CLAIMS

We claim:

1. A recombinant adeno-associated virus vector (rAAV) comprising a codon-optimized sequence encoding a human phenylalanine hydroxylase (PAH), wherein the codon-optimized sequence has at least 70% identity to one of SEQ ID Nos: 11-27.

2. The rAAV of claim 1, wherein the codon-optimized sequence has at least 75%, 80%, 85%, 90%, 95% or 99% identity to one of SEQ ID Nos: 11-27 or is identical to one of SEQ ID Nos: 11-27.

3. The rAAV of claim 1 or 2, wherein the rAAV encodes an AAV8 capsid, optionally wherein the AAV8 capsid is a modified AAV8 capsid with improved liver tropism compared to the wild-type AAV8 capsid, optionally wherein the AAV8 capsid has at least 70%, 75%, 80%, 85%, 90%, 95% or 99% identity to the wild-type AAV8 capsid.

4. The rAAV of any one of the preceding claims, wherein the rAAV further comprises a WPRE sequence, optionally wherein the WPRE sequence is (i) a naturally-occurring WPRE sequence, or (ii) a modified WPRE sequence.

5. The rAAV of any one of the preceding claims, wherein the rAAV further comprises a liver-specific promoter, optionally wherein the liver-specific promoter is a transthyretin promotor (TTR).

6. The rAAV of any one of the preceding claims, wherein the rAAV comprises a cis-acting regulatory module (CRM), optionally wherein (i) the vector comprises one, two, three, four, five or more CRM repeats, and/or (ii) the CRM is CRM8.

7. The rAAV of any one of the preceding claims, wherein the rAAV further comprises an intron upstream of the PAH sequence, optionally wherein the intron is a minute virus of mice (MVM) intron.

8. A recombinant adeno-associated virus (rAAV) comprising a codon-optimized sequence encoding a human phenylalanine hydroxylase (PAH) for use in treating

phenylketonuria (PKU) in a subject in need of treatment, wherein the codon-optimized sequence has at least 70% identity to one of SEQ ID Nos: 11-27.

9. The rAAV for use according to claim 8, wherein administering the rAAV results in (a) a decrease in plasma phenylalanine (Phe) level in the subject compared to a control, and/or (b) an increase in plasma tyrosine level in the subject compared to a control, and/or (c) an increase in plasma tryptophan level in the subject compared to a control, optionally wherein the control is (i) the pre-treatment level in the subject, or (ii) a reference level based on historical data.

10. The rAAV for use according to claim 8 or 9, wherein the codon-optimized sequence has at least 75%, 80%, 85%, 90%, 95% or 99% identity to one of SEQ ID Nos: 11-27 or is identical to one of SEQ ID Nos: 11-27.

11. The rAAV for use according to any one of claims 8-10, wherein the rAAV encodes an AAV8 capsid, optionally wherein the AAV8 capsid is a modified AAV8 capsid with improved liver tropism compared to the wild-type AAV8 capsid, optionally wherein the AAV8 capsid has at least 70%, 75%, 80%, 85%, 90%, 95% or 99% identity to the wild-type AAV capsid.

12. The rAAV for use according to any one of claims 8-11, wherein the rAAV further comprises a WPRE sequence, optionally wherein the WPRE sequence is (i) a naturally-occurring WPRE sequence, or (ii) a modified WPRE sequence.

13. The rAAV for use according to any one of claims 8-12, wherein the rAAV further comprises a liver-specific promoter, optionally wherein the liver-specific promoter is a transthyretin promotor (TTR).

14. The rAAV for use according to any one of claims 8-13, wherein the rAAV comprises a cis-acting regulatory module (CRM), optionally wherein the vector comprises (i) one, two, three, four, five or more CRM repeats, and/or (ii) the CRM is CRM8.

15. The rAAV for use according to any one of claims 8-14, wherein the rAAV further comprises an intron upstream of the PAH sequence, optionally wherein the intron is a minute virus of mice (MVM) intron.

16. The rAAV for use according to any one of claims 8-15, wherein the rAAV is to be administered at dose of about $1x10^{10}$ vg/kg, about $1x10^{11}$ vg/kg, about $1x10^{12}$ vg/kg, about $1x10^{13}$ vg/kg, about $1x10^{14}$ vg/kg, or about $1x10^{15}$ vg/kg.

17. The rAAV for use according to any one of claims 8-16, wherein the rAAV is to be administered systemically or intravenously.

18. A pharmaceutical composition comprising a recombinant adeno-associated virus (rAAV) comprising a codon-optimized sequence encoding a human phenylalanine hydroxylase (PAH) for treating phenylketonuria (PKU), wherein the rAAV comprises:
    (a) a modified AAV8 capsid with improved liver tropism compared to the wild-type AAV8 capsid;
    (b) a WPRE sequence;
    (c) a liver-specific promoter, optionally a transthyretin promoter (TTR);
    (d) a cis-acting regulatory module (CRM), optionally CRM8; and
    (e) an intron upstream of the PAH sequence, optionally a minute virus of mice (MVM) intron.