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 one or more times at 21 day intervals, 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.

2. The use of the ActRII signaling inhibitor of claim 1, wherein the genotype of the subject is selected from the group consisting of β^0/β^0, β^+/β^+, β^0/β^+, β^0/HbE, and β^+/HbE.

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

4. The use of the ActRII signaling inhibitor of claim 1, wherein the genotype of the subject comprises coinheritance of two severe hemoglobin beta chain mutations, and wherein the subject has alpha-thalassemia.

5. The use of the ActRII signaling inhibitor of claim 1, wherein the genotype of the subject comprises coinheritance of two severe hemoglobin beta chain mutations, and wherein the subject has hereditary persistence of fetal hemoglobin.

6. The use of the ActRII signaling inhibitor of any of claims 1 to 5, wherein the beta-thalassemia is transfusion-dependent beta-thalassemia.

7. The use of the ActRII signaling inhibitor of any of claims 1 to 5, wherein the beta-thalassemia is non-transfusion-dependent beta-thalassemia.

8. The use of the ActRII signaling inhibitor of any of claims 1 to 7, 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, wherein the subsequent dose of the ActRII

signaling inhibitor is to be administered subcutaneously in the upper arm, abdomen, or thigh or the subject.

9. The use of the ActRII signaling inhibitor of any of claims to 7 1, 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, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered subcutaneously in the upper arm, abdomen, or thigh or the subject.

10. The use of the ActRII signaling inhibitor of any of claims 1 to 7, 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, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered subcutaneously in the upper arm, abdomen, or thigh or the subject.

11. The use of the ActRII signaling inhibitor of any of claims 1 to 7, 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 when or after a second measurement of hemoglobin concentration, hematocrit, or fetal hemoglobin concentration has been taken for a period of time after a first measurement, wherein the subsequent dose of the ActRII signaling inhibitor is to be administered via subcutaneous injection in the upper arm, abdomen or thigh of the subject.

12. The use of the ActRII signaling inhibitor of any of claims 8 to 11, wherein the first measurement of hemoglobin concentration, hematocrit, or fetal hemoglobin concentration is taken prior to the subject has been administered with the initial dose the ActRII signaling inhibitor.

13. The use of the ActRII signaling inhibitor of any of claims 8 to 12, wherein the first measurement of hemoglobin concentration, hematocrit, or fetal hemoglobin concentration is taken immediately after the initial dose 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.

14. The use of the ActRII signaling inhibitor of any one of claims 8 to 13, 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 the ActRII signaling inhibitor has been administered to the subject .

15. The use of the ActRII signaling inhibitor of claim 11, wherein the administration of the initial dose is discontinued for 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 when or after the second measurement has been taken.

16. The use of the ActRII signaling inhibitor of any one of claims 8 to 15, 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.

17. The use of the ActRII signaling inhibitor of any one of claims 11 to 15, wherein

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

(b) 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

(c) the subsequent dose is equal to the initial dose.

18. The use of the ActRII signaling inhibitor of any one of claims 11 to 15, wherein

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

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

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

19. The use of the ActRII signaling inhibitor of any one of claims 11 to 15, 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;

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

(c) the discontinuation of the initial dose 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.

20. The use of the ActRII signaling inhibitor of any one of claims 11 to 15, 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) the discontinuation of the initial dose consists of 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.

21. The use of the ActRII signaling inhibitor of any one of claims 11 to 15, 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) the discontinuation of the initial dose 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.

22. The use of the ActRII signaling inhibitor of any of claims 12 to 21, wherein the subsequent dose is to be administered once every 21 days.

23. The use of an ActRII signaling inhibitor in the manufacture of a medicament for the treatment of increasing fetal hemoglobin levels in the subject.

24. The use of the ActRII signaling inhibitor of any of claims 1 to 23, wherein the ActRII signaling inhibitor is an inhibitor of ActRIIA signaling.

25. The use of the ActRII signaling inhibitor of any of claims 1 to 23, wherein the ActRII signaling inhibitor is a polypeptide comprising the extracellular domain of ActRIIA and the Fc portion of an IgG1 antibody.

26. The use of the ActRII signaling inhibitor of claim 24, wherein the ActRIIA signaling inhibitor is a polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) 90% identical to SEQ ID NO:2;
(b) 95% identical to SEQ ID NO:2;
(c) 98% identical to SEQ ID NO:2;
(d) SEQ ID NO:2;
(e) 90% identical to SEQ ID NO:3;
(f) 95% identical to SEQ ID NO:3;
(g) 98% identical to SEQ ID NO:3;
(h) SEQ ID NO:3;
(i) 90% identical to SEQ ID NO:6;
(j) 95% identical to SEQ ID NO:6;
(k) 98% identical to SEQ ID NO:6;
(l) SEQ ID NO:6;
(m) 90% identical to SEQ ID NO:7;
(n) 95% identical to SEQ ID NO:7;
(o) 98% identical to SEQ ID NO:7; and
(p) SEQ ID NO:7.

27. The use of the ActRII signaling inhibitor of claim 24, wherein the ActRII signaling inhibitor is a polypeptide comprising the amino acid sequence of SEQ ID NO:7.

28. The use of the ActRII signaling inhibitor of any of claimsto 23 1 , wherein the ActRII signaling inhibitor is an inhibitor of ActRIIB signaling.

29. The use of the ActRII signaling inhibitor of any of claims 1 to 23, wherein the ActRII signaling inhibitor is a polypeptide comprising the extracellular domain of ActRIIB and the Fc portion of an IgG1 antibody.

30. The use of the ActRII signaling inhibitor of claim 28, wherein the ActRIIB inhibitor is a polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) 90% identical to SEQ ID NO:17;
(b) 95% identical to SEQ ID NO:17;
(c) 98% identical to SEQ ID NO:17;
(d) SEQ ID NO:17;
(e) 90% identical to SEQ ID NO:20;
(f) 95% identical to SEQ ID NO:20;
(g) 98% identical to SEQ ID NO:20;
(h) SEQ ID NO:20;
(i) 90% identical to SEQ ID NO:21;
(j) 95% identical to SEQ ID NO:21;
(k) 98% identical to SEQ ID NO:21;
(l) SEQ ID NO:21;
(m) 90% identical to SEQ ID NO:25;
(n) 95% identical to SEQ ID NO:25;
(o) 98% identical to SEQ ID NO:25; and
(p) SEQ ID NO:25.

31. The use of the ActRII signaling inhibitor of claim 28, wherein the ActRIIB signaling inhibitor is a polypeptide comprising the amino acid sequence of SEQ ID NO:25.

32. The use of the ActRII signaling inhibitor of any of the preceding claims, wherein the subject expresses hemoglobin E.

33. The use of the ActRII signaling inhibitor of any of the preceding claims, wherein the subject does not express hemoglobin S.

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

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

36. The use of the ActRII signaling inhibitor of claim 35, wherein the container contains 37.5 mg of the ActRII signaling inhibitor.

37. The use of the ActRII signaling inhibitor of claim 35, wherein the container contains 75 mg of the ActRII signaling inhibitor.