

CLAIMS

1. Use of a lipid nanoparticle (LNP) composition comprising an effective amount of:
 - (i) an mRNA encoding a Cas nuclease, and
 - (ii) a guide RNA that targets the TTR genein the manufacture of a medicament for treating amyloidosis associated with TTR (ATTR) in a human subject,

wherein the medicament is adapted for systemic administration and wherein the medicament is adapted to administer the mRNA encoding a Cas nuclease and the guide RNA that targets the TTR gene at a combined dose of 50 mg $\pm$ 10% of 50 mg; 55 mg $\pm$ 10% of 55 mg; 80 mg $\pm$ 10% of 80 mg; 0.3 mg/kg; 0.7 mg/kg; or 1.0 mg/kg.
2. The use of a lipid nanoparticle (LNP) composition comprising an effective amount of:
 - (i) an mRNA encoding a Cas nuclease, and
 - (ii) a guide RNA that targets the TTR genein the manufacture of a medicament for treating amyloidosis associated with TTR (ATTR) in a human subject,

wherein the medicament is adapted for systemic administration and wherein the medicament is adapted to administer the mRNA encoding a Cas nuclease and the guide RNA that targets the TTR gene at a combined dose of 55 mg.
3. The use of claim 1 or claim 2, wherein the LNP comprises (9Z, 12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9, 12-dienoate.
4. The use of claim 3, wherein the LNP comprises a PEG lipid.
5. The use of claim 4, wherein the PEG lipid comprises PEG2k-DMG.
6. The use of any one of claims 1-5, wherein the LNP composition has an N/P ratio of about 5-7.

7. The use of any one of claims 1-6, wherein the guide RNA and the mRNA encoding the Cas nuclease are present in a ratio ranging from about 5:1 to about 1:5 by weight.
8. The use of any one of claims 1-7, wherein the mRNA encodes an *S. pyogenes* Cas9 nuclease.
9. The use of any one of claims 1-8, wherein the mRNA encoding the Cas nuclease is codon-optimized.
10. The use of any one of claims 1-9, wherein at least one of the guide RNA and the mRNA comprise a modification.
11. The use of claim 10, wherein the modification includes a 2'-O-methyl modified nucleotide or a phosphorothioate bond between nucleotides of the guide RNA and/or N1-methylpseudouridine in the mRNA.
12. The use of any one of claims 1-11, wherein the ATTR is hereditary transthyretin amyloidosis.
13. The use of any one of claims 1-11, wherein the ATTR is wild-type transthyretin amyloidosis.
14. The use of any one of claims 1-12, wherein the ATTR is hereditary transthyretin amyloidosis with polyneuropathy.
15. The use of any one of claims 1-12 wherein the ATTR is hereditary transthyretin amyloidosis with cardiomyopathy.
16. The use of claim 13, wherein the ATTR is wildtype transthyretin amyloidosis with cardiomyopathy.

17. The use of claim 15 or 16, wherein the subject is classified under the New York Heart Association (NYHA) classification as having Class I, Class II, or Class III cardiomyopathy.
18. The use of any one of claims 1 or 3-17, wherein the total RNA is 50 mg $\pm$ 5% of 50 mg, 55 mg $\pm$ 5% of 55 mg, or 80 mg $\pm$ 5% of 80 mg.
19. The use of any one of claims 1-18, wherein the medicament is adapted to reduce or knock down expression of the TTR gene by at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 98%, 99% or by 100%, as compared to baseline before administration of the composition.
20. The use of any one of claims 1-19, wherein the medicament is adapted to reduce serum TTR level in the subject by at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 98%, 99% or by 100% as compared to serum TTR level before administration of the composition.
21. The use of any one of claims 1-19, wherein the medicament is adapted to reduce serum TTR levels in the subject to less than about 50 μ g/mL, 40 μ g/mL, 30 μ g/mL, 20 μ g/mL, or 10 μ g/mL after administration of the composition.
22. The use of any one of claims 1-21, wherein the medicament is adapted to administer with a second therapeutic agent.
23. The use of claim 22, wherein the second therapeutic agent is a stabilizer of the tetrameric form of TTR.
24. The use of claim 23, wherein the second therapeutic agent is diflunisal or tafamidis.