Claims

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

(a) ~~a~~ the first RNAi agent ~~comprising~~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) ~~a~~ the second RNAi agent ~~comprising~~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 ~~about 25~~100-400 mg per 28 days.

2. The ~~pharmaceutical composition~~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~~pharmaceutical composition~~ of Claim 2, wherein the targeting ligand comprises N-acetyl-galactosamine.

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

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

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

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

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

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

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

17. The usepharmaceutical composition of any one of Claims 1-16, wherein the first and second RNAi agents are to be administered in a combined amount of about any of 25, 35, 50, 100, 200, 300 mg or 400 mg per 28 days.

18. The usepharmaceutical composition of any one of Claims 1-16, wherein the first and second RNAi agents are to be administered in a combined amount of about 40 mg, about 100 mg, or about 200 mg per 28 days.

Claim 19. The pharmaceutical composition of Claim 18, wherein the first and second RNAi agents are administered in a combined amount of about 40 mg per 28 days.

Claim 1920. The usepharmaceutical composition of Claim 18, wherein the first and second RNAi agents are to be administered in a combined amount of about 100 mg per 28 days.

Claim 2120. The usepharmaceutical composition of Claim 18, wherein the first and second RNAi agents are to be administered in a combined amount of about 200 mg per 28 days.

2221. The usepharmaceutical composition of any one of Claims 1-2120, wherein the first and second RNAi agents are to be administered in 7-day, 14-day, 21-day or 28-day intervals.

~~23~~22. The use~~pharmaceutical composition~~ of any one of Claims 1-~~21~~20, wherein the first and second RNAi agents are to be administered in 28-day intervals.

~~24~~23. The use~~pharmaceutical composition~~ of Claim ~~23~~22, wherein the first and second RNAi agents are administered in a combined amount of ~~about 40 mg, about~~ 100 mg~~,~~ or ~~about~~ 200 mg per 28 days and in 28-day intervals.

~~25. .The pharmaceutical composition of Claim 24, wherein the first and second RNAi agents are administered in a combined amount of about 40 mg per 28 days and in 28-day intervals.~~

~~26~~24. The use~~pharmaceutical composition~~ of Claim ~~24~~23, wherein the first and second RNAi agents are to be administered in a combined amount of ~~about~~ 100 mg per 28 days and in 28-day intervals.

~~27~~25. The use~~pharmaceutical composition~~ of Claim ~~24~~23, wherein the first and second RNAi agents are to be administered in a combined amount of ~~about~~ 200 mg per 28 days and in 28-day intervals.

~~28~~26. The use~~pharmaceutical composition~~ of any one of Claims 1-~~27~~25, wherein the composition is to be administered to the subject for up to 6 months.

~~29~~27. The use~~pharmaceutical composition~~ of any one of Claims 1-~~28~~26, ~~further comprising administering~~wherein the pharmaceutical composition is to be administered to the subject in combination with a second active agent.

~~30~~28. The use~~pharmaceutical composition~~ of Claim ~~29~~27, wherein the second active agent is a nucleoside analog.

~~31~~29. The use~~pharmaceutical composition~~ of Claim ~~30~~28, wherein the nucleoside analog is Entecavir or Tenofovir.

Claim ~~32~~30. The use~~pharmaceutical composition~~ of any one of Claims 1-~~31~~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 ~~33~~31. The use~~pharmaceutical composition~~ of any one of Claims 1-~~32~~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 ~~34~~32. The use~~pharmaceutical composition~~ of Claim ~~33~~31, wherein the disease associated with the HBV infection is chronic hepatitis B or chronic HBV infection.