restore immunological control in the majority of patients. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects infected with HBV or having an HBV-associated disease.

SUMMARY

In one aspect, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10) and the antisense strand comprises 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16); wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (Agn) is adenosine-glycol nucleic acid (GNA); s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the dsRNA agent as described herein and a pharmaceutical excipient. In another aspect, the present disclosure provides a method of inhibiting Hepatitis B virus (HBV) gene expression or inhibiting replication of a HBV in a cell *in vitro*, the method comprising contacting the cell with the dsRNA agent as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression or replication of the HBV gene in the cell. In still another aspect, the present disclosure provides use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for reducing the level of a Hepatitis B virus (HBV) antigen or reducing the viral load of HBV in a subject infected with HBV. In another aspect, the present disclosure provides use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating ~~a subject having~~ a Hepatitis B virus (HBV) infection in a subject. In another aspect, the present disclosure provides use of the dsRNA agent as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating ~~a subject having~~ a Hepatitis B virus (HBV)-associated disorder in a subject, wherein the HBV-associated disorder is hepatitis D virus infection, delta hepatitis, acute hepatitis B, acute fulminant hepatitis B, chronic hepatitis, liver fibrosis, end-stage liver disease, hepatocellular carcinoma, or any combination thereof. In another aspect, the present disclosure provides the

CLAIMS

1. A double stranded ribonucleic acid (dsRNA) agent, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10) and the antisense strand comprises 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16);

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA);

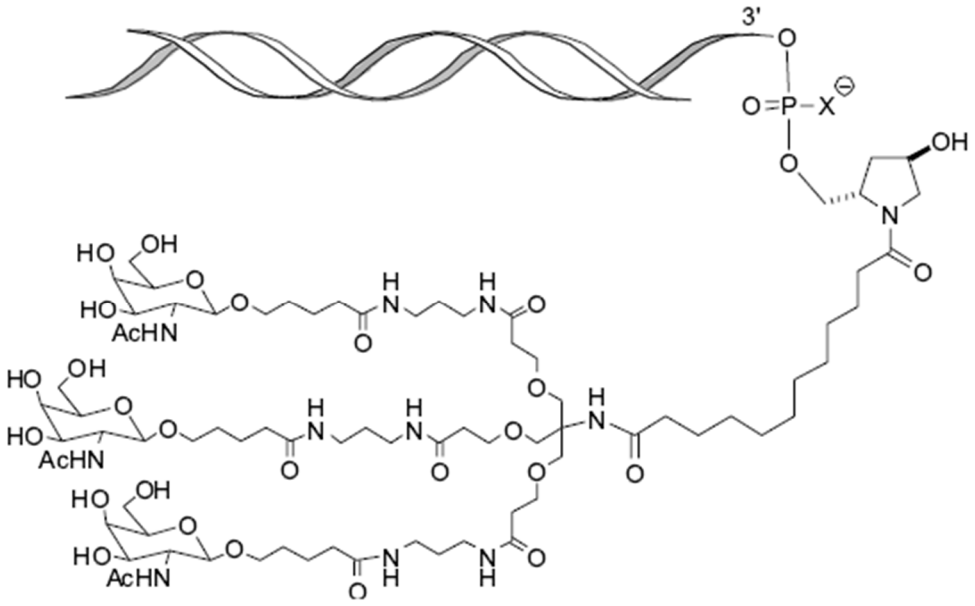
s is a phosphorothioate linkage; and

L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

2. The dsRNA agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

3. The dsRNA agent of any one of claims 1-2, wherein at least one strand comprises a 3' overhang of 2 nucleotides.

4. The dsRNA agent of any one of claims 1-3, wherein the L96 is conjugated to the 3' end of the sense strand as shown in the following schematic



,

wherein X is O or S.

5. The dsRNA agent of claim 4, wherein the X is O.

6. The dsRNA agent of any one of claims 1-5, wherein the dsRNA agent inhibits expression of hepatitis B virus (HBV) in a cell.

7. A cell containing the dsRNA agent of any one of claims 1-6.

8. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-6 and a pharmaceutical excipient.

9. A method of inhibiting Hepatitis B virus (HBV) gene expression or inhibiting replication of a HBV in a cell *in vitro*, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-6, or the pharmaceutical composition of claim 8, thereby inhibiting expression or replication of the HBV gene in the cell.

10. The method of claim 9, wherein the HBV gene expression or replication of HBV in the cell is inhibited by at least 80%, 90%, 95%, or 98%, or to below the level of detection of the assay method.

11. Use of the dsRNA agent of any one of claims 1-6, or the pharmaceutical composition of claim 8, in the manufacture of a medicament for reducing the level of a Hepatitis B virus (HBV) antigen or reducing the viral load of HBV in a subject infected with HBV.

12. The use of claim 11, wherein the HBV antigen is HBsAg or HBeAg.

13. The use of any one of claims 11-12, wherein the HBV antigen level is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

14. The use of claim 11, wherein the HBV viral load is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

15. The use of any one of claims 11-14, wherein the subject is HBeAg positive.

16. The use of any one of claims 11-14, wherein the subject is HBeAg negative.

17. Use of the dsRNA agent of any one of claims 1-6, or the pharmaceutical composition of claim 8, in the manufacture of a medicament for treating ~~a subject having~~ a Hepatitis B virus (HBV) infection in a subject.

18. Use of the dsRNA agent of any one of claims 1-6, or a pharmaceutical composition of claim 8, in the manufacture of a medicament for treating ~~a subject having~~ a Hepatitis B virus (HBV)-associated disorder in a subject, wherein the HBV-associated disorder is hepatitis D virus infection, delta hepatitis, acute hepatitis B, acute fulminant hepatitis B, chronic hepatitis, liver fibrosis, end-stage liver disease, hepatocellular carcinoma, or any combination thereof.

19. The use of claim 18, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive.

20. The use of claim 18, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

21. The use of claim 18, wherein the HBV-associated disorder is hepatitis D virus infection.

22~~21~~. The use of any one of claims 11-21~~20~~, wherein the dsRNA agent is to be administered to the subject at a dose of 0.01 mg/kg to 10 mg/kg, 0.5 mg/kg to 50 mg/kg, or 3 mg/kg to 10 mg/kg.

23~~22~~. The use of any one of claims 11-21~~20~~, wherein the dsRNA agent is to be administered to the subject at a fixed dose of 50 mg to 200 mg or 50 to 900 mg.

24~~23~~. The use of any one of claims 11-23~~22~~, wherein the dsRNA agent is to be administered to the subject subcutaneously.

25~~24~~. The use of any one of claims 11-24~~23~~, wherein the dsRNA agent is to be administered to the subject in two or more doses.

26~~25~~. The use of any one of claims 11-25~~24~~, wherein the dsRNA agent is to be administered to the subject once per month, once every two months, or once every three months.

27~~26~~. The use of any one of claims 11-26~~25~~, wherein the subject is to be or has been administered one or more additional therapeutic agents.

28~~27~~. The use of claim 27~~26~~, wherein the additional therapeutic agent is an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HBsAg, a capsid inhibitor, or a covalently closed circular (ccc) HBV DNA inhibitor, or a combination of any of the foregoing.

29~~28~~. The use of claim 27~~26~~, wherein the additional therapeutic agent is a reverse transcriptase inhibitor.

3029. The use of claim 2726, wherein the additional therapeutic agents are a reverse transcriptase inhibitor and an immune stimulator.

3130. The use of claim 29 or 30 ~~28 or 29~~, wherein the reverse transcriptase inhibitor is Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009.

3231. The use of claim 3029, wherein the immune stimulator is pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, or a Toll-like receptor 7 (TLR7) agonist.

3332. The dsRNA agent of any one of claims 1-6, or the pharmaceutical composition of claim 8 for use in therapy.