polymerase, are provided by the host cell, and the HDV envelope is provided by HBV. When introduced into permissive cells, the HDV RNA genome replicates and associates with multiple copies of the HDV-encoded proteins to assemble a ribonucleoprotein (RNP) complex. The RNP is exported from the cell by the HBV envelope proteins, which are able to assemble lipoprotein vesicles that bud into the lumen of a pre-Golgi compartment before being secreted. Moreover, the HBV envelope proteins also provide a mechanism for the targeting of HDV to an uninfected cell, thereby ensuring the spread of HDV.

Complications caused by HDV include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest fatality rate of all the hepatitis infections, at 20% (Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm SW. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. Gut. 2000 Mar;46(3):420-6). The only approved therapy for chronic HDV infection is interferon-alpha. However, treatment of HDV with interferon-alpha is relatively inefficient and is not well-tolerated. Treatment with interferon-alpha results in sustained virological response six months post-treatment in one-fourth of the patients. Also, nucleos(t)ide analogs (NAs) have been widely tested in hepatitis delta, but they appear to be ineffective. Combination treatment using NAs with interferon also proved to be disappointing (Zaigham Abbas, Minaam Abbas Management of hepatitis delta: Need for novel therapeutic Options. World J Gastroenterol 2015 August 28; 21(32): 9461-9465).

Accordingly, new therapeutic options, such as new therapies with neutralizing activity against Hepatitis B and/or D infection are needed.

SUMMARY

In one aspect, the present disclosure relates to an antibody, or an antigen-binding fragment thereof, comprisinga heavy chain variable region (VH) comprising a CDRH1 amino acid sequence, a CDRH2 amino acid sequence, and a CDRH3 amino acid sequence; and a light chain variable region (VL) comprising a CDRL1 amino acid

sequence, a CDRL2 amino acid sequence, and a CDRL3 amino acid sequence, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences are according to SEQ ID NOs.:(i) 34, 35, 37, 41, 49, and 55, respectively; (ii)34, 35, 37, 41, 46, and 55, respectively; (iii) 34, 35, 37, 41, 47, and 55, respectively; (iv) 34, 35, 37, 41, 48, and 55, respectively; (v) 34, 35, 37, 41, 45, and 55, respectively; (vi) 34, 35, 37, 41, 50, and 55, respectively; (vii) 34, 35, 37, 41, 51, and 55, respectively;(viii) 34, 35, 37, 41, 52, and 55, respectively; (ix) 34, 35, 37, 41, 53, and 55, respectively; or (x) 34, 35, 37, 41, 44, and 55, respectively; wherein CDRs are defined according to the CCG numbering system, wherein, optionally, the VL comprises a R60N substitution mutation, a R60A substitution mutation, a R60K substitution mutation, a S64A substitution mutation, a I74A substitution mutation, or any combination thereof, relative to SEQ ID NO.:58 and wherein the amino acid numbering of the substitution mutation(s) is according to SEQ ID NO.:58, and still further optionally wherein the VL does not comprise any further mutation(s) relative to SEQ ID NO.:58, and wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and, optionally, neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof.

In another aspect, the present disclosure relates to an antibody or antigen-binding fragment, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: (i) 38 and 62, respectively; (ii) 38 and 66, respectively; (iii) 38 and 67, respectively; (iv) 38 and 68, respectively; or (v) 38 and 72, respectively, wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof.

In another aspect, the present disclosure relates to an antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:75, optionally with the C-terminal lysine removed; and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

In another aspect, the present disclosure relates to an antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:76, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

In another aspect, the present disclosure relates to an antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:77, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

In another aspect, the present disclosure relates to an antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:78, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

In another aspect, the present disclosure relates to a polynucleotide comprising a nucleotide sequence that encodes the antibody, or the antigen-binding fragment as disclosed herein.

In another aspect, the present disclosure relates to a polynucleotide encoding a light chain variable region (VL) and, optionally, a light chain constant domain (CL) of the antibody, or the antigen-binding fragment, as disclosed herein.

In another aspect, the present disclosure relates to a vector comprising the polynucleotide as disclosed herein.

In another aspect, the present disclosure relates to a host cell comprising the polynucleotide and/or the vector as disclosed herein.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising: (i) the antibody or antigen binding fragment as disclosed herein; (ii) the polynucleotide as disclosed herein; (iii) the vector according as disclosed herein; (iv) the

host cell as disclosed herein; or (v) any combination of (i)-(iv), and a pharmaceutically acceptable excipient, diluent or carrier.

In another aspect, the present disclosure relates to a kit comprising: (a) a component selected from:(i) the antibody or antigen-binding fragment as disclosed herein; (ii) the polynucleotide as disclosed herein; (iii) the vector as disclosed herein; (iv) the host cell as disclosed herein; (v) the pharmaceutical composition as disclosed herein; or (vi) any combination of (i)-(vi); and (b) (1) instructions for using the component to prevent, treat, attenuate, and/or diagnose a hepatitis B virus infection and/or a hepatitis D virus infection and/or (2) a means for administering the component to the subject.

In another aspect, the present disclosure relates to a method of producing the antibody or antigen binding fragment as disclosed herein, comprising culturing the host cell as disclosed herein under conditions and for a time sufficient to produce the antibody or antigen-binding fragment.

In yet another aspect, the present disclosure relates to use of: (i) the antibody or antigen-binding fragment as disclosed herein; (ii) the polynucleotide asd disclosed herein; (iii) the vector as disclosed herein; (iv) the host cell as disclosed herein; and/or (v) the pharmaceutical composition as disclosed herein in the manufacture of a medicament to prevent, treat, attenuate, and/or diagnose a hepatitis B virus infection and/or a hepatitis D virus infection in a subject.

In yet another aspect, the present disclosure relates to an antibody or antigen-binding fragment as disclosed herein, the polynucleotide as disclosed herein, the vector as disclosed herein, the host cell as disclosed herein, and/or the pharmaceutical composition as disclosed herein for use as a medicament.

In yet another aspect, the present disclosure relates to a pharmaceutical composition comprising the antibody or antigen-binding fragment as disclosed herein at a concentration ranging from 100 mg/mL to 200 mg/mL, and a pharmaceutically acceptable carrier, excipient, or diluent.

In yet another aspect, the present disclosure relates to a method for *in vitro* diagnosis of a hepatitis B virus infection, the method comprising: (i) contacting a sample from a subject with an antibody or antigen-binding fragment as disclosed herein; and (ii) detecting a complex comprising an antigen and the antibody, or comprising an antigen and the antigen-binding fragment.

In yet another aspect, the present disclosure relates to a method for detecting the presence or absence of an epitope in a correct conformation in an anti-hepatitis-B and/or an anti-hepatitis-D vaccine, the method comprising: (i) contacting the vaccine with an antibody or antigen-binding fragment as disclosed herein; and (ii) determining whether a complex comprising an antigen and the antibody, or comprising an antigen and the antigen binding fragment, has been formed.

In yet another aspect, the present disclosure relates to use of an anti-HBV antibody as disclosed herein in the manufacture of a medicament for treating chronic HBV infection in a subject in need thereof, wherein the anti-HBV antibody is to be administered to the subject with an agent that reduces HBV antigenic load; and/or an inhibitor of HBV gene expression; wherein the agent that reduces HBV antigenic load and/or the inhibitor of HBV gene expression is an RNAi agent that inhibits expression of an HBV transcript.

In yet another aspect, the present disclosure relates to an antibody or antigen-binding fragment comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: 38 and 62, respectively; wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof and/or capable of neutralizing infection by a hepatitis D virus (HDV).

In yet another aspect, the present disclosure relates to an antibody or antigen-binding fragment, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: 38 and 66, respectively; wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof and/or capable of neutralizing infection by a hepatitis D virus (HDV).

In yet another aspect, the present disclosure relates to use of an anti-HBV antibody as disclosed herein in the manufacture of a medicament for treating chronic HBV infection and/or HDV infection in a subject in need thereof.

In yet another aspect, the present disclosure relates to use of an anti-HBV antibody as disclosed herein in the manufacture of a medicament for treating chronic HBV infection and/or HDV infection in a subject in need thereof, wherein the anti-HBV antibody is to be administered to the subject with an siRNA, wherein the siRNA has a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:124) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:125); 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; s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

BRIEF DESCRIPTION OF THE DRAWINGS

The figures provided herein are intended to illustrate subject matter included in the present disclosure in more detail. The figures are not intended to limit the disclosure in any way.

CLAIMS

1. An antibody, or an antigen-binding fragment thereof, comprisinga heavy chain variable region (VH) comprising a CDRH1 amino acid sequence, a CDRH2 amino acid sequence, and a CDRH3 amino acid sequence; and a light chain variable region (VL) comprising a CDRL1 amino acid sequence, a CDRL2 amino acid sequence, and a CDRL3 amino acid sequence, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences are according to SEQ ID NOs.:

(i) 34, 35, 37, 41, 49, and 55, respectively;

(ii) 34, 35, 37, 41, 46, and 55, respectively;

(iii) 34, 35, 37, 41, 47, and 55, respectively;

(iv) 34, 35, 37, 41, 48, and 55, respectively;

(v) 34, 35, 37, 41, 45, and 55, respectively;

(vi) 34, 35, 37, 41, 50, and 55, respectively;

(vii) 34, 35, 37, 41, 51, and 55, respectively;

(viii) 34, 35, 37, 41, 52, and 55, respectively;

(ix) 34, 35, 37, 41, 53, and 55, respectively; or

(x) 34, 35, 37, 41, 44, and 55, respectively;

wherein CDRs are defined according to the CCG numbering system,

wherein, optionally, the VL comprises a R60N substitution mutation, a R60A substitution mutation, a R60K substitution mutation, a S64A substitution mutation, a I74A substitution mutation, or any combination thereof, relative to SEQ ID NO.:58 and wherein the amino acid numbering of the substitution mutation(s) is according to SEQ ID NO.:58, and still further optionally wherein the VL does not comprise any further mutation(s) relative to SEQ ID NO.:58,

and wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and, optionally, neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof.

2. The antibody or antigen-binding fragment of claim 1, wherein the VH and the VL comprise or consist of amino acid sequences having at least RNN identity to the amino acid sequences set forth in SEQ ID NOs.: (i) 38 and 62, respectively; (ii) 38 and 59, respectively; (iii) 38 and 60, respectively; (iv) 38 and 61, respectively; (v) 38 and 58, respectively; (vi) 38 and 63, respectively; (vii) 38 and 64, respectively; (viii) 38 and 65, respectively; (ix) 38 and 66, respectively; (x) 38 and 71, respectively; or (xi) 38 and 72, respectively.

3. The antibody or antigen-binding fragment of any one of claims 1 or 2, wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.:

(i) 38 and 62, respectively;
(ii) 38 and 59, respectively;
(iii) 38 and 60, respectively;
(iv) 38 and 61, respectively;
(v) 38 and 58, respectively;
(vi) 38 and 63, respectively;
(vii) 38 and 64, respectively;
(viii) 38 and 65, respectively;
(ix) 38 and 66, respectively;
(x) 38 and 71, respectively; or
(xi) 38 and 72, respectively.

4. An antibody or antigen-binding fragment, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.:

(i) 38 and 62, respectively;
(ii) 38 and 66, respectively;
(iii) 38 and 67, respectively;
(iv) 38 and 68, respectively; or

(v) 38 and 72, respectively,

wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof.

5. The antibody or antigen-binding fragment of any one of claims 1-4, which is capable of neutralizing infection by a hepatitis D virus (HDV).

6. The antibody or antigen-binding fragment of any one of claims 1-5, wherein, in a sample comprising a plurality of the antibody or antigen-binding fragment, less than 12%, 11% or less, 10% or less, 9% or less, 8% or less, 7% or less, 6% or less, 5% or less, 4% or less, 3% or less, or 2% or less of the plurality is comprised in a dimer when the sample has been incubated for 120 to 168 hours at about 40ºC, wherein the presence of dimer is determined by absolute size-exclusion chromatography; and/or

wherein incubation of a plurality of the antibody or antigen-binding fragment results in reduced formation of a dimer as compared to incubation of a plurality of a reference antibody or antigen-binding fragment,

wherein the reference antibody or antigen-binding fragment comprises the VH amino acid sequence set forth in SEQ ID NO.:38 and the VL amino acid sequence set forth in SEQ ID NO.:57,

and wherein the presence of antibody dimer is determined by absolute size-exclusion chromatography.

7. The antibody or antigen-binding fragment of any one of claims 1-6, which forms a lower amount of dimer, and/or forms dimers at a reduced frequency and/or as a lower percentage of total antibody or antigen-binding fragment molecules in a sample or composition as compared to a reference antibody:

(i) in a 5-day, a 15-day, and/or a 32-day incubation at 4◦C;

(ii) in a 5-day, a 15-day, and/or a 32-day incubation at 25◦C; and/or

(iii) in a 5-day, a 15-day, and/or a 32-day incubation at 40◦C,

wherein the reference antibody or antigen-binding fragment comprises the VH amino acid sequence set forth in SEQ ID NO.:38 and the VL amino acid sequence set forth in SEQ ID NO.:57.

8. The antibody or antigen-binding fragment of any one of claims 1-7, wherein the antibody or antigen-binding fragment is capable of binding to a HBsAg (adw) with an EC50 (ng/ml) of about 3.2 or less, less than 3.0, less than 2.5, less than 2.0, less than 1.5, or less than 1.0.

9. The antibody or antigen-binding fragment of any one of claims 1-8, wherein the antibody, or the antigen-binding fragment thereof, comprises a human antibody, a monoclonal antibody, a purified antibody, a single chain antibody, a Fab, a Fab', a F(ab')2, a Fv, or a scFv.

10. The antibody or antigen-binding fragment of any one of claims 1-9, wherein the antibody or antigen-binding fragment is a multi-specific or a bispecific antibody or antigen-binding fragment.

11. The antibody of any one of claims 1-10, or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment comprises a Fc moiety.

12. The antibody or antigen-binding fragment of claim 11, wherein the Fc moiety comprises a mutation that enhances binding to FcRn as compared to a reference Fc moiety that does not comprise the mutation.

13. The antibody or antigen-binding fragment of claim 11 or 12, wherein the Fc moiety comprises a mutation that enhances binding to a FcγR as compared to a reference Fc moiety that does not comprise the mutation.

14. The antibody or antigen-binding fragment of any one of claims 11-13, wherein the Fc moiety is an IgG isotype, or is derived from an IgG isotype.

15. The antibody or antigen-binding fragment of any one of claims 11-14, which comprises or is derived from Ig G1m17, 1 (IgHG1*01).

16. The antibody or antigen-binding fragment of any one of claims 12-15, wherein the mutation that enhances binding to FcRn comprises:

(i) M428L/N434S;

(ii) M252Y/S254T/T256E;

(iii) T250Q/M428L;

(iv) P257I/Q311I;

(v) P257I/N434H;

(vi) D376V/N434H;

(vii) T307A/E380A/N434A; or

(viii) any combination of (i)-(vii),

wherein amino acid numbering of the Fc moiety is according to the EU numbering system.

17. The antibody or antigen-binding fragment of claim 16, wherein the mutation that enhances binding to FcRn comprises M428L/N434S.

18. The antibody or antigen-binding fragment of any one of claims 13-17, wherein the mutation that enhances binding to a FcγR comprises S239D; I332E; A330L; G236A; or any combination thereof, wherein amino acid numbering of the Fc moiety is according to the EU numbering system.

19. The antibody or antigen-binding fragment of claim 18, wherein the mutation that enhances binding to a FcγR comprises:

(i) S239D/I332E;

(ii) S239D/A330L/I332E;

(iii) G236A/S239D/I332E; or

(iv) G236A/A330L/I332E.

20. The antibody or antigen-binding fragment of claim 18 or 19, wherein the mutation that enhances binding to a FcγR comprises or consists of G236A/A330L/I332E, and optionally wherein the antibody or antigen-binding fragment does not comprise S239D, and wherein the antibody or antigen-binding fragment further optionally comprises a native S at position 239.

21. The antibody or antigen-binding fragment of any one of claims 11-20, wherein the Fc moiety comprises the amino acid substitution mutations: M428L; N434S; G236A; A330L; and I332E, and optionally does not comprise S239D.

22. The antibody or antigen-binding fragment of any one of claims 1-21, comprising a light chain constant region (CL) that comprises or consists of an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence of SEQ ID NO.:79.

23. The antibody or antigen-binding fragment of any one of claims 1-22, comprising a CH1-CH2-CH3 that comprises or consists of an amino acid sequence having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to the amino acid sequence of SEQ ID NO.:73, or a variant thereof that comprises one or more of the following amino acid substitutions (EU numbering): G236A; A330L; I332E; M428L; N434S.

24. The antibody or antigen-binding fragment of claim 23, wherein the CH1-CH2-CH3 has a C-terminal lysine removed.

25. An antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:75, optionally with the C-terminal lysine removed; and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

26. The antibody of claim 25, wherein the LC comprises the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 66, 67, and 72.

27. An antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:76, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

28. The antibody of claim 27, wherein the LC comprises the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 66, 67, and 72.

29. An antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:77, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

30. The antibody of claim 29, wherein the LC comprises the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 66, 67, and 72.

31. An antibody comprising: a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:78, optionally with the C-terminal lysine removed, and a light chain (LC), wherein the LC comprises or consists of (i) the

VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 58-61, and 63-72 and (ii) the CL amino acid sequence set forth in SEQ ID NO.:79.

32. The antibody of claim 31, wherein the LC comprises the VL amino acid sequence set forth in any one of SEQ ID NOs.:62, 66, 67, and 72.

33. A polynucleotide comprising a nucleotide sequence that encodes the antibody, or the antigen-binding fragment, of any one of claims 1-32.

34. A polynucleotide encoding a light chain variable region (VL) and, optionally, a light chain constant domain (CL) of the antibody, or the antigen-binding fragment, of any one of claims 1-32.

35. The polynucleotide of claim 33 or 34, wherein the nucleotide sequence that encodes the antibody or the antigen-binding fragment is codon optimized for expression in a host cell.

36. The polynucleotide of claim 35, comprising a nucleotide sequence having at least 50% identity to the nucleotide sequence according to any one of SEQ ID Nos.:89, 85-88, and 90-99.

37. The polynucleotide of any one of claims 33-36, comprising (i) the polynucleotide sequence set forth in SEQ ID NO.:81 or SEQ ID NO.:82, and (ii) the polynucleotide sequence set forth in any one or more of SEQ ID NOs.:89, 85-88, and 90-99.

38. The polynucleotide of any one of claims 33-36, comprising (i) the polynucleotide sequence set forth in SEQ ID NO.:83, and (ii) the polynucleotide sequence set forth in any one or more of SEQ ID NOs.:89, 85-88, and 90-99.

39. The polynucleotide of any one of claims 33-36, comprising (i) the polynucleotide sequence set forth in SEQ ID NO.:84, and (ii) the polynucleotide sequence set forth in any one or more of SEQ ID NOs.:89, 85-88, and 90-99.

40. A vector comprising the polynucleotide of any one of claims 33-39.

41. The vector of claim 40, wherein the vector comprises a lentiviral vector or a retroviral vector.

42. A host cell comprising the polynucleotide of any one of claims 33-39 and/or the vector of claim 40 or 41.

43. A pharmaceutical composition comprising:

(i) the antibody or antigen binding fragment of any one of claims 1-32;

(ii) the polynucleotide according to any one of claims 33-39;

(iii) the vector according to claim 40 or 41;

(iv) the host cell of claim 42; or

(v) any combination of (i)-(iv),

and a pharmaceutically acceptable excipient, diluent or carrier.

44. A kit comprising:

(a) a component selected from:

(i) the antibody or antigen-binding fragment of any one of claims 1-32;

(ii) the polynucleotide according to any one of claims 33-39;

(iii) the vector according to claim 40 or 41;

(iv) the host cell of claim 42;

(v) the pharmaceutical composition of claim 43; or

(vi) any combination of (i)-(vi); and

(b) (1) instructions for using the component to prevent, treat, attenuate, and/or diagnose a hepatitis B virus infection and/or a hepatitis D virus infection and/or (2) a means for administering the component to the subject.

45. The composition of claim 42 or the kit of claim 44, further comprising:

(i) a polymerase inhibitor, wherein the polymerase inhibitor optionally comprises Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir, or any combination thereof;

(ii) an interferon, wherein the interferon optionally comprises IFNbeta and/or IFNalpha;

(iii) a checkpoint inhibitor, wherein the checkpoint inhibitor optionally comprises an anti-PD-1 antibody or antigen binding fragment thereof, an anti-PD-L1 antibody or antigen binding fragment thereof, and/or an anti-CTLA4 antibody or antigen binding fragment thereof;

(iv) an agonist of a stimulatory immune checkpoint molecule; or

(v) any combination of (i)-(iv).

46. A method of producing the antibody or antigen binding fragment of any one of claims 1-32, comprising culturing the host cell of claim 42 under conditions and for a time sufficient to produce the antibody or antigen-binding fragment.

47. Use of: (i) the antibody or antigen-binding fragment of any one of claims 1-32; (ii) the polynucleotide of any one of claims 33-39; (iii) the vector of claim 40 or 41; (iv) the host cell of claim 42; and/or (v) the pharmaceutical composition of claim 43 or 45, in the manufacture of a medicament to prevent, treat, attenuate, and/or diagnose a hepatitis B virus infection and/or a hepatitis D virus infection in a subject.

48. An antibody or antigen-binding fragment of any one of claims 1-32, the polynucleotide of any one of claims 33-39, the vector of claim 40 or 41, the host cell of

claim 42, and/or the pharmaceutical composition of any one of claims 43 or 44 for use as a medicament.

49. The use of claim 47, wherein the use comprises that any one of the following is to be administered to the subject: a single dose of the medicament comprising the pharmaceuticalcomposition comprising the antibody or antigen-binding fragment; and/or

the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in a range from 2 to 18 mg/kg (subject body weight); and/or

the single dose of the medicament comprising the pharmaceutical composition comprises up to 6 mg, up to 10 mg, up to 15 mg, up to 18 mg, up to 25 mg, up to 30 mg, up to 35 mg, up to 40 mg, up to 45 mg, up to 50 mg, up to 55 mg, up to 60 mg, up to 75 mg, up to 90 mg, up to 300 mg, up to 900 mg, or up to 3000 mg of the antibody,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 3000 mg, or in a range from 5 mg to 3000 mg, or in a range from 10 mg to 3000 mg, or in a range from 25 mg to 3000 mg, or in a range from 30 mg to 3000 mg, or in a range from 50 mg to 3000 mg, or in a range from 60 mg to 3000 mg, or in a range from 75 mg to 3000 mg, or in a range from 90 mg to 3000 mg, or in a range from 100 mg to 3000 mg, or in a range from 150 mg to 3000 mg, or in a range from 200 mg to 3000 mg, or in a range from 300 mg to 3000 mg, or in a range from 500 mg to 3000 mg, or in a range from 750 mg to 3000 mg, or in a range from 900 mg to 3000 mg, or in a range from 1500 mg to 3000 mg, or in a range from 2000 mg to 3000 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 900 mg, or in a range from 5 mg to 900 mg, or in a range from 10 mg to 900 mg, or in a range from 25 mg to 900 mg, or in a range from 30 mg to 900 mg, or in a range from 50 mg to 900 mg, or in a range from 60 mg to 900 mg, or in a range from 75 mg to 900 mg, or in a range from 90 mg to 900 mg, or in a range from 100 mg to 900 mg, or in a range from 150 mg to 900 mg, or in a range from 200 mg to 900 mg, or in a range from

300 mg to 900 mg, or in a range from 500 mg to 900 mg, or in a range from 750 mg to 900 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is wherein the single dose of the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 500 mg, or in a range from 5 mg to 500 mg, or in a range from 10 mg to 500 mg, or in a range from 25 mg to 500 mg, or in a range from 30 mg to 500 mg, or in a range from 50 mg to 500 mg, or in a range from 60 mg to 500 mg, or in a range from 75 mg to 500 mg, or in a range from 90 mg to 500 mg, or in a range from 100 mg to 500 mg, or in a range from 150 mg to 500 mg, or in a range from 200 mg to 500 mg, or in a range from 300 mg to 500 mg, or in a range from 400 mg to 500 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 300 mg, or in a range from 5 mg to 300 mg, or in a range from 10 mg to 300 mg, or in a range from 25 mg to 300 mg, or in a range from 30 mg to 300 mg, or in a range from 50 mg to 300 mg, or in a range from 60 mg to 300 mg, or in a range from 75 mg to 300 mg, or in a range from 90 mg to 300 mg, or in a range from 100 mg to 300 mg, or in a range from 150 mg to 300 mg, or in a range from 200 mg to 300 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 200 mg, or in a range from 5 mg to 200 mg, or in a range from 10 mg to 200 mg, or in a range from 25 mg to 200 mg, or in a range from 30 mg to 200 mg, or in a range from 50 mg to 200 mg, or in a range from 60 mg to 200 mg, or in a range from 75 mg to 200 mg, or in a range from 90 mg to 200 mg, or in a range from 100 mg to 200 mg, or in a range from 150 mg to 200 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 100 mg, or in a range from 5 mg to 100 mg, or in a range from 10 mg to 100 mg, or in a range from 25 mg to 100 mg, or in a range from 30 mg to 100 mg, or in a range from 50

mg to 100 mg, or in a range from 60 mg to 100 mg, or in a range from 75 mg to 100 mg, or in a range from 75 mg to 100 mg, or in a range from 90 mg to 100 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 25 mg, or in a range from 5 mg to 25 mg, or in a range from 10 mg to 25 mg, or in a range from 15 mg to 25 mg, or in a range from 20 mg to 25 mg,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is in a range from 1 mg to 50 mg, or in a range from 1 mg to 25 mg, or in a range from 5 mg to 50 mg, or in a range from 5 mg to 25 mg, or in a range from 10 to 50 mg, or in a range from 10 to 25 mg, or in a range from 1 to 15 mg, or in a range from 5 mg to 15 mg, or in a range from 10 mg to 15 mg,or wherein the single dose of the medicament comprising the pharmaceutical composition comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495, 500, 505, 510, 515, 520, 525, 530, 535, 540, 545, 550, 555, 560, 565, 570, 575, 580, 585, 590, 595, 600, 605, 610, 615, 620, 625, 630, 635, 640, 645, 650, 655, 660, 665, 670, 675, 680, 685, 690, 695, 700, 705, 710, 715, 720, 725, 730, 735, 740, 745, 750, 755, 760, 765, 770, 775, 780, 785, 790, 795, 800, 805, 810, 815, 820, 825, 830, 835, 840, 845, 850, 855, 860, 865, 870, 875, 880, 885, 890, 895, 900, 905, 910, 915, 920, 925, 930, 935, 940, 945, 950, 955, 960, 965, 970, 975, 980, 985, 990, 995, or 1000 mg, or more, of the antibody,

or wherein the single dose of the medicament comprising the pharmaceutical composition comprises the antibody in an amount that is less than 3000 mg, less than 2500 mg, less than 2000 mg, less than 1500 mg, less than 1000 mg, less than 900 mg, less than 500 mg, less than 300 mg, less than 200 mg, less than 100 mg, less than 90 mg, less than 75 mg, less than 50 mg, less than 25 mg, or less than 10 mg, but is more

than 1 mg, more than 2 mg, more than 3 mg, more than 4 mg, or more than 5 mg; and/or

the single dose of the medicament comprising the pharmaceutical composition comprises the antibody at a concentration in a range from 100 mg/mL to 200 mg/mL.

50. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-32 at a concentration ranging from 100 mg/mL to 200 mg/mL, and a pharmaceutically acceptable carrier, excipient, or diluent.

51. The pharmaceutical composition of claim 50, wherein the pharmaceutical composition comprises water, optionally USP water; and/or.

the pharmaceutical composition comprises histidine, optionally at a concentration from 10 mM to 40 mM in the pharmaceutical composition;and/or

the pharmaceutical composition comprises a disaccharide, optionally at 5%, 6%, 7%, 8%, or 9%; and/or

the pharmaceutical composition comprises a surfactant, optionally a polysorbate, wherein, optionally, the polysorbate is present in a range from 0.01% to 0.05% (w/v); and/or

the pharmaceutical composition has a pH ranging from 5.8 to 6.2, ranging from 5.9 to 6.1, or of 5.8, of 5.9, of 6.0, of 6.1, or of 6.2.

52. The pharmaceutical composition of any one of claims 50 or 51, wherein the pharmaceutical composition comprises:

(i) the antibody at 150 mg/mL;

(ii) USP water;

(iii) 20 mM histidine;

(iv) 7% sucrose; and

(v) 0.02% PS80,

wherein the pharmaceutical composition comprises a pH of 6.

53. A method for *in vitro* diagnosis of a hepatitis B virus infection, the method comprising:

(i) contacting a sample from a subject with an antibody or antigen-binding fragment of any one of claims 1-32; and

(ii) detecting a complex comprising an antigen and the antibody, or comprising an antigen and the antigen-binding fragment.

54. A method for detecting the presence or absence of an epitope in a correct conformation in an anti-hepatitis-B and/or an anti-hepatitis-D vaccine, the method comprising:

(i) contacting the vaccine with an antibody or antigen-binding fragment of any one of claims 1-32; and

(ii) determining whether a complex comprising an antigen and the antibody, or comprising an antigen and the antigen binding fragment, has been formed.

55. Use of an anti-HBV antibody from any one of claims 1-32 in the manufacture of a medicament for treating chronic HBV infection in a subject in need thereof, wherein the anti-HBV antibody is to be administered to the subject with

an agent that reduces HBV antigenic load; and/or

an inhibitor of HBV gene expression; wherein the agent that reduces HBV antigenic load and/or the inhibitor of HBV gene expression is an RNAi agent that inhibits expression of an HBV transcript.

56. The use according to claim 55, wherein the RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 1579-1597 of SEQ ID NO:116.

57. The use according to any one of claims 55 or 56, wherein the double-stranded region of the RNAi agent is 15-30 nucleotide pairs in length, or wherein each strand of the RNAi agent has 15-30 nucleotides.

58. The use according to any one of the claims 55-57, wherein the RNAi agent is an siRNA.

59. The use according to claim 58, wherein (a)the siRNA inhibits expression of an HBV transcript that encodes an HBsAg protein, an HBcAg protein, and HBx protein, or an HBV DNA polymerase protein;

(b)the siRNA binds to at least 15 contiguous nucleotides of a target encoded by: P gene, nucleotides 2309-3182 and 1-1625 of NC_003977.2; S gene (encoding L, M, and S proteins), nucleotides 2850-3182 and 1-837 of NC_003977.2; HBx, nucleotides 1376-1840 of NC_003977.2; or C gene, nucleotides 1816-2454 of NC_003977.2;

(c) the siRNA that comprises an antisense strand, wherein the antisense strand of the siRNA comprises at least 15 contiguous nucleotides of the nucleotide sequence of 5'- UGUGAAGCGAAGUGCACACUU -3' (SEQ ID NO:119); and/or

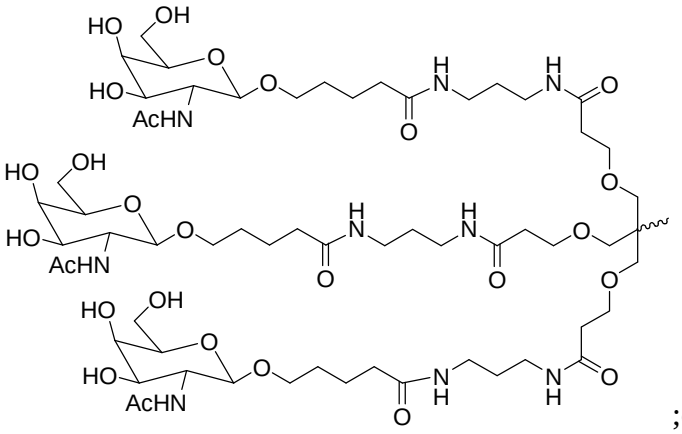
(d) the siRNA that comprises an antisense strand, wherein the antisense strand of the siRNA comprises at least 15 contiguous nucleotides of the nucleotide sequence of 5'- UAAAAUUGAGAGAAGUCCACCAC -3' (SEQ ID NO:121).

60. The use according to any one of claims 58-59, wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, and

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

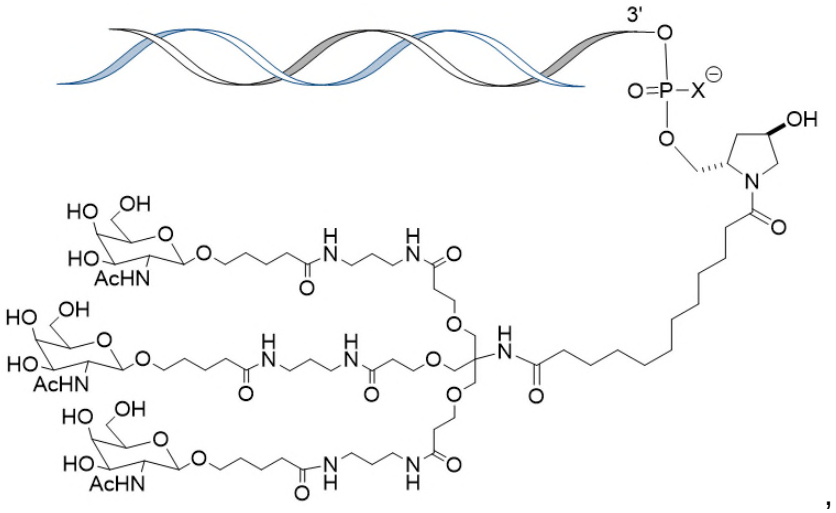
61. The use according to claim 60, wherein (a) the ligand is one or more GalNAc derivatives attached through a monovalent linker, bivalent branched linker, or trivalent branched linker; or

(b) the ligand is



;or

the siRNA is conjugated to the ligand as shown in the following structure:



,

wherein X is O or S.

62. The use according to any one of claims 58-61, wherein at least one nucleotide of the siRNA is a modified nucleotide comprising a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxyl-modified nucleotide, a 2'-methoxyethyl

modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, an adenosine-glycol nucleic acid, or a nucleotide comprising a 5'-phosphate mimic; and/or

the siRNA comprises a phosphate backbone modification, a 2' ribose modification, 5' triphosphate modification, or a GalNAc conjugation modification; and/or

the phosphate backbone modification comprises a phosphorothioate bond; and/or

the 2' ribose modification comprises a fluoro or -O-methyl substitution.

63. The use according to any one of claims 58-62, wherein

(a) the siRNA has a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:122) and an antisense strand comprising 5'- usGfsugaAfgCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:123),

(b) the siRNA has a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:124) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:125), and/or

(c) the siRNA has a sense strand comprising 5'-gsgsuggaCfuUfCfUfcucaAfUfuuuaL96 -3' (SEQ ID NO:126) and an antisense strand comprising 5'- usAfsaaaUfuGfAfgagaAfgUfccaccsasc -3' (SEQ ID NO:127); and

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;

s is a phosphorothioate linkage; and

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

64. An antibody or antigen-binding fragment comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: 38 and 62, respectively;

wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof and/or capable of neutralizing infection by a hepatitis D virus (HDV).

65. An antibody or antigen-binding fragment, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and the VL comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: 38 and 66, respectively;

wherein the antibody or antigen-binding fragment thereof is capable of binding to the antigenic loop region of HBsAg and neutralizing infection by a hepatitis B virus (HBV) of genotype D, A, B, C, E, F, G, H, I, or J, or any combination thereof and/or capable of neutralizing infection by a hepatitis D virus (HDV).

66. The antibody of claim 64 or 65, wherein the antibody comprises:

a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:76, and

a light chain constant region (CL) that comprises or consists of an amino acid sequence set forth in SEQ ID NO.:79.

67. The antibody of claim 64 or 65, wherein the antibody comprises:

a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:77, and

a light chain constant region (CL) that comprises or consists of an amino acid sequence set forth in SEQ ID NO.:79.

68. The antibody of claim 64 or 65, wherein the antibody comprises:

a heavy chain (HC) comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:78, and

a light chain constant region (CL) that comprises or consists of an amino acid sequence set forth in SEQ ID NO.:79.

69. Use of an anti-HBV antibody from any one of claims 64-68 in the manufacture of a medicament for treating chronic HBV infection and/or HDV infection in a subject in need thereof.

70. Use of an anti-HBV antibody from any one of claims 64-68 in the manufacture of a medicament for treating chronic HBV infection and/or HDV infection in a subject in need thereof, wherein the anti-HBV antibody is to be administered to the subject with an siRNA, wherein the siRNA has a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:124) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:125);

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;

s is a phosphorothioate linkage; and

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