CLAIMS

1. Use of a therapeutically effective amount of an adeno-associated virus (AAV) viral particle in the manufacture of a medicament for treating Hemophilia A in a juvenile subject in need thereof, wherein the AAV viral particle comprises an AAV serotype 5 capsid protein, and an AAV vector, wherein the AAV vector comprises a Factor VIII transgene flanked by one or more AAV terminal repeat sequences (ITRs) and operably linked to one or more transcription regulatory elements, wherein the Factor VIII transgene encodes a functionally active Factor VIII, and wherein the therapeutically effective amount is an absolute AAV vector genome concentration, based on a per kilogram (kg) body weight of an adult subject.

2. Use of a therapeutically effective amount of an adeno-associated virus (AAV) viral particle in the manufacture of a medicament for ameliorating at least one symptom of Hemophilia A in a juvenile subject in need thereof, wherein the AAV viral particle comprises an AAV serotype 5 capsid protein, and an AAV vector, wherein the AAV vector comprises a Factor VIII transgene flanked by one or more AAV terminal repeat sequences (ITRs) and operably linked to one or more transcription regulatory elements, wherein the Factor VIII transgene encodes a functionally active Factor VIII, and wherein the therapeutically effective amount is an absolute AAV vector genome concentration, based on a per kilogram (kg) body weight of an adult subject.

3. Use of a therapeutically effective amount of an adeno-associated virus (AAV) viral particle in the manufacture of a medicament for reducing bleeding time of a bleeding episode in a juvenile subject with Hemophilia A, wherein the AAV viral particle comprises an AAV serotype 5 capsid protein, and an AAV vector, wherein the AAV vector comprises a Factor VIII transgene flanked by one or more AAV terminal repeat sequences (ITRs) and operably linked to one or more transcription regulatory elements, wherein the Factor VIII transgene encodes a functionally active Factor VIII, and wherein the therapeutically effective amount is an absolute AAV vector genome concentration, based on a per kilogram (kg) body weight of an adult subject.

4. The use of claim 6, wherein the medicament is for administration at least three weeks prior to the bleeding episode.

5. Use of a therapeutically effective amount of an adeno-associated virus (AAV) viral particle in the manufacture of a medicament for increasing Factor VIII protein expression in a juvenile subject with Hemophilia A, wherein the AAV viral particle comprises an AAV serotype 5 capsid protein, and an AAV vector, wherein the AAV vector comprises a Factor VIII transgene flanked by one or more AAV terminal repeat sequences (ITRs) and operably linked to one or more transcription regulatory elements, wherein the Factor VIII transgene encodes a functionally active Factor VIII, and wherein the therapeutically effective amount is an absolute AAV vector genome concentration, based on a per kilogram (kg) body weight of an adult subject.

6. The use of any one of claims 1 to 5, wherein the therapeutically effective amount is from about 1E12 vg/kg to about 1E15 vg/kg, from about 2E13 vg/kg to about 2E16 vg/kg, from about 5E13 vg/kg to about 5E14 vg/kg, from about 1E12 vg/kg to about 2E16 vg/kg, from about 6E12 vg/kg to about 6E13 vg/kg, or from about 6E13 vg/kg to about 6E14 vg/kg of the absolute AAV vector genome concentration.

7. The use of any one of claims 1 to 5, wherein the therapeutically effective amount is 1E12 vg/kg to 2E14 vg/kg of the absolute AAV vector genome concentration.

8. The use of any one of claims 1 to 5, wherein the therapeutically effective amount is 2E13 vg/kg of the absolute AAV vector genome concentration

9. The use of any one of claims 1 to 5, wherein the therapeutically effective amount results in an increased and/or stable total amount of circulating Factor VIII in the juvenile subject.

10. The use of claim 9, wherein the therapeutically effective amount results in maintaining therapeutic Factor VIII levels into adulthood.

11. The use of claim 9, wherein the therapeutically effective amount results in about or at least about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, or 150% of the expression level of the Factor VIII found in a normal juvenile subject in the bloodstream of the juvenile subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more weeks after administration.

12. The use of any one of claims 1 to 11, wherein the Factor VIII transgene encodes Factor VIII-SQ.

13. The use of any one of claims 1 to 11, wherein the functionally active Factor VIII is human Factor VIII.

14. The use of any one of claims 1 to 11, wherein the Factor VIII transgene comprises the nucleic acid sequence of any one of SEQ ID NOS:1-45.

15. The use of any one of claims 1 to 14, wherein administration of the medicament allows for normal growth in liver weight and body weight of the juvenile subject.

16. The use of any one of claims 1 to 15, wherein the juvenile subject is a juvenile human.

17. The use of claim 16, wherein the juvenile human is less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 year(s) of age.

18. The use of claim 16, wherein the juvenile human is less than 18 years of age.

19. The use of claim 16, wherein the juvenile human is less than 5 years of age.

20. The use of claim 16, wherein the juvenile human is less than 1 year of age.

21. The use of any one of claims 1 to 20, wherein the medicament is formulated for intravenous administration.

22. The use of any one of claims 1 to 21, wherein the medicament is formulated as a pharmaceutical composition comprising:

sodium phosphate dibasic at a concentration of from about 0.1 mg/ml to about 3 mg/ml, sodium phosphate monobasic at a concentration of from about 0.1 mg/ml to about 3 mg/ml, sodium chloride at a concentration of from about 1 mg/ml to about 20 mg/ml, mannitol at a concentration of from about 5 mg/ml to about 40 mg/ml, and poloxamer 188 at a concentration of from about 0.1 mg/ml to about 4 mg/ml.

23. The use of any one of claims 1 to 22, wherein the medicament or composition is formulated as a pharmaceutical composition comprising:

1.38 mg/ml of the sodium phosphate monobasic, 1.42 mg/ml of the sodium phosphate dibasic, 8.18 mg/ml of the sodium chloride, 20 mg/ml of the mannitol and 2.0 mg/ml of the poloxamer 188, wherein the formulation is stable during storage at <65° C for at least 2 weeks.

24. The use of any one of claims 1 to 21, wherein the medicament further comprises a buffering agent.

25. The use of claim 24, wherein the buffering agent comprises sodium phosphate dibasic at a concentration of 0.1 mg/mL to 3 mg/mL, 0.5 mg/mL to 2.5 mg/mL, 1 mg/mL to 2 mg/mL, or 1.4 mg/mL to 1.6 mg/mL.

26. The use of claim 24, wherein the buffering agent comprises 1.42 mg/mL of sodium phosphate, dibasic (dried), or 1.38 mg/mL of sodium phosphate, monobasic monohydrate.

27. The use of any one of claims 1 to 21, wherein the medicament further comprises an isotonicity agent.

28. The use of claim 27, wherein the isotonicity agent comprises sodium chloride.

29. The use of claim 28, wherein the sodium chloride is at a concentration of 1 mg/mL to 20 mg/mL.

30. The use of claim 28, wherein the sodium chloride is at a concentration of 1 mg/mL to 10 mg/mL, 5 mg/mL to 15 mg/mL, or 8 mg/mL to 20 mg/mL

31. The use of claim 28, wherein the sodium chloride is at a concentration of 8.18 mg/mL.

32. The use of any one of claims 1 to 21, wherein medicament further comprises a bulking agent.

33. The use of claim 32, wherein the bulking agent comprises mannitol, sucrose, dextran, lactose, trehalose, or povidone (PVP K24).

34. The use of claim 32, wherein the bulking agent comprises mannitol.

35. The use of claim 34, wherein the mannitol is present at a concentration of 5 mg/mL to 40 mg/mL, 10 mg/mL to 30 mg/mL, or 15 mg/mL to 25 mg/mL.

36. The use of claim 34, wherein the mannitol is present at a concentration of 20 mg/mL.

37. The use of any one of claims 1 to 21, wherein the medicament further comprises a surfactant.

38. The use of claim 37, wherein the surfactant is an ionic surfactant, non-ionic surfactant, or combinations thereof.

39. The use of claim 37, wherein the surfactant comprises polysorbate 80, sodium dodecylsulfate, sodium stearate, ammonium lauryl sulfate, TRITON AG 98 (Rhone-Poulenc), poloxamer 407, poloxamer 188, or combinations thereof.

40. The use of claim 37, wherein the surfactant comprises poloxamer 188.

41. The use of claim 40, wherein the poloxamer 188 is present at a concentration of 0.1 mg/mL to 4 mg/mL, 0.5 mg/mL to 3 mg/mL, 1 mg/mL to 3 mg/mL, 1.5 mg/mL to 2.5 mg/mL, or 1.8 mg/mL to 2.2 mg/mL.

42. The use of claim 40, wherein the poloxamer 188 is present at a concentration of 2.0 mg/mL.

43. The use of any one of claims 1 to 42, wherein the medicament is for use in combination prophylactically with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.

44. The use of any one of claims 1 to 42, wherein the medicament is for use in combination therapeutically with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.

45. The use of any one of claims 1 to 42, wherein the medicament is for use in combination with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day

over a continuous period of at least 3, 4, 5, 6, 7, 8, 9, or 10 weeks or greater.

46. The use of any one of claims 1 to 45, wherein the level of anti-AAV capsid antibody in a serum sample obtained from the juvenile subject is determined after administration of the medicament to the juvenile subject.

47. The use of claim 46, wherein the medicament is for use in combination with an effective amount of a corticosteroid if the anti-AAV capsid antibody is present in the serum sample.

48. The use of any one of claims 1 to 47, wherein administration of the medicament to the juvenile subject results in the expression of at least about 5 IU/dl of functional Factor VIII protein in the juvenile subject.

49. The use of any one of claims 1 to 47, wherein administration of the medicament to the juvenile subject results in an increase in functional Factor VIII protein of at least about 1 IU/dl in the juvenile subject.

50. The use of any one of claims 1 to 49, wherein the one or more transcription regulatory elements are one or more liver-specific transcription regulatory elements.

51. The use of claim 50, wherein the one or more liver-specific transcription elements are selected from the group consisting of: a mouse thyretin promoter (mTTR), an endogenous human factor VIII promoter (F8), a human alpha-1-antitrypsin promoter (hAAT), a human albumin minimal promoter, a mouse albumin promoter, and a microglobulin enhancer sequence and the 186 base human alpha anti-trypsin (AAT) proximal promoter.