

CLAIMS

1. A method of ameliorating the symptoms of a genetic disorder in a juvenile subject suffering from the genetic disorder comprising administering to the juvenile subject a therapeutically effective amount of a therapeutic AAV virus encoding a therapeutic protein, wherein the expression of the therapeutic protein ameliorates the symptoms of the genetic disorder.
2. A use of a therapeutic AAV virus for the preparation of a medicament for ameliorating symptoms of a genetic disorder in a juvenile subject suffering from the genetic disorder, wherein the medicament comprises a therapeutically effective amount of a therapeutic AAV virus encoding a therapeutic protein, wherein the expression of the therapeutic protein ameliorates the symptoms of the genetic disorder.
3. A composition comprising a therapeutically effective amount of a therapeutic AAV virus encoding a therapeutic protein for use in ameliorating symptoms of a genetic disorder in a juvenile subject suffering from the genetic disorder.
4. The method, use or composition of any one of claims 1-3, wherein the therapeutic protein is a functional copy of a non-functional endogenous protein.
5. The method, use or composition of any one of claims 1-3, wherein the therapeutic protein is a modified version of the endogenous protein.
6. The method, use or composition of any one of claims 1-3, wherein the therapeutic protein is a heterologous protein that compensates for a non-functional endogenous protein.
7. The method, use or composition of any of the preceding claims, wherein the juvenile subject is a juvenile human.
8. The method, use or composition of claim 7, wherein the juvenile human is less than 18 years old.

9. The method, use or composition of claim 7, wherein the juvenile human is less than 12 years old.
10. The method, use or composition of any of the preceding claims, wherein the therapeutic protein is expressed by the hepatocytes of the juvenile subject following administration of the therapeutic AAV virus.
11. The method of any of the preceding claims, wherein the therapeutic AAV virus is administered intravenously.
12. The use or composition of any of the preceding claims, wherein the medicament is formulated for intravenous administration.
13. The method, use or composition of any of the preceding claims, wherein the genetic disorder is a hemophilia.
14. The method, use or composition of claim 13, wherein the hemophilia is hemophilia A and the therapeutic protein is Factor VIII.
15. The method, use or composition of claim 14, wherein the Factor VIII is Factor VIII-SQ.
16. The method, use or composition of claim 14, wherein the therapeutic AAV virus is AAV5-FVIII-SQ.
17. The method, use or composition of claim 13, wherein the hemophilia is hemophilia B and the therapeutic protein is Factor IX.
18. The method, use or composition of claim 17, wherein the Factor IX is R338L Factor IX.

19. The method, use or composition of any one of claims 1 to 12, wherein the genetic disorder is phenylketonuria (PKU) and the therapeutic protein is phenylalanine hydroxylase (PAH).
20. The method, use or composition of any of the preceding claims, wherein the amount of therapeutic AAV virus administered to the juvenile subject corresponds to the same absolute number of therapeutic AAV virus that is effective in adult subjects.
21. The method, use or composition of claim 20, wherein from about 1E12 vg/kg to about 1E15 vg/kg of the therapeutic AAV virus are administered to the juvenile subject.
22. The method, use or composition of claim 20, wherein from about 6E13 vg/kg to about 6E14 vg/kg of the therapeutic AAV virus are administered to the juvenile subject.
23. The method, use or composition of any one of claims 20 to 22, wherein the AAV virus 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 monohydrate 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.
24. The method, use or composition of any one of claims 20 to 23, wherein the juvenile subject is treated prophylactically with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.
25. The method, use or composition of any one of claims 20 to 23, wherein the juvenile subject is treated therapeutically with a corticosteroid at a concentration from 5 mg/day to 60 mg/day.
26. The method, use or composition of any one of claims 20 to 25, which results in the expression of at least about 5 IU/dl of functional Factor VIII protein in the juvenile subject.

27. The method, use or composition of any one of claims 20 to 25, which results in an increase in functional Factor VIII protein of at least about 1 IU/dl in the juvenile subject.

28. A method of reducing bleeding time of a bleeding episode in a juvenile subject suffering from hemophilia comprising administering to the juvenile subject, prior to the bleeding episode, a therapeutically effective amount of a therapeutic AAV virus.

29. A use of a therapeutically effective amount of a therapeutic AAV virus for the preparation of a medicament for reducing bleeding time of a bleeding episode in a juvenile subject suffering from hemophilia, wherein the medicament is administered to the juvenile subject prior to the bleeding episode.

30. A composition comprising a therapeutically effective amount of a therapeutic AAV virus useful for reducing bleeding time of a bleeding episode in a juvenile subject suffering from hemophilia, wherein the composition is administered to the juvenile subject prior to the bleeding episode

31. The method, composition or use of any one of claims 28-30, wherein the administering occurs at least three weeks prior to the bleeding episode.

32. The method of any one of claims 28-31, wherein the therapeutic AAV virus is administered intravenously.

33. The use or composition of any one of claims 28-31, wherein the therapeutic AAV is formulated for intravenous administration

34. The method, use or composition any one of claims 28-33, wherein the hemophilia is hemophilia A and the therapeutic AAV virus expresses Factor VIII.

35. The method, use or composition of claim 34, wherein the Factor VIII is Factor VIII-SQ.

36. The method, use or composition of claim 34, wherein the therapeutic AAV virus is AAV5-FVIII-SQ.

37. The method, use or composition of claim 28-33, wherein the hemophilia is hemophilia B and the therapeutic AAV virus expresses Factor IX.

38. The method, use or composition of claim 37, wherein the Factor IX is R338L Factor IX.

39. The method, use or composition of any one of claims 28 to 38, wherein the amount of therapeutic AAV virus administered to the juvenile subject corresponds to the same absolute number of therapeutic AAV virus that is effective in adult subjects.

40. The method, use or composition of claim 39, wherein from about $1E12$ vg/kg to about $1E15$ vg/kg of the therapeutic AAV virus are administered to the juvenile subject.

41. The method, use or composition of claim 39, wherein from about $6E13$ vg/kg to about $6E14$ vg/kg of the therapeutic AAV virus are administered to the juvenile subject.

42. The method, use or composition of any one of claims 28 to 41, wherein therapeutic AAV virus is formulated in a solution comprising sodium phosphate, dibasic at a concentration of from about 0.1 mg/ml to about 3 mg/ml, sodium phosphate monobasic monohydrate 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.

43. A method of increasing Factor VIII protein expression in a juvenile subject in need thereof comprising administering to the juvenile subject a therapeutic virus, wherein the therapeutic AAV virus is AAV5-FVIII-SQ.

44. Use of a therapeutic AAV virus for the preparation of a medicament for increasing Factor VIII protein expression in a juvenile subject in need thereof, wherein the AAV virus is AAV5-FVIII-SQ.
45. A composition comprising a therapeutic AAV virus for increasing Factor VIII protein expression in a juvenile subject in need thereof, wherein the AAV virus is AAV5-FVIII-SQ.
46. The method of claim 43, wherein the therapeutic AAV virus is administered intravenously.
47. The use or composition of claim 44 or 45, wherein the AAV virus is formulated for intravenous administration
48. The method, use or composition of any one of claims 43-47, wherein the amount of therapeutic AAV virus administered to the juvenile subject corresponds to the same absolute number of therapeutic AAV virus that is effective in adult subjects.
49. The method, use or composition of claim 48, wherein from about $1\text{E}12$ vg/kg to about $1\text{E}15$ vg/kg of the therapeutic AAV virus are administered to the juvenile subject.
50. The method, use or composition of claim 48, wherein from about $6\text{E}13$ vg/kg to about $6\text{E}14$ vg/kg of the therapeutic AAV virus are administered to the juvenile subject.
51. The method, use or composition of any one of claims 43-50 which results in expression of at least about 5 IU/dl of functional Factor VIII protein in the juvenile subject.
52. The method, use or composition of claim 51 which results in expression of at least about 1 IU/dl of functional Factor VIII protein in the juvenile subject.
53. The method, use or composition of any one of claims 43- 52 which results in an increase in functional FVIII activity of at least about 1 IU/dl in the juvenile subject.

54. The method, use or composition of any one of claims 41-50, wherein the juvenile subject is treated with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.
55. The method, use or composition of claim 54, wherein the corticosteroid treatment is performed prophylactically.
56. The method, use or composition of claim 54, wherein the corticosteroid treatment is performed therapeutically.
57. The method, use or composition of claim 54-56, wherein the juvenile subject is treated 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.
58. The method of any one of claims 54- 57 further comprising a step of determining the absence or presence of anti-AAV capsid antibodies in the serum of the juvenile subject after administration of the therapeutically effective amount of the AAV5-FVIII-SQ.
59. The method of claim 58 further comprising the step of administering an effective amount of a corticosteroid to the subject after a determination of the presence of anti-AAV capsid antibodies in the serum of the juvenile subject is made.
60. A method of increasing phenylalanine hydroxylase (PAH) protein expression in a juvenile subject in need thereof comprising administering to the juvenile subject a therapeutic virus, wherein the therapeutic AAV virus comprises a nucleic acid sequence encoding a functionally active PAH .
61. Use of a therapeutic AAV virus for the preparation of a medicament for increasing phenylalanine hydroxylase (PAH) protein expression in a juvenile subject in need thereof, wherein the AAV virus comprises a nucleic acid sequence encoding a functionally active PAH.

62. A composition comprising a therapeutic AAV virus for increasing phenylalanine hydroxylase (PAH) protein expression in a juvenile subject in need thereof, wherein the AAV virus comprises a nucleic acid sequence encoding a functionally active PAH .

63. The method of claim 60, wherein the therapeutic AAV virus is administered intravenously.

64. The use or composition of claim 61 or 62, wherein the AAV virus is formulated for intravenous administration

65. The method, use or composition of any one of claims 60-64, wherein about 1E12 vg/kg to about 2E16 vg/kg of the therapeutic AAV virus are administered to the juvenile subject.

65. The method, use or composition of any one of claims 60-64, wherein about 2E12 vg/kg to about 2E14 vg/kg of the therapeutic AAV virus are administered to the juvenile subject.

66. The method, use or composition of any one of claims 60-64, wherein about 6E12 vg/kg to about 2E14 vg/kg of the therapeutic AAV virus are administered to the juvenile subject.

67. The method, use or composition of any one of claim 60-66, wherein the juvenile subject is 3 weeks to 5 weeks of age.

68. The method of any one of claims 60-67 further comprising a step of determining the absence or presence of anti-AAV capsid antibodies in the serum of the juvenile subject after administration of the therapeutically effective amount of the AAV virus comprising a nucleic acid sequence encoding a functionally active PAH.