CLAIMS

1. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 3 ± 2.0 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 2-fold to 6-fold the amount to be administered daily during the quiescent period is to be administered daily to the subject.

2. The use of claim 1, wherein during the non-quiescent period the palovarotene, or a pharmaceutically acceptable salt thereof, is to be initially administered in a daily loading dose of 3.5-fold to 6-fold the amount to be administered daily during the quiescent period followed by a daily maintenance dose of 2-fold to 3-fold the amount to be administered daily during the quiescent period.

3. The use of claim 2, wherein the amount to be administered during the quiescent period is 3 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 12.5 ± 1.0 mg daily and a daily maintenance dose of 6.0 ± 1.0 mg daily.

4. The use of claim 3, wherein the subject weighs from 20 to 40 kg.

5. The use of claim 2, wherein the amount to be administered during the quiescent period is 4 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 15 ± 1.0 mg daily and a daily maintenance dose of 7.5 ± 1.0 mg daily.

6. The use of claim 5, wherein the subject weighs from 40 to 60 kg.

7. The use of claim 1, wherein the amount to be administered during the quiescent period is 5 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 20 ± 1.0 mg daily and a daily maintenance dose of 10 ± 1.0 mg daily.

8. The use of claim 7, wherein the subject weighs greater than 60 kg.

9. The use of claim 1, wherein the amount to be administered during the quiescent period is 2 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 10 ± 1.0 mg daily and a daily maintenance dose of 5 ± 1.0 mg daily.

10. The use of claim 9, wherein the subject weighs less than 20 kg.

11. The use of any one of claims 2-10, wherein the daily loading dose is to be administered for a period of 20 to 40 days.

12. The use of any one of claims 2-11, wherein the daily maintenance dose is to be administered for at least a period of 14 to 84 days.

13. The use of claim 12, wherein at the end of 84 days the daily maintenance dose is to be continued for an additional 28 days if the subject continues to experience flare-ups.

14. The use of claim 12 wherein a daily loading dose of 20 mg is to be administered for 28 days, a daily maintenance dose of 10 mg is to be administered for 56 days and the amount to be administered during the quiescent period is 5 mg/day.

15. The use of claim 12 wherein a daily loading dose of 15 mg is to be administered for 28 days, a daily maintenance dose of 10 mg is to be administered for 56 days, and the amount to be administered during the quiescent period is 5 mg/day.

16. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the severity of flare-ups in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 3 ± 2 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 2-fold to 6-fold the amount to be administered daily during the quiescent period is to be administered daily to the subject.

17. The use of claim 16, wherein during the non-quiescent period the palovarotene, or a pharmaceutically acceptable salt thereof, is to be initially administered in a daily loading dose of 3.5-fold to 6-fold the amount to be administered daily during the quiescent period followed by a daily maintenance dose of 2-fold to 3-fold the amount to be administered daily during the quiescent period.

18. The use of claim 17, wherein the amount to be administered during the quiescent period is 3 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 12.5 ± 1.0 mg daily and a daily maintenance dose of 6.0 ± 1.0 mg daily.

19. The use of claim 18, wherein the subject weighs from 20 to 40 kg.

20. The use of claim 17, wherein the amount to be administered during the quiescent period is 4 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 15 ± 1.0 mg daily and a daily maintenance dose of 7.5 ± 1.0 mg daily.

21. The use of claim 20, wherein the subject weighs from 40 to 60 kg.

22. The use of claim 16, wherein the amount to be administered during the quiescent period is 5 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 20 ± 1.0 mg daily and a daily maintenance dose of 10 ± 1.0 mg daily.

23. The use of claim 22, wherein the subject weighs greater than 60 kg.

24. The use of claim 16, wherein the amount to be administered during the quiescent period is 2 ± 0.5 mg daily and the amount to be administered during the non-quiescent period comprises a daily loading dose of 10 ± 1.0 mg daily and a daily maintenance dose of 5 ± 1.0 mg daily.

25. The use of claim 24, wherein the subject weighs less than 20 kg.

26. The use of any one of claims 17-25, wherein the daily loading dose is to be administered for a period of 20 to 40 days.

27. The use of any one of claims 17-26, wherein the daily maintenance dose is to be administered for at least a period of 14 to 84 days.

28. The use of claim 27, wherein at the end of 84 days the daily maintenance dose is to be continued for an additional 28 days if the subject continues to experience flare-ups.

29. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein during the non-quiescent period: (i) a loading dose in an amount of from 9 to 21 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered to the subject daily during a first time period and (ii) following the first time period, a maintenance dose of 40% to 60% of the amount to be administered in the loading dose is to be administered daily to the subject.

30. The use of claim 29, wherein the daily loading dose is 12.5 ± 1.0 mg daily and the maintenance dose is 6.0 ± 1.0 mg daily.

31. The use of claim 30, wherein the subject weighs from 20 to 40 kg.

32. The use of claim 29, wherein the loading dose is 15 ± 1.0 mg daily and the maintenance dose is 7.5 ± 1.0 mg daily.

33. The use of claim 32, wherein the subject weighs from 40 to 60 kg.

34. The use of claim 29, wherein the loading dose is 20 ± 1.0 mg daily and the maintenance dose is 10 ± 1.0 mg daily.

35. The use of claim 34, wherein the subject weighs greater than 60 kg.

36. The use of claim 29, wherein the loading dose is 10 ± 1.0 mg daily and the maintenance dose is 5 ± 1.0 mg daily.

37. The use of claim 36, wherein the subject weighs less than 20 kg.

38. The use of any one of claims 29-37, wherein the loading dose is to be administered for a period of 20 to 40 days.

39. The use of any one of claims 29-38, wherein the maintenance dose is to be administered for at least a period of 14 to 84 days.

40. The use of claim 39, wherein at the end of 84 days the maintenance dose is to be continued for an additional 28 days if the subject continues to experience flare-ups.

41. The use of any one of claims 1-40, wherein the subject has not achieved 90% skeletal maturity.

42. The use of any one of claims 1-41, wherein an antihistamine is to be administered to the subject.

43. The use of claim 42, wherein the antihistamine is to be administered topically.

44. The use of claim 42, wherein the antihistamine is to be administered systemically.

45. The use of any one of claims 1-41, wherein an emollient is to be administered to the skin of the subject.

46. Use of a BMP signaling inhibitor in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, a first amount of the BMP signaling inhibitor is to be administered daily to the subject, and (ii) during the non-quiescent period, 2-fold to 6-fold the amount to be administered daily during the quiescent period is to be administered daily to the subject.

47. The use of claim 46, wherein during the non-quiescent period the BMP signaling inhibitor is to be initially administered in a daily loading dose of 3.5-fold to 6-fold the amount to be administered daily during the quiescent period followed by a daily maintenance dose of 2-fold to 3-fold the amount to be administered daily during the quiescent period.

48. The use of claim 46 or 47, wherein the BMP signaling inhibitor is an activin receptor-like 2 (ALK2) kinase inhibitor.

49. The use of claim 48, wherein the ALK2 kinase inhibitor is LDN-193189 (4-(6-(4-(piperazin-1-yl)phenyl)pyrazolo[1,5-a]pyrimidin-3-yl)-quinolone), LDN-212854 (5-[6-[4-(1-piperazinyl)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl]-quinoline), dorsomorphin (6-[4-[2-(1-Piperidinyl)ethoxy]phenyl]-3-(4-pyridinyl)-pyrazolo[1,5-*a*]-pyrimidine), K02288 (3-[(6-Amino-5-(3,4,5-trimethoxyphenyl)-3-pyridinyl]-phenol), DMH-1 (4-[6-[4-(1-Methylethoxy)phenyl]pyrazolo[1,5-*a*]pyrimidin-3-yl]-quinoline), or ML-347 (5-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]-quinolone).

50. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein : (i) during the quiescent period, an amount of 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 20 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

51. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 10 to 20 kg, wherein: (i) during the quiescent period, an amount of 2.5 mg of palovarotene, or a

pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

52. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 20 to 40 kg, wherein: (i) during the quiescent period, an amount of 3 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 12.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 6 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

53. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 40 to 60 kg, wherein: (i) during the quiescent period, an amount of 4 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 15 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 7.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

54. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs 60 kg or more, wherein: (i) during the quiescent period, an amount of 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 20 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily for the subject for 28 days, to be followed by administering daily to the subject 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

55. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 4 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 15 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered to the subject for 28 days, to be followed

by administering daily to the subject 7.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

56. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 10 to 20 kg, wherein: (i) during the quiescent period, an amount of 1 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 7.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 3 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

57. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 20 to 40 kg, wherein: (i) during the quiescent period, an amount of 2.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

58. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs from 40 to 60 kg, wherein: (i) during the quiescent period, an amount of 3 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 12.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 6 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

59. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein the subject weighs 60 kg or more, wherein: (i) during the quiescent period, an amount of 4 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 15 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 7.5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

60. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for at least 56 days.

61. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 15 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.

62. Use of palovarotene, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing heterotopic ossification in a subject with fibrodysplasia ossificans progressiva characterized by a quiescent period and a non-quiescent period, wherein: (i) during the quiescent period, an amount of 5 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject, and (ii) during the non-quiescent period, 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, is to be administered daily to the subject for 28 days, to be followed by administering daily to the subject 10 mg of palovarotene, or a pharmaceutically acceptable salt thereof, for at least 56 days.