. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the subject expresses hemoglobin E.

~~23~~11. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the subject does not express hemoglobin S.

~~24~~12. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the subject is a human.

~~25~~13. The use of the ActRII signaling inhibitor of any one of the preceding claims, wherein the ~~ActRII signaling inhibitor~~medicament is packaged in a container as a sterile, preservative-free lyophilized cake, intended for ~~stored~~storage between 2 ºC and 8 ºC prior to administration to the subject.

~~26~~14. The use of the ActRII signaling inhibitor of claim ~~25~~13, wherein the container contains 25 mg of the ActRII signaling inhibitor.

~~27~~15. The use of the ActRII signaling inhibitor of claim ~~25~~13, wherein the container contains 37.5 mg of the ActRII signaling inhibitor.

~~28~~16. The use of the ActRII signaling inhibitor of claim ~~25~~13, wherein the container contains 75 mg of the ActRII signaling inhibitor.

17. The use of the ActRII signaling inhibitor of any one of claims 1-16, wherein the initial dose of the ActRII signaling inhibitor is about 0.8 mg/kg.

18. The use of the ActRII signaling inhibitor of any one of claims 1-17, wherein the subject is receiving iron chelation therapy.

19. The use of the ActRII signaling inhibitor of any one of clams 1-18, wherein the subject has a baseline liver iron concentration of greater than 7 mg/g dw prior to administration of the ActRII signaling inhibitor.

20. The use of the ActRII signaling inhibitor of any one of clams 1-19, wherein the subject has leg ulcers prior to administration of the ActRII signaling inhibitor.