CLAIMS

1. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ treating a subject with hemophilia A and low bone mineral density (BMD), ~~the method comprising:~~

~~(i) selecting a subject having hemophilia A and low BMD, and~~

~~(ii) administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc);~~

wherein ~~administration of~~ the chimeric protein inhibits reduction of BMD in the subject.

2. The ~~method~~ use of claim 1, wherein the chimeric protein comprises an amino acid sequence at least 95% identical to an amino acid sequence according to SEQ ID NO: 1.

3. The ~~method~~ use of claim 1, wherein the chimeric protein comprises an amino acid sequence at least 95% identical to an amino acid sequence according to SEQ ID NO: 2.

4. The ~~method~~ use of claim 1, wherein the chimeric protein comprises an amino acid sequence according to SEQ ID NO: 1.

5. The ~~method~~ use of claim 1, wherein the chimeric protein comprises an amino acid sequence at least 95% identical to an amino acid sequence according to SEQ ID NO: 5.

6. The ~~method~~ use of claim 1, wherein the chimeric protein comprises an amino acid sequence according to SEQ ID NO: 5.

7. The ~~method~~ use of claim 1, wherein the chimeric protein comprises a first polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence according to SEQ ID NO: 5 and a second polypeptide chain comprising an amino acid sequence at least 95% identical to the amino acid sequence according to SEQ ID NO: 4.

8. The ~~method~~ use of claim 1, wherein the chimeric protein comprises a first polypeptide chain comprising an amino acid sequence according to SEQ ID NO: 5 and a

second polypeptide chain comprising an amino acid sequence according to SEQ ID NO: 4.

9. The ~~method~~ use of claim 8, wherein the first polypeptide chain is covalently bound to the second polypeptide chain via a disulfide bond.

10. The ~~method~~ use of claim 9, wherein the first polypeptide chain is covalently bound to the second polypeptide chain via two disulfide bonds in a hinge region of the Fc domain.

11. The ~~method~~ use of claim 1 or 10, wherein the chimeric protein is efmoroctocog alfa.

12. The ~~method~~ use of any one of claims 1 to 11, wherein the chimeric protein has been produced by human cells.

13. The ~~method~~ use of claim 12, wherein the human cells are human embryonic kidney 293 (HEK293) cells.

14. The ~~method~~ use of any one of claims 1 to 13, wherein the chimeric protein is administered at a dose of 25-65 IU/kg every 3-5 days.

15. The ~~method~~ use of any one of claims 1 to 14, wherein the Fc domain is the Fc domain of human immunoglobulin G1 (IgG1).

16. The ~~method~~ use of any one of claims 1 to 15, wherein BMD in the subject is measured by Dual X-Ray Absorptiometry (DXA).

17. The ~~method~~use of any one of claims 1 to 16, wherein the subject is 50 years of age or older.

18. The ~~method~~use of any one of claims 1 to 17, wherein BMD in the subject is determined by T-score.

19. The ~~method~~use of claim 18, wherein the subject is determined to have low BMD if the subject has a T-score of less than -1.0.

20. The ~~method~~use of claim 18, wherein the subject is determined to have low BMD and osteopenia if the subject has T-score between -1.0 and -2.4.

21. The ~~method~~use of claim 18, wherein the subject is determined to have low BMD and osteoporosis if the subject has a T-score of less than -2.5.

22. The ~~method~~use of any one of claims 1 to 16, wherein the subject is younger than 50 years of age.

23. The ~~method~~use of claim 22, wherein BMD in the subject is determined by Z-score.

24. The ~~method~~use of claim 23, wherein the subject is determined to have low BMD if the subject has a Z-score of less than -2.0.

25. The ~~method~~use of any one of claims 1 to 24, wherein the subject is predicted to have low BMD based on the levels of one or more biomarkers of bone formation, bone resorption, and/or bone loss.

26. The ~~method~~use of claim 25, wherein the biomarker is assessed from the peripheral blood or urine of the subject.

27. The ~~method~~use of claim 26, wherein the one or more biomarkers of bone formation comprise bone-specific alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), procollagen type 1 C-terminal propeptide (P1CP), and/or osteocalcin.

28. The ~~method~~use of claim 26, wherein the one or more biomarkers of bone resorption comprise total alkaline phosphatase in serum, the receptor activator of nuclear factor kappa B (RANKL), osteoprotegerin (OPG), tartrate-resistant acid phosphatase (TRAP), hydroxylysine, hydroxyproline, deoxypyridinoline (DPD), pyridinoline (PYD), bone sialoprotein, cathepsin K, tartrate-resistant acid phosphatase 5b (TRAP5b), matrix metalloproteinase 9 (MMP9), and/or C- and/or N-terminal cross-linked telopeptide for type 1 collagen (CTX-1 and NTX-1).

29. The ~~method~~use of any one of claims 1-28, wherein the subject does not have a vitamin D deficiency.

30. The ~~method~~use of any one of claims 1-29, wherein the subject has been previously treated with a Factor VIII without an Fc portion.

31. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a

medicament for ~~A method of~~ treating a subject with hemophilia A and an increased risk of fracture, ~~the method comprising:~~

~~(i) selecting a subject having hemophilia A and an increased risk of fracture, and~~

~~(ii) administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc);~~

wherein ~~administration of~~ the chimeric protein reduces the risk of fracture in the subject.

32. The ~~method~~use of claim 31, wherein the risk of fracture in the subject is determined by the fracture risk assessment tool (FRAX).

33. The ~~method~~use of claim 32, wherein the risk of fracture in the subject is determined by assessment of low BMD risk factors.

34. The ~~method~~use of claim 33, wherein the low BMD risk factors comprise arthropathy, reduced physical activity, infection with HIV or HCV, vitamin D deficiency, low body mass index (BMI), and/or hypogonadism.

35. Use of a therapeutically effective amount of a chimeric protein comprising a coagulation factor and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ reducing the rate of bone mineral density (BMD) loss in a subject~~, the method comprising:~~

~~(i) selecting a subject with low BMD; and~~

~~(ii) administering to the subject a therapeutically effective amount of a chimeric protein comprising a coagulation factor and a Fc domain (rFVIIIFc),~~

~~such that administration of the chimeric protein reduces the rate of BMD loss in the subject~~.

36. The ~~method~~use of any one of claims 1 to 35, wherein the subject has mild hemophilia A.

37. The ~~method~~use of any one of claims 1 to 35, wherein the subject has moderate hemophilia A.

38. The ~~method~~use of any one of claims 1 to 35, wherein the subject has severe hemophilia A.

39. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ increasing bone mineral density (BMD) and prophylactically treating bleeding episodes in a subject who has hemophilia A, ~~the method comprising:~~

~~(i) identifying a~~wherein the subject ~~who is receiving~~had received treatment for hemophilia A with a FVIII protein without an Fc portion, wherein the subject has had adequate blood clotting during the treatment, and wherein the subject has low BMD~~; and (ii) discontinuing treatment with the FVIII protein without an Fc portion and administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), wherein administration of the chimeric protein increases BMD and prophylactically treats bleeding episodes in the subject~~.

40. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ increasing bone mineral density (BMD) and prophylactically treating bleeding episodes in a subject who has hemophilia A, ~~the method comprising: (i) identifying a~~wherein the subject ~~who is~~ had ~~receiving~~ received treatment for hemophilia A with a non-factor replacement protein, wherein the subject has had adequate blood clotting during the treatment, and wherein the subject has low BMD~~; and (ii) discontinuing treatment with the non-factor replacement protein and administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), wherein administration of the chimeric protein increases BMD and prophylactically treats bleeding episodes in the subject~~.

41. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ increasing bone mineral density (BMD) and prophylactically treating bleeding episodes in a subject, ~~the method comprising administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc),~~ wherein the subject has been identified as having hemophilia A and low BMD~~, and wherein administration of the chimeric protein increases BMD and prophylactically treats bleeding episodes in the subject~~.

42. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ reducing risk of fracture and prophylactically treating bleeding episodes in a subject, ~~the method comprising administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc),~~ wherein the subject has been identified as having hemophilia A and an increased risk of fracture~~, and wherein administration of the~~

~~chimeric protein reduces the risk of fracture and prophylactically treats bleeding episodes in the subject~~.

43. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ reducing rate of bone mineral density (BMD) loss and prophylactically treating bleeding episodes in a subject, ~~the method comprising administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc),~~ wherein the subject has been identified as having hemophilia A and BMD loss~~, and wherein administration of the chimeric protein reduces the rate of BMD loss and prophylactically treats bleeding episodes in the subject~~.

44. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ increasing bone mineral density (BMD) and prophylactically treating bleeding episodes in a subject who has hemophilia A and is being treated with a FVIII protein without an Fc portion, ~~the method comprising discontinuing treatment with the FVIII protein without an Fc portion and administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc),~~ wherein the subject has been identified as having low BMD and adequate blood clotting during treatment with the FVIII protein without an Fc portion~~, and wherein administration of the chimeric protein increases BMD and prophylactically treats bleeding episodes in the subject~~.

45. Use of a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc), in the manufacture of a medicament for ~~A method of~~ increasing bone mineral density (BMD) and prophylactically treating bleeding episodes in a subject who has hemophilia A and is being treated with a non-factor replacement protein, ~~the method comprising discontinuing treatment with the non-factor replacement protein and administering to the subject a therapeutically effective amount of a chimeric protein comprising a recombinant FVIII protein and a Fc domain (rFVIIIFc),~~ wherein the subject has been identified as having low BMD and adequate blood clotting during treatment with the non-factor replacement protein~~, and wherein administration of the chimeric protein increases BMD and prophylactically treats bleeding episodes in the subject~~.

46. The ~~method~~use of any one of claims 1-45, wherein the subject has been previously treated to reduce bleeding associated with hemophilia A using a Factor VIII protein without an Fc portion.

47. The ~~method~~use of any one of claims 39, 44, or 46, wherein the Factor VIII protein without an Fc portion is PEGylated FVIII that is not fused to a Fc domain.

48. The ~~method~~use of any one of claims 39, 44, or 46, wherein the Factor VIII protein without an Fc portion is single-chain FVIII that is not fused to a Fc domain.

49. The ~~method~~use of any one of claims 39, 44, or 46, wherein the Factor VIII protein without an Fc portion is recombinant FVIII that does not comprise a moiety that extends half-life thereof in humans.

50. The ~~method~~use of any one of claims 39, 44, or 46, wherein the Factor VIII protein without an Fc portion is blood-derived FVIII or plasma-derived FVIII.

51. The ~~method~~use of any one of claims 39, 44, or 46, wherein the Factor VIII protein without an Fc portion is damoctocog alfa pegol, turoctocog alfa pegol, turoctocog alfa, lonoctocog alfa, simoctocog alfa, rurioctocog alfa pegol, or octocog alfa.

52. The ~~method~~use of any one of claims 1-51, wherein the subject has been previously treated to reduce bleeding associated with hemophilia A using a non-factor replacement protein.

53. The ~~method~~use of claim 52, wherein the non-factor replacement protein is emicizumab.

54. The ~~method~~use of claim 53, wherein the emicizumab is emicizumab-kxwh.

55. The ~~method~~use of any one of claims 30 or 36-54, wherein the subject had adequate blood clotting during treatment with the Factor VIII protein without an Fc portion or the non-factor replacement protein.

56. The ~~method~~use of any one of claims 1-55, wherein the subject has low BMD at a bone site and/or joint where bleeding has not been detected.