Claims

1. Use of a first RNAi agent and a second RNAi agent in the manufacture of a pharmaceutical composition for treating or preventing a disease associated with an infection caused by Hepatitis B Virus in a human subject, wherein an effective amount of the pharmaceutical composition is to be administered to the human subject, wherein:

(a) the first RNAi agent comprises:

(i) an antisense strand comprising a nucleotide sequence of any one of the following: SEQ ID NO:100, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:171, SEQ ID NO: 179 and SEQ ID NO: 180, and

(ii) a sense strand comprising a nucleotide sequence of any one of the following: SEQ ID NO:229, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:273, SEQ ID NO:302, and SEQ ID NO:319 and

(b) the second RNAi agent comprises:

(i) an antisense strand comprising a nucleotide sequence of any one of the following: SEQ ID NO:140, SEQ ID NO: 107, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO:188, SEQ ID NO: 154 and SEQ ID NO: 162, and

(ii) a sense strand comprising a nucleotide sequence of any one of the following: SEQ ID NO:262, SEQ ID NO:271, SEQ ID NO: 216, SEQ ID NO: 248, SEQ ID NO:274, SEQ ID NO:328, SEQ ID NO: 292, and SEQ ID NO: 294;

and wherein the first and second RNAi agents are to be administered in a combined amount of 100-400 mg per 28 days.

2. The use of Claim 1, wherein the first and/or second RNAi agent further comprises a targeting ligand conjugated to the sense or antisense strand.

3. The use of Claim 2, wherein the targeting ligand comprises N-acetyl-galactosamine.

4. The use of Claim 3, wherein the targeting ligand is (NAG25), (NAG25)s, (NAG31), (NAG31)s, (NAG37), or (NAG37)s.

5. The use of any one of Claims 2-4, wherein the targeting ligand is conjugated to the 5’ end or to the 3’ end of sense strand of the RNAi agent.

6. The use of any one of Claims 2-4, wherein the targeting ligand is conjugated to the 3’ end of the antisense strand of the RNAi agent.

7. The useof any one of Claims 1-6, wherein the first RNAi agent is to be administered in the amount of 20-275 mg.

8. The use of any one of Claims 1-7, wherein the second RNAi agent is to be administered in the amount of 10-150 mg.

9. The use of any one of Claims 1-8, wherein the pharmaceutical composition comprises RNAi agent comprising a duplex structure of AD04511 (SEQ ID NO: 100 and SEQ ID NO:229), AD04872 (SEQ ID NO: 126 and SEQ ID NO:252), AD04873 (SEQ ID NO: 127 and SEQ ID NO:252), AD04874 (SEQ ID NO: 128 and SEQ ID NO:253), AD05070 (SEQ ID NO:140 and SEQ ID NO:262), AD05148 (SEQ ID NO:140 and SEQ ID NO:271), AD05164 (SEQ ID NO:126 and SEQ ID NO:273), AD05165 (SEQ ID NO:140 and SEQ IDNO:274), or a mixture of any of the foregoing.

10. The use of Claim 9, wherein the pharmaceutical composition comprises an RNAi agent comprising the duplex structure of AD04872 (SEQ ID NO: 126 and SEQ ID NO:252) and an RNAi agent comprising the duplex structure of AD05070 (SEQ ID NO:140 and SEQ ID NO:262).

11. The use of Claim 10, wherein the duplex structure of AD04872 is conjugated to (NAG37) and the duplex structure of AD05070 is conjugated to (NAG37).

12. The use of Claim 11, wherein the (NAG37) is conjugated to the 5’ end of the respective sense strands of the duplex of AD04872 and the duplex of AD05070.

13. The use of any one of Claims 10-12, wherein the ratio of the duplex of AD04872 and the duplex of AD05070 is between 1:2 to 5:1.

14. The use of Claim 13, wherein the ratio of the duplex of AD04872 and the duplex of AD05070 is 2:1.

15. The use of any one of Claims 1-14, wherein the composition further comprises a pharmaceutically acceptable excipient.

16. The use of any one of Claims 1-15, wherein the composition is to be administered subcutaneously.

17. The use of any one of Claims 1-16, wherein the first and second RNAi agents are to be administered in a combined amount of any of 100, 200, 300 mg or 400 mg per 28 days.

18. The use of any one of Claims 1-16, wherein the first and second RNAi agents are to be administered in a combined amount of 100 mg or 200 mg per 28 days.

Claim 19. The use of Claim 18, wherein the first and second RNAi agents are to be administered in a combined amount of 100 mg per 28 days.

Claim 20. The use of Claim 18, wherein the first and second RNAi agents are to be administered in a combined amount of 200 mg per 28 days.

21. The use of any one of Claims 1-20, wherein the first and second RNAi agents are to be administered in 7-day, 14-day, 21-day or 28-day intervals.

22. The use of any one of Claims 1-20, wherein the first and second RNAi agents are to be administered in 28-day intervals.

23. The use of Claim 22, wherein the first and second RNAi agents are administered in a combined amount of 100 mg or 200 mg per 28 days and in 28-day intervals.

24. The use of Claim 23, wherein the first and second RNAi agents are to be administered in a combined amount of 100 mg per 28 days and in 28-day intervals.

25. The use of Claim 23, wherein the first and second RNAi agents are to be administered in a combined amount of 200 mg per 28 days and in 28-day intervals.

26. The use of any one of Claims 1-25, wherein the composition is to be administered to the subject for up to 6 months.

27. The use of any one of Claims 1-26, wherein the pharmaceutical composition is to be administered to the subject in combination with a second active agent.

28. The useof Claim 27, wherein the second active agent is a nucleoside analog.

29. The use of Claim 28, wherein the nucleoside analog is Entecavir or Tenofovir.

Claim 30. The use of any one of Claims 1-29, wherein the level of HBsAg, HBeAg, or serum HBV DNA in the human subject is to be reduced by at least 40% after the administration of the composition.

Claim 31. The use of any one of Claims 1-30, wherein the disease associated with the HBV infection is a chronic liver disease or disorder, liver inflammation, liver fibrotic condition, a proliferative hepatocellular disorder, hepatocellular carcinoma, Hepatitis D virus infection, acute HBV infection, chronic hepatitis B or chronic HBV infection.

Claim 32. The use of Claim 31, wherein the disease associated with the HBV infection is chronic hepatitis B or chronic HBV infection.