

vectors and/or recombinant Factor VIII AAV particles/viruses comprising any of the herein described AAV FVIII vectors, associated pharmaceutical formulations, and associated methods of administration for the treatment of hemophilia A in subjects suffering therefrom.

SUMMARY

[0007a] In one aspect, the present disclosure refers to use of a recombinant AAV5 FVIII-SQ virus in the manufacture of a medicament for treating a subject suffering from hemophilia A, wherein the medicament comprises (a) sodium phosphate, dibasic at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium phosphate monobasic at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium chloride at a concentration of from 1 mg/ml to 20 mg/ml, mannitol at a concentration of from 5 mg/ml to 40 mg/ml, and poloxamer 188 at a concentration of from 0.1 mg/ml to 4 mg/ml, ~~or (b) sodium phosphate, dibasic at a concentration of 3.05 mg/ml, sodium phosphate monobasic at a concentration of 0.23 mg/ml, sodium chloride at a concentration of 8.18 mg/ml, mannitol at a concentration of 20 mg/ml, and poloxamer 188 at a concentration of 2 mg/ml~~, wherein AAV5-FVIII-SQ comprises an AAV2 5' inverted terminal repeat (ITR), a liver specific transcriptional regulatory region, a functionally active FVIII coding region, a polyadenylation sequence, an AAV2 3' ITR, and optionally one or more introns, wherein the functionally active FVIII coding region comprises nucleotides 403-4776 of SEQ ID NO: 1 and wherein the medicament is to be administered intravenously, ~~and wherein the recombinant AAV5-FVIII-SQ comprises a liver specific regulatory element.~~

[0007b] In another aspect, the present disclosure refers to a pharmaceutical formulation comprising a recombinant AAV5-FVIII-SQ virus, a buffering agent, an isotonicity agent, a bulking agent and a surfactant, wherein the formulation comprises a) sodium phosphate dibasic, at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium phosphate monobasic at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium chloride at a concentration of from 1 mg/ml to 20 mg/ml, mannitol at a concentration of from 5 mg/ml to 40 mg/ml, and poloxamer 188 at a concentration of from 0.1 mg/ml to 4 mg/ml, ~~or b) sodium phosphate, dibasic at a concentration of 3.05 mg/ml, sodium phosphate monobasic at a concentration of 0.23 mg/ml, sodium chloride at a concentration of 8.18 mg/ml, mannitol at a concentration of 20 mg/ml, and poloxamer 188 at a concentration of 2 mg/ml~~, wherein AAV5-FVIII-SQ comprises an AAV2 5' inverted terminal repeat (ITR), a liver specific transcriptional regulatory region, a functionally active FVIII coding region, a polyadenylation sequence, an AAV2 3' ITR, and optionally one or more introns, wherein the functionally active FVIII coding region comprises nucleotides 403-4776 of SEQ ID NO: 1 and wherein the medicament formulation is to be administered intravenously, ~~and wherein the recombinant AAV5-FVIII-SQ comprises a liver specific regulatory element.~~

CLAIMS

~~1.~~—Use of a recombinant -AAV5-FVIII-SQ virus in the manufacture of a medicament for treating a subject suffering from hemophilia A, wherein the medicament comprises

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

~~1. (b) sodium phosphate, dibasic at a concentration of 3.05 mg/ml, sodium phosphate monobasic at a concentration of 0.23 mg/ml, sodium chloride at a concentration of 8.18 mg/ml, mannitol at a concentration of 20 mg/ml, and poloxamer 188 at a concentration of 2 mg/ml,~~

wherein AAV5-FVIII-SQ comprises an AAV2 5' inverted terminal repeat (ITR), a liver specific transcriptional regulatory region, a functionally active FVIII coding region, a polyadenylation sequence, an AAV2 3' ITR, and optionally one or more introns, wherein the functionally active FVIII coding region comprises nucleotides 403-4776 of SEQ ID NO: 1

and wherein the medicament is to be administered intravenously, ~~and wherein the recombinant AAV5-FVIII-SQ comprises a liver specific regulatory element.~~

2. The use of Claim 1, wherein from 1E12 vg/kg to 1E14 vg/kg recombinant AAV5-FVIII-SQ virus is to be administered to said subject.

3. The use of Claim 1, wherein from 6E12 vg/kg to 6E13 vg/kg recombinant AAV5-FVIII-SQ virus is to be administered to said subject.

4. The use of any one of Claims 1-3 which results in expression of at least 5 IU/dl of functional Factor VIII protein in said subject.

5. The use of any one of Claims 1-4, wherein said subject expresses at least 5 IU/dl of functional Factor VIII protein 3 weeks or more after said administration.

6. The use of any one of Claims 1-4 which results in an increase in functional FVIII activity of at least 1 IU/dl in said subject.

7. The use of any one of Claims 1-6, wherein the medicament is stable during storage at $\leq 65^{\circ}\text{C}$ for at least 2 weeks.
8. The use of any one of Claims 1-7, wherein the medicament is liquid.
9. The use of any one of Claims 1-8, wherein the medicament comprises said AAV5-FVIII-SQ virus at a concentration of from $1\text{E}12$ vg/ml to $2\text{E}14$ vg/ml.
10. The use of claim 9, wherein the medicament comprises said AAV5-FVIII-SQ virus at a concentration of $2\text{E}13$ vg/ml.
11. The use of any one of Claims 1-10, wherein the medicament is useful for IV administration to a patient suffering from hemophilia A.
12. The use of any one of Claims 1-11, wherein said subject is to be treated prophylactically with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.
13. The use of any one of Claims 1-12 wherein said subject is to be treated prophylactically 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.
14. The use of any one of Claims 1-13 wherein said subject is to be treated therapeutically with a corticosteroid at a concentration ranging from 5 mg/day to 60 mg/day.
15. The use of any one of Claims 1-14 wherein said subject is to be treated therapeutically 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.
16. The use of any one of Claims 1-15 wherein the absence or presence of anti-AAV capsid antibodies in the serum of said subject is to be determined before administration of said therapeutically effective amount of said recombinant AAV5-FVIII-SQ virus.
17. The use of any one of Claim 1-15 wherein the absence or presence of hepatotoxicity in the subject is to be determined after administration of said therapeutically effective amount of said recombinant AAV5-FVIII-SQ virus.

18. A pharmaceutical formulation comprising a recombinant AAV5-FVIII-SQ virus, a buffering agent, an isotonicity agent, a bulking agent and a surfactant, wherein the formulation comprises ~~a) sodium phosphate, dibasic~~ at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium phosphate monobasic at a concentration of from 0.1 mg/ml to 3 mg/ml, sodium chloride at a concentration of from 1 mg/ml to 20 mg/ml, mannitol at a concentration of from 5 mg/ml to 40 mg/ml, and poloxamer 188 at a concentration of from 0.1 mg/ml to 4 mg/ml, ~~or~~
~~b) sodium phosphate, dibasic at a concentration of 3.05 mg/ml, sodium phosphate monobasic at a concentration of 0.23 mg/ml, sodium chloride at a concentration of 8.18 mg/ml, mannitol at a concentration of 20 mg/ml, and poloxamer 188 at a concentration of 2 mg/ml,~~

wherein AAV5-FVIII-SQ comprises an AAV2 5' inverted terminal repeat (ITR), a liver specific transcriptional regulatory region, a functionally active FVIII coding region, a polyadenylation sequence, an AAV2 3' ITR, and optionally one or more introns, wherein the functionally active FVIII coding region comprises nucleotides 403-4776 of SEQ ID NO: 1

and wherein the medicament formulation is to be administered intravenously, ~~and wherein the recombinant AAV5-FVIII-SQ comprises a liver specific regulatory element.~~

19. The pharmaceutical formulation of Claim 18 which is liquid.

20. The pharmaceutical formulation of Claim 18 which comprises said AAV5-FVIII-SQ virus at a concentration of from 1E12 vg/ml to 2E14 vg/ml.

21. The pharmaceutical formulation of Claim 20 which comprises said AAV5-FVIII-SQ virus at a concentration of 2E13 vg/ml.