ANTI-SARS-COV-2-SPIKE GLYCOPROTEIN ANTIBODIES AND ANTIGEN-BINDING FRAGMENTS

SEQUENCE LISTING

[0001] This application incorporates by reference a computer readable Sequence Listing in ST.26 XML format, titled 11007WO01-Sequence, created on July 12, 2022, and containing 1,488,419 bytes.

FIELD OF THE INVENTION

[0002] The present invention relates to antibodies and antigen-binding fragments that bind specifically to coronavirus spike proteins and methods for treating or preventing coronavirus infections with said antibodies and fragments.

BACKGROUND OF THE INVENTION

[0003] Newly identified viruses, such as coronaviruses, can be difficult to treat because they are not sufficiently characterized. The emergence of these newly identified viruses highlights the need for the development of novel antiviral strategies. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly-emergent coronavirus which causes a severe acute respiratory disease, COVID-19. SARS-CoV-2 was first identified from an outbreak in Wuhan, China and as of July 8, 2022, the World Health Organization has reported 551,296,228 confirmed cases, resulting in 6,345,595 deaths. Clinical features of COVID-19 include fever, dry cough, and fatigue, and the disease can cause respiratory failure resulting in death.

[0004] In view of the continuing threat to human health, and in particular the emergence of new variants of the SARS-CoV-2 virus, there is still an urgent need for preventive and therapeutic antiviral therapies for SARS-CoV-2 control. Because this virus uses its spike glycoprotein for interaction with the cellular receptor ACE2 and the serine protease TMPRSS2 for entry into a target cell, this spike protein represents an attractive target for antibody therapeutics. In particular, fully human antibodies that specifically bind to the SARS-CoV-2-Spike protein (SARS-CoV-2-S) with high affinity and that inhibit virus infectivity could be important in the prevention and treatment of COVID-19.

SUMMARY OF THE INVENTION

[0005] There is a need for neutralizing therapeutic anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies and their use for treating or preventing viral infection. The present disclosure addresses this need, in part, by providing human anti-SARS-CoV-2-S antibodies, such as those of Table 4, and combinations thereof including, for example, combinations with other therapeutics (e.g., anti-inflammatory agents, antimalarial agents, antiviral agents, or other antibodies or antigen-binding fragments), and methods of use thereof for treating viral infections.

[0006] The present disclosure provides neutralizing human antigen-binding proteins that specifically bind to SARS-CoV-2-S, for example, antibodies or antigen-binding fragments thereof.

[0007] In one aspect, the present disclosure provides an isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to a coronavirus spike protein (CoV-S), wherein the antibody has one or more of the following characteristics: (a) binds to CoV-S with an EC_{50} of less than about 10^{-8} M; (b) demonstrates an increase in survival in a coronavirus-infected animal after administration to said coronavirus-infected animal, as compared to a comparable coronavirus-infected animal without said administration; and/or (c) comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) comprising an amino acid sequence having at least about 90% sequence identity to an HCVR of Table 4; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) comprising an amino acid sequence having at least about 90% sequence identity to an LCVR Table 4.

[0008] In some cases, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region (*e.g.,* an immunoglobulin HCVR) comprising the HCDR1, HCDR2, and HCDR3 of an antibody of Table 4; and/or (b) a light chain variable region (*e.g.,* an immunoglobulin LCVR) comprising the LCDR1, LCDR2, and LCDR3 of an antibody of Table 4.

[0009] In some cases, the antibody or antigen-binding fragment comprises: (a) a heavy chain immunoglobulin variable region comprising an amino acid sequence having at least 90% amino acid sequence identity to an HCVR sequence of Table 4; and/or (b) a light chain immunoglobulin variable region comprising an amino acid sequence having at least 90% amino acid sequence identity to an LCVR sequence of Table 4.

[00010] In some embodiments, the antibody or antigen-binding fragment comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of a single antibody of Table 4. In some embodiments, the antibody or antigen-binding fragment comprises an immunoglobulin that comprises the HCVR and the LCVR of a single antibody of Table 4.

[00011] In some embodiments, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region (HCVR) comprising three complementarity determining regions (CDRs) contained within the amino acid sequence of SEQ ID NO: 212; (b) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 214, 216 and 218, respectively; (c) a HCVR comprising the amino acid sequence of SEQ ID NO: 212; (d) a light chain variable region (LCVR) comprising three CDRs contained within the amino acid sequence of SEQ ID NO: 220; (e) a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 222, 126 and 224, respectively; (f) a LCVR comprising the amino acid sequence of SEQ ID NO: 220; (g) a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 226; (h) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 228; (i) a HCVR/LCVR pair comprising the CDRs contained within the amino acid sequences of SEQ ID NOs: 212/222, respectively; (j) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 214, 216 and 218, respectively, and a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 222, 126 and 224, respectively; (k) a HCVR comprising the amino acid sequence of SEQ ID NO: 212 and a LCVR comprising the amino acid sequence of SEQ ID NO: 220; or (l) a HC comprising the amino acid sequence of SEQ ID NO: 226 and a LC comprising the amino acid sequence of SEQ ID NO: 228.

[00012] In some embodiments, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region (HCVR) comprising three complementarity determining regions (CDRs) contained within the amino acid sequence of SEQ ID NO: 362; (b) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 364, 366 and 368, respectively; (c) a HCVR comprising the amino acid sequence of SEQ ID NO: 362; (d) a light chain variable region (LCVR) comprising three CDRs contained within the amino acid sequence of SEQ ID NO: 370; (e) a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 372, 106 and 374, respectively; (f) a LCVR comprising the amino acid sequence of SEQ ID NO: 370; (g) a heavy chain (HC) comprising the amino acid

sequence of SEQ ID NO: 376; (h) a HC comprising the amino acid sequence of SEQ ID NO: 1077; (i) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 378; (j) a HCVR/LCVR pair comprising the CDRs contained within the amino acid sequences of SEQ ID NOs: 362/370, respectively; (k) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 364, 366 and 368, respectively, and a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 372, 106 and 374 respectively; (l) a HCVR comprising the amino acid sequence of SEQ ID NO: 362 and a LCVR comprising the amino acid sequence of SEQ ID NO: 370; (m) a HC comprising the amino acid sequence of SEQ ID NO: 376 and a LC comprising the amino acid sequence of SEQ ID NO: 378; or (n) a HC comprising the amino acid sequence of SEQ ID NO: 1077 and a LC comprising the amino acid sequence of SEQ ID NO: 378.

[00013] In some embodiments, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region (HCVR) comprising three complementarity determining regions (CDRs) contained within the amino acid sequence of SEQ ID NO: 493; (b) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 495, 497 and 499, respectively; (c) a HCVR comprising the amino acid sequence of SEQ ID NO: 493; (d) a light chain variable region (LCVR) comprising three CDRs contained within the amino acid sequence of SEQ ID NO: 501; (e) a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 503, 505 and 507, respectively; (f) a LCVR comprising the amino acid sequence of SEQ ID NO: 501; (g) a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 509; (h) a HC comprising the amino acid sequence of SEQ ID NO: 1075; (i) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 511; (j) a HCVR/LCVR pair comprising the CDRs contained within the amino acid sequences of SEQ ID NOs: 493/501, respectively; (k) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 495, 497 and 3499 respectively, and a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 503, 505 and 507 respectively; (l) a HCVR comprising the amino acid sequence of SEQ ID NO: 493 and a LCVR comprising the amino acid sequence of SEQ ID NO: 501; (m) a HC comprising the amino acid sequence of SEQ ID NO: 509 and a LC comprising the amino acid sequence of SEQ ID NO: 511; or (n) a HC comprising the amino acid sequence of SEQ ID NO: 1075 and a LC comprising the amino acid sequence of SEQ ID NO: 511.

[00014] In some embodiments, the antibody or antigen-binding fragment comprises: (a) a heavy chain variable region (HCVR) comprising three complementarity determining regions (CDRs) contained within the amino acid sequence of SEQ ID NO: 887; (b) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 889, 891 and 893, respectively; (c) a HCVR comprising the amino acid sequence of SEQ ID NO: 887; (d) a light chain variable region (LCVR) comprising three CDRs contained within the amino acid sequence of SEQ ID NO: 895; (e) a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 897, 164 and 899, respectively; (f) a LCVR comprising the amino acid sequence of SEQ ID NO: 895; (g) a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 901; (h) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 903; (i) a HCVR/LCVR pair comprising the CDRs contained within the amino acid sequences of SEQ ID NOs: 887/895, respectively; (j) a HCVR comprising HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 889, 891 and 893, respectively, and a LCVR comprising LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 897, 164 and 899, respectively; (k) a HCVR comprising the amino acid sequence of SEQ ID NO: 887 and a LCVR comprising the amino acid sequence of SEQ ID NO: 895; or (l) a HC comprising the amino acid sequence of SEQ ID NO: 901 and a LC comprising the amino acid sequence of SEQ ID NO: 903.

[00015] In one aspect, the present disclosure provides an antigen-binding protein that competes with the antibody or antigen-binding fragment as discussed above or herein for binding to CoV-S.

[00016] In one aspect, the present disclosure providees an antigen-binding protein that binds to the same epitope as, or to an overlapping epitope on, CoV-S as the antibody or antigen-binding fragment discussed above or herein.

[00017] In some embodiments, the antibody or antigen-binding fragment discussed above or herein is multispecific.

[00018] In some embodiments, the antibody or antigen-binding fragment comprises one or more of the following properties: (a) inhibits growth of coronavirus; (b) binds to the surface of a coronavirus; (c) limits spread of coronavirus infection of cells *in vitro*; and (d) protects mice engineered to express the human ACE2 or TMPRSS2 protein from death and/or weight loss caused by coronavirus infection.

[00019] In any of the various embodiments discussed above or herein, said CoV-S may be SARS-CoV-2-S.

[00020] In one aspect, the present disclosure provides a complex comprising an antibody or antigen-binding fragment as discussed above or herein bound to a CoV-S polypeptide. In some cases, the CoV-S is SARS-CoV-2-S.

[00021] In one aspect, the present disclosure provides a method for making an antibody or antigen-binding fragment as discussed above or herein, comprising: (a) introducing into a host cell one or more polynucleotides (*e.g.*, a polynucleotide or pair of polynucleotides, as discussed below) encoding said antibody or antigen-binding fragment; (b) culturing the host cell under conditions favorable to expression of the one or more polynucleotides; and (c) optionally, isolating the antibody or antigen-binding fragment from the host cell and/or a medium in which the host cell is grown. In some cases, the host cell is a Chinese hamster ovary cell.

[00022] In one aspect, the present disclousre provides an antibody or antigen-binding fragment which is a product of the method discussed above.

[00023] In one aspect, the present disclosure provides a polypeptide comprising: (a) HCDR1, HCDR2, and HCDR3 of an HCVR domain of an antibody or antigen-binding fragment that comprises an HCVR amino acid sequence set forth in Table 4; or (b) LCDR1, LCDR2, and LCDR3 of an LCVR domain of an immunoglobulin chain that comprises an LCVR amino acid sequence set forth in Table 4.

[00024] In various embodiments, the present disclosure provides a polynucleotide encoding the polypeptide discussed above, a vector comprising the polynucleotide, and/or a host cell comprising the antibody or antigen-binding fragment or polypeptide or polynucleotide or vector. In various embodiments, the present disclosure provides a polynucleotide that encodes a HCVR, a LCVR, or both a HCVR and a LCVR of an antibody or antigen-binding fragment thereof as discussed above or herein. The HCVR and/or LCVR may be defined by the CDRs contained within the HCVR sequence, the LCVR sequence, or both the HCVR sequence and the LCVR sequence, respectively, as set forth in Table 4. The HCVR and/or LCVR may also be defined by the heavy chain CDR sequences, the light chain CDR sequences, or both the heavy and light chain CDR sequences, respectively, as set forth in Table 4. The HCVR and/or LCVR may also be defined by the HCVR sequence, the LCVR sequence, or both the HCVR and LCVR sequences, respectively, as set forth in Table 4. In various embodiments, the present disclosure

provides a polynucleotide that encodes a heavy chain, a light chain, or both a heavy chain and a light chain of an antibody as discussed above or herein. The heavy chain and/or light chain may be defined by the heavy and light chain sequences, respectively, as set forth in Table 4. In various embodiments, the polynucleotide comprises a nucleic acid sequence as set forth in Table 5. In various embodiments, the present disclosure provides a vector or vectors comprising the polynucleotides discussed above, and/or a host cell comprising the polynucleotides or vectors, or HCVR or LCVR, or an assembled antibody or antigen-binding fragment thereof as discussed above or herein. In various embodiments, the present disclosure provides a pair of polynucleotides, wherein (a) the first polynucleotide encodes: (i) a HCVR comrpising the CDR sequences contained in a HCVR of an antibody of Table 4, (ii) a HCVR comprising the HCDR1, HCDR2 and HCDR3 sequences as set forth for an antibody in Table 4, (iii) a HCVR comprising the HCVR sequence of an antibody of Table 4, or (iv) a heavy chain (HC) comprising the HC sequence of an antibody of Table 4; and (b) the second polynucleotide encodes: (i) a LCVR comrpising the CDR sequences contained in a LCVR of an antibody of Table 4, (ii) a LCVR comprising the LCDR1, LCDR2 and LCDR3 sequences as set forth for an antibody in Table 4, (iii) a LCVR comprising the LCVR sequence of an antibody of Table 4, or (iv) a light chain (LC) comprising the LC sequence of an antibody of Table 4. In various embodiments, the present disclosure provides a pair of vectors comprising, respectively, the first and second polynucleotides discussed above, and/or a host cell comprising the pair of vectors.

[00025] In some embodiments, the pair of polynucleotides encodes components of an antibody or antigen-binding fragment thereof, such as: (a) the first polynucleotide encodes a HCVR comprising the CDRs contained in a HCVR comprising the amino acid sequence of SEQ ID NO: 212, and the second polynucleotide encodes a LCVR comprising the CDRs contained in a LCVR comprising the amino acid sequence of SEQ ID NO: 220; (b) the first polynucleotide encodes a HCVR comprising the HCDR1, HCDR2 and HCDR2 amino acid sequences of SEQ ID NOs: 214, 216 and 218, respectively, and the second polynucleotide encodes a LCVR comprising the LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 222, 126 and 224, respectively; (c) the first polynucleotide encodes a HCVR comprising the amino acid sequence of SEQ ID NO: 212, and the second polynucleotide encodes a LCVR comprising the amino acid sequence of SEQ ID NO: 220; or (d) the first polynucleotide encodes a HC comprising the amino

acid sequence of SEQ ID NO: 226, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 228.

[00026] In some embodiments, the pair of polynucleotides encodes components of an antibody or antigen-binding fragment thereof, such as: (a) the first polynucleotide encodes a HCVR comprising the CDRs contained in a HCVR comprising the amino acid sequence of SEQ ID NO: 362, and the second polynucleotide encodes a LCVR comprising the CDRs contained in a LCVR comprising the amino acid sequence of SEQ ID NO: 370; (b) the first polynucleotide encodes a HCVR comprising the HCDR1, HCDR2 and HCDR2 amino acid sequences of SEQ ID NOs: 364, 366 and 368, respectively, and the second polynucleotide encodes a LCVR comprising the LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 372, 106 and 374, respectively; (c) the first polynucleotide encodes a HCVR comprising the amino acid sequence of SEQ ID NO: 362, and the second polynucleotide encodes a LCVR comprising the amino acid sequence of SEQ ID NO: 370; (d) the first polynucleotide encodes a HC comprising the amino acid sequence of SEQ ID NO: 376, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 378; or (e) the first polynucleotide encodes a HC comprising the amino acid sequence of SEQ ID NO: 1077, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 378.

[00027] In some embodiments, the pair of polynucleotides encodes components of an antibody or antigen-binding fragment thereof, such as: (a) the first polynucleotide encodes a HCVR comprising the CDRs contained in a HCVR comprising the amino acid sequence of SEQ ID NO: 493, and the second polynucleotide encodes a LCVR comprising the CDRs contained in a LCVR comprising the amino acid sequence of SEQ ID NO: 501; (b) the first polynucleotide encodes a HCVR comprising the HCDR1, HCDR2 and HCDR2 amino acid sequences of SEQ ID NOs: 495, 497 and 499, respectively, and the second polynucleotide encodes a LCVR comprising the LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 503, 505 and 507, respectively; (c) the first polynucleotide encodes a HCVR comprising the amino acid sequence of SEQ ID NO: 493, and the second polynucleotide encodes a LCVR comprising the amino acid sequence of SEQ ID NO: 501; (d) the first polynucleotide encodes a HC comprising the amino acid sequence of SEQ ID NO: 509, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 511; or (e) the first polynucleotide encodes a HC

comprising the amino acid sequence of SEQ ID NO: 1075, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 511.

[00028] In some embodiments, the pair of polynucleotides encodes components of an antibody or antigen-binding fragment thereof, such as: (a) the first polynucleotide encodes a HCVR comprising the CDRs contained in a HCVR comprising the amino acid sequence of SEQ ID NO: 887, and the second polynucleotide encodes a LCVR comprising the CDRs contained in a LCVR comprising the amino acid sequence of SEQ ID NO: 895; (b) the first polynucleotide encodes a HCVR comprising the HCDR1, HCDR2 and HCDR2 amino acid sequences of SEQ ID NOs: 889, 891 and 893, respectively, and the second polynucleotide encodes a LCVR comprising the LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 897, 164 and 899, respectively; (c) the first polynucleotide encodes a HCVR comprising the amino acid sequence of SEQ ID NO: 887, and the second polynucleotide encodes a LCVR comprising the amino acid sequence of SEQ ID NO: 895; or (d) the first polynucleotide encodes a HC comprising the amino acid sequence of SEQ ID NO: 901, and the second polynucleotide encodes a LC comprising the amino acid sequence of SEQ ID NO: 903.

[00029] In one aspect, the present disclosure provides a composition or kit comprising the antibody or antigen-binding fragment discussed above or herein in association with a further therapeutic agent.

[00030] In one aspect, the present disclosure provides a pharmaceutical composition comprising the antigen-binding protein discussed above or herein and pharmaceutically acceptable carrier and, optionally, a further therapeutic agent. In some cases, the composition or kit is in association with a further therapeutic agent which is an anti-viral drug or a vaccine. In some embodiments, the further therapeutic agent is selected from the group consisting of: an anti-inflammatory agent, an antimalarial agent, an antibody or antigen-binding fragment thereof that specifically binds TMPRSS2, and an antibody or antigen-binding fragment thereof that specifically binds to CoV-S. In some embodiments, the antimalarial agent is chloroquine or hydroxychloroquine. In some embodiments, the anti-inflammatory agent is an antibody. In some cases, this antibody is sarilumab, tocilizumab, or gimsilumab. In some cases, the composition or kit comprises a second antibody or antigen-binding fragment comprising the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of Table 4. In some cases, the antibody that binds to CoV-S is casirivimab or imdevimab,

[00031] In one aspect, the present disclosure provides a vessel or injection device comprising the antigen-binding protein or composition discussed above or herein.

[00032] In one aspect, the present disclosure provides a method for treating or preventing infection with a coronavirus, in a subject in need thereof, via administration of a therapeutically effective amount of antigen-binding protein as discussed above or herein. In some cases, the coronavirus is selected from the group consisting of SARS-CoV-2, SARS-CoV, and MERS-CoV.

[00033] In some embodiments, the subject is administered one or more further therapeutic agents. In some cases, the one or more further therapeutic agents is an anti-viral drug or a vaccine. In some cases, the one or more further therapeutic agents is selected from the group consisting of: an anti-inflammatory agent, an antimalarial agent, an antibody or antigen-binding fragment thereof that specifically binds TMPRSS2, and an antibody or antigen-binding fragment thereof that specifically binds to CoV-S. In some embodiments, the antimalarial agent is chloroquine or hydroxychloroquine. In some embodiments, the anti-inflammatory agent is an antibody. In some cases, this antibody is sarilumab, tocilizumab, or gimsilumab. In some cases, the subject is administered a second antibody or antigen-binding fragment comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of Table 4. In some cases, the subject is administered a second antibody or antigen-binding fragment comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of an antbody described in U.S. Patent No. 10,787,501, e.g., mAb10933, mAb10987, or mAb10985. In some cases, the antibody that binds to CoV-S is casirivimab or imdevimab,

[00034] In one aspect, the present disclsure provides a method for administering an antibody or antigen-binding fragment as discussed above or herein into the body of a subject comprising injecting the antibody or antigen-binding fragment into the body of the subject. In some cases, the antibody or antigen-binding fragment is injected into the body of the subject subcutaneously, intravenously or intramuscularly.

[00035] In any of the various embodiments of the antibody or antigen-binding fragment, composition, kit, complex, polypeptide, polynucleotide, vector, cell, or methods discussed above or herein, the antibody or antigen-binding binding fragment may comprise a VH3-66 or Vk1-33 variable domain sequence.

[00036] In one aspect, the present disclosure provides an isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said isolated antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 887, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 895.

[00037] In some cases, the HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 889, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 891, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 893, LCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 897, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 164, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 899. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 887. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 895. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 887 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 895.

[00038] In one aspect, the present disclosure provides an isolated antibody that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 887, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 895.

[00039] In some cases, the HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 889, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 891, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 893, LCDR1 comprises the amino

acid sequence set forth in SEQ ID NO: 897, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 164, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 899. In some cases, the isolated antibody comprises an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 887 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 895. In some cases, the isolated antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 901 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 903. In some embodiments, the isolated antibody comprises an immunoglobulin constant region that is an IgG1 constant region. In some embodiments, the isolated antibody is a recombinant antibody. In some cases, the isolated antibody is multispecific.

[00040] In one aspect., the present disclosure provides a pharmaceutical composition comprising the isolated antibody discussed above and a pharmaceutically acceptable carrier or diluent. In some cases, the pharmaceutical composition further comprises a second therapeutic agent. In some cases, the second therapeutic agent is selected from the group consisting of: a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, an anti-inflammatory agent, an antimalarial agent, and an antibody or antigen-binding fragment thereof that binds TMPRSS2. In some cases, the the second therapeutic agent is a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008. In some embodiments, the the second antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 212, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 220. In some embodiments, the second antibody or antigen-binding fragment thereof comprises: HCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 214; HCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 216; HCDR3, comprising the amino acid sequence set forth in SEQ ID NO: 218; LCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 222; LCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 126; and LCDR3, comprising the amino acid sequence set forth in SEQ ID NO: 224. In some embodiments, the second antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence

set forth in SEQ ID NO: 212 and an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 220. In some embodiments, the second antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 226 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 228.

[00041] In one aspect, the present disclosure provides an isolated antibody or antigen-binding fragment thereof that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said isolated antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 212, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 220.

[00042] In some cases, the HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 214, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 216, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 218, LCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 222, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 126, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 224. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an HCVR that comprises an amino acid sequence set forth in SEQ ID NO: 212. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an LCVR that comprises an amino acid sequence set forth in SEQ ID NO: 220. In some cases, the isolated antibody or antigen-binding fragment thereof comprises an HCVR that comprises an amino acid sequence set forth in SEQ ID NO: 212 and an LCVR that comprises an amino acid sequence set forth in SEQ ID NO: 220.

[00043] In one aspect, the present disclosure provides an isolated antibody that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 212, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2

and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 220.

[00044] In some cases, the HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 214, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 216, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 218, LCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 222, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 126, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 224. In some cases, the isolated antibody comprises an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 212 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 220. In some cases, the isolated antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 226 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 228. In some embodiments, the isolated antibody comprises an immunoglobulin constant region that is an IgG1 constant region. In some embodiments, the isolated antibody is a recombinant antibody. In some embodiments, the isolated antibody is multispecific.

[00045] In one aspect, the present disclosure provides a pharmaceutical composition comprising the isolated antibody discussed above and a pharmaceutically acceptable carrier or diluent. In some cases, the pharmaceutical composition further comprises a second therapeutic agent. In some cases, the second therapeutic agent is selected from the group consisting of: a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, an anti-inflammatory agent, an antimalarial agent, and an antibody or antigen-binding fragment thereof that binds TMPRSS2. In some cases, the second therapeutic agent is a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008. In some cases, the second antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 887, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 895. In some cases, the second antibody or antigen-binding fragment thereof comprises: HCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 889; HCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 891; HCDR3, comprising

the amino acid sequence set forth in SEQ ID NO: 893; LCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 897; LCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 164; and LCDR3, comprising the amino acid sequence set forth in SEQ ID NO: 899. In some cases, the second antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 887 and an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 895. In some cases, the second antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 901 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 903.

[00046] In one aspect, the present disclosure provides an isolated antibody that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 270, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 278.

[00047] In some embodiments, HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 272, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 274, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 276, LCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 280, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 106, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 282. In some cases, the antibody comprises an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 270 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 278. In some cases, the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 284 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 286. In some embodiments, the immunoglobulin constant region is an IgG1 constant region. In some cases, the antibody is a recombinant antibody. In some cases, the antibody is multispecific.

[00048] In one aspect, the present disclosure provides, the present disclosure provides a pharmaceutical composition comprising the isolated antibody discussed above and a pharmaceutically acceptable carrier or diluent.

[00049] In some cases, the pharmaceutical composition further comprises a second therapeutic agent. In some cases, the second therapeutic agent is selected from the group consisting of: a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, an anti-inflammatory agent, an antimalarial agent, and an antibody or antigen-binding fragment thereof that binds TMPRSS2.

[00050] In some embodiments, the second therapeutic agent is a second antibody, or an antigen-binding fragment thereof, that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008. In some cases, the second antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 212, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 220. In some cases, the second antibody or antigen-binding fragment thereof comprises: HCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 214; HCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 216; HCDR3, comprising the amino acid sequence set forth in SEQ ID NO: 218; LCDR1, comprising the amino acid sequence set forth in SEQ ID NO: 222; LCDR2, comprising the amino acid sequence set forth in SEQ ID NO: 126; and LCDR3, comprising the amino acid sequence set forth in SEQ ID NO: 224. In some cases, the second antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 212 and an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 220. In some cases, the second antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 226 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 228.

[00051] In one aspect, the present disclosure provides a pharmaceutical composition compring: a) a first isolated antibody that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said first isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR)

comprising the amino acid sequence set forth in SEQ ID NO: 887, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 895; and b) a second isolated antibody that binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said second isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1030, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1038.

[00052] In some embodiments, the first isolated antibody comprises: HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 889, HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 891, HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 893, LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 897, LCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 164, and LCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 899. In some cases, the first isolated antibody comprises: an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 887 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 895. In some cases, the first isolated antibody comprises: a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 901 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 903. In some embodiments, the first isolated antibody comprises: an immunoglobulin constant region that is an IgG1 constant region. In some cases, the first isolated antibody is a recombinant antibody. In some cases, the first isolated antibody is multispecific.

[00053] In some embodiments, the pharmaceutical composition further comrpises a pharmaceutically acceptable carrier or diluent.

[00054] In some embodiments, the second isolated antibody comprises: HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1032, HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 1034, HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 1036, LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1040, LCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 1042, and LCDR3

comprising the amino acid sequence set forth in SEQ ID NO: 1044. In some cases, the second isolated antibody comprises: an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 1030 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 1038. In some cases, the second isolated antibody comprises: a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1048 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 1048.

[00055] In some embodiments, the pharmaceutical composition further comprises a third isolated antibody.

[00056] In some embodiments, the third isolated antibody binds a SARS-CoV-2 spike protein comprising the amino acid sequence set forth in SEQ ID NO: 1008, wherein said third isolated antibody comprises an immunoglobulin constant region, three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1010, and three light chain complementarity determining regions (CDRs) (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 1018. In some cases, the third isolated antibody comprises: HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1012, HCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 1014, HCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 1016, LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 1020, LCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 1022, and LCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 1024. In some cases, the third isolated antibody comprises: an HCVR that comprises the amino acid sequence set forth in SEQ ID NO: 1010 and an LCVR that comprises the amino acid sequence set forth in SEQ ID NO: 1018. In some cases, the third isolated antibody comprises: a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1026 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 1028.

[00057] In one aspect, the present disclosure provides a method for treating or preventing infection with an Omicron variant SARS-CoV-2, in a subject in need thereof, comprising administering a therapeutically effective amount of an antibody or antigen binding fragment thereof comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) comprising an

amino acid sequence having at least about 90% sequence identity to an HCVR of Table 4; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) comprising an amino acid sequence having at least about 90% sequence identity to an LCVR Table 4.

[00058] In one aspect, the present disclosure provides a method for preventing one or more COVID-19 symptoms resulting from infection with an Omicron variant SARS-CoV-2, in a subject in need thereof, comprising administering a therapeutically effective amount of an antibody or antigen binding fragment thereof comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) comprising an amino acid sequence having at least about 90% sequence identity to an HCVR of Table 4; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) comprising an amino acid sequence having at least about 90% sequence identity to an LCVR Table 4.

[00059] In some embodiments of the methods, preventing comprises pre-exposure prophylaxis. In some embodiments of the methods, preventing comprises post-exposure prophylaxis.

[00060] In some cases, the antibody or antigen-binding fragment comprises: (a) an immunoglobulin heavy chain variable region comprising the HCDR1, HCDR2, and HCDR3 of an antibody of Table 4; and/or (b) an immunoglobulin light chain variable region comprising the LCDR1, LCDR2, and LCDR3 of an antibody of Table 4.

[00061] In some cases, the antibody or antigen-binding fragment comprises the HCDR1, HCDR2, and HCDR3 of an antibody of Table 4 and the LCDR1, LCDR2, and LCDR3 of said antibody of Table 4.

[00062] In some embodiments of the methods, the subject is administered one or more further therapeutic agents. In some cases, the one or more further therapeutic agents is an anti-viral drug or a vaccine. In some cases, the one or more further therapeutic agents is selected from the group consisting of: an anti-inflammatory agent, an antimalarial agent, an antibody or antigen-binding fragment thereof that specifically binds TMPRSS2, and an antibody or antigen-binding fragment thereof that specifically binds to CoV-S. In some embodiments, the anti-inflammatory agent is an antibody, such as sarilumab, tocilizumab, or gimsilumab. In some cases, the antibody that binds to CoV-S is casirivimab or imdevimab,

[00063] In some embodiments of the methods, the antibody or antigen-binding fragment comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of a second antibody of Table 4.

[00064] In some embodiments of the methods, administering comprises injecting the antibody or antigen-binding fragment into the body of the subject. In some cases, the antibody or antigen-binding fragment is injected into the body of the subject subcutaneously, intravenously or intramuscularly.

[00065] In one aspect, the present disclosure provides a method for treating or preventing one or more COVID-19 symptoms resulting from infection with SARS-CoV-2, in a subject in need thereof, comprising administering a therapeutically effective amount of an antibody or antigen binding fragment thereof comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 362; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 370.

[00066] In some embodiments, HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 364, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 366, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 368, LCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 372, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 106, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 374. In some cases, the antibody or antigen-binding fragment comprises an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 362. In some cases, the antibody or antigen-binding fragment comprises an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 370. In some cases, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 376. In some cases, the antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence set forth in SEQ ID NO: 378.

[00067] In some embodiments, administering comprises administering the antibody or antigen-binding fragment via injection. In some cases, injection is intravenous. In some cases, injection is subcutaneous.

[00068] In some embodiments, administering comprises administering 300 mg of said antibody or antigen-binding fragment thereof. In some embodiments, administering comprises administering 600 mg of said antibody or antigen-binding fragment thereof. In some embodiments, administering comprises administering 1200 mg of said antibody or antigen-binding fragment thereof.

[00069] In some embodiments, administering comprises administering two doses of said antibody or antigen-binding fragment thereof. In some cases, each of the two doses comprises 300 mg of the antibody or antigen-binding fragment thereof. In some cases, the two doses are administered 4 weeks apart, 5 weeks apart, 6 weeks apart, 7 weeks apart, 8 weeks apart, 9 weeks apart, 10 weeks apart, 11 weeks apart, 12 weeks apart, 13 weeks apart, 14 weeks apart, 15 weeks apart, or 16 weeks apart. In some cases, the two doses are administered 8-16 weeks apart. In some cases, the two doses are administered 12 weeks apart. In some cases, the two doses are administered 8 weeks apart.

[00070] In some embodiments, administering reduces the viral load of SARS-CoV-2 in said subject.

[00071] In some embodiments, administration of the antibody or antigen-binding fragment thereof occurs prior to SARS-CoV-2 infection.

[00072] In one aspect, the present disclosure provides a method for treating or preventing one or more COVID-19 symptoms resulting from infection with SARS-CoV-2, in a subject in need thereof, comprising administering a therapeutically effective amount of an antibody or antigen binding fragment thereof comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2, and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence set forth in SEQ ID NO: 362; and three light chain CDRs (LCDR1, LCDR2, and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence set forth in SEQ ID NO: 370, wherein said administering comprises administering to said subject two doses of said antibody or antigen-binding fragment thereof, each does comprising 300 mg of said antibody or antigen-binding fragment thereof.

[00073] In some embodiments, administering is subcutaneous.

[00074] In some embodiments, HCDR1 comprises the amino acid sequence set forth in SEQ ID NO: 364, HCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 366, HCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 368, LCDR1 comprises the amino

acid sequence set forth in SEQ ID NO: 372, LCDR2 comprises the amino acid sequence set forth in SEQ ID NO: 106, and LCDR3 comprises the amino acid sequence set forth in SEQ ID NO: 374. In some cases, the antibody or antigen-binding fragment comprises an HCVR comprising the amino acid sequence set forth in SEQ ID NO: 362. In some cases, the antibody or antigen-binding fragment comprises an LCVR comprising the amino acid sequence set forth in SEQ ID NO: 370. In some cases, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 376. In some cases, the antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence set forth in SEQ ID NO: 378.

[00075] In one aspect, the present disclosure provides a polynucleotide encoding an antibody or antigen-binding fragment thereof; or a HCVR and/or a LCVR; or a heavy chain and/or a light chain of an antibody or antigen-binding fragment thereof, as discussed above or herein. The present disclosure further provides a vector or vectors comprising the polynucleotide discussed above or herein, and a host cell comprising the antibody or antigen-binding fragment, the polynucleotide or polynucleotides, and/or the vector or vectors discussed above or herein.

[00076] In some embodiments, admistering comprises administering 600 mg of the antibody or antigen-binding fragment thereof. In some embodiments, administering comprises administering 300 mg of the antibody or antigen-binding fragment thereof.

[00077] In any of the various embodiments of the antibodies or antigen-binding fragments thereof discussed above or herein, the antibody or antigen-binding fragment may neutralize an omicron variant of SARS-CoV-2. In various embodiments, the omicron variant is selected from BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3, or BA.4/BA.5.

[00078] In various embodiments, any of the features or components of embodiments discussed above or herein may be combined, and such combinations are encompassed within the scope of the present disclosure. Any specific value discussed above or herein may be combined with another related value discussed above or herein to recite a range with the values representing the upper and lower ends of the range, and such ranges are encompassed within the scope of the present disclosure.

BRIEF DESCRIPTION OF THE FIGURES

[00079] FIG. 1 shows cross-competition between 41 anti-SARS-CoV-2-S monoclonal antibodies upon binding to immobilized SARS-Cov-2 RBD-MMH (SEQ ID NO: 1069). Red: Pre-bound mAb-1 reduced binding of mAb-2 to SARS-CoV-2 RBD-MMH by greater than 50%, and binding to SARS-CoV-2 RBD-MMH was also reduced by greater than 50% when the binding order of mAb-1 and mAb-2 was reversed. Yellow: Pre-bound mAb-1 reduced binding of mAb-2 to SARS-CoV-2 RBD-MMH by greater than 50%, but binding to SARS-CoV-2 RBD-MMH was reduced by less than 50% when the binding order of mAb-1 and mAb-2 was reversed.

[00080] FIG. 2 shows cross-competition between 15 anti-SARS-CoV-2-S monoclonal antibodies upon binding to immobilized SARS-Cov-2 RBD-MMH. Red: Pre-bound mAb-1 reduced binding of mAb-2 to SARS-CoV-2 RBD-MMH by greater than 50%, and binding to SARS-CoV-2 RBD-MMH was also reduced by greater than 50% when the binding order of mAb-1 and mAb-2 was reversed. Yellow: Pre-bound mAb-1 reduced binding of mAb-2 to SARS-CoV-2 RBD-MMH by greater than 50%, but binding to SARS-CoV-2 RBD-MMH was reduced by less than 50% when the binding order of mAb-1 and mAb-2 was reversed.

[00081] FIG. 3 depicts the cryo-EM structure of mAb14256, mAb10987, and the receptor binding domain (RBD) of the SARS-CoV-2 spike glycoprotein, in complex, at 3.9 Å resolution.

[00082] FIG. 4 shows that mAb14256 binds at the top of the RBD, thereby blocking ACE2 binding. mAb14256 competes with mAb10933 (middle structure) and mAb10985 (not depicted).

[00083] FIG. 5 depicts the cryo-EM structure of mAb15160, mAb14315, and the receptor binding domain (RBD) of the SARS-CoV-2 spike glycoprotein, in complex, at 3.18 Å resolution.

[00084] FIG. 6 depicts the cryo-EM structure of antigen-binding fragments of mAb1428 and mAb15160 with the receptor binding domain (RBD) from the Wuhan-Hu-1 strain and BA.1 lineage, in complex, at 3.3 and 3.4 Å resolution, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[00085] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[00086] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

[00087] The term "coronavirus" or "CoV" refers to any virus of the coronavirus family, including but not limited to SARS-CoV-2, MERS-CoV, and SARS-CoV. SARS-CoV-2 has also been known as 2019-nCoV and Wuhan coronavirus. It binds via the viral spike protein to human host cell receptor angiotensin-converting enzyme 2 (ACE2). The spike protein also binds to and is cleaved by TMPRSS2, which activates the spike protein for membrane fusion of the virus.

[00088] The term "CoV-S", also called "S" or "S protein" refers to the spike protein of a coronavirus, and can refer to specific S proteins such as SARS-CoV-2-S, MERS-CoV S, and SARS-CoV S. The SARS-CoV-2-Spike protein is a 1273 amino acid type I membrane glycoprotein which assembles into trimers that constitute the spikes or peplomers on the surface of the enveloped coronavirus particle. The protein has two essential functions, host receptor binding and membrane fusion, which are attributed to the N-terminal (S1) and C-terminal (S2) halves of the S protein. CoV-S binds to its cognate receptor via a receptor binding domain (RBD) present in the S1 subunit. The amino acid sequence of full-length SARS-CoV-2 spike protein is exemplified by the amino acid sequence provided in SEQ ID NO: 1008. The term "CoV-S" includes protein variants of CoV spike protein isolated from different CoV isolates as well as recombinant CoV spike protein or a fragment thereof. The term also encompasses CoV spike protein or a fragment thereof coupled to, for example, a histidine tag, mouse or human Fc, or a signal sequence such as ROR1.

[00089] The term "coronavirus infection" or "CoV infection," as used herein, refers to infection with a coronavirus such as SARS-CoV-2, MERS-CoV, or SARS-CoV. The term includes coronavirus respiratory tract infections, often in the lower respiratory tract. Symptoms can include high fever, dry cough, shortness of breath, pneumonia, gastro-intestinal symptoms such as diarrhea, organ failure (kidney failure and renal dysfunction), septic shock, and death in severe cases.

Viruses

[00090] The present invention includes methods for treating or preventing a viral infection in a subject. The term "virus" includes any virus whose infection in the body of a subject is treatable or preventable by administration of an anti-CoV-S antibody or antigen-binding fragment thereof (*e.g.*, wherein infectivity of the virus is at least partially dependent on CoV-S). In an embodiment of the invention, a "virus" is any virus that expresses spike protein (e.g., CoV-S). The term "virus" also includes a CoV-S-dependent respiratory virus which is a virus that infects the respiratory tissue of a subject (*e.g.*, upper and/or lower respiratory tract, trachea, bronchi, lungs) and is treatable or preventable by administration of an anti-CoV-S antibody or antigen-binding fragment thereof. For example, in an embodiment of the invention, virus includes coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), SARS-CoV (severe acute respiratory syndrome coronavirus), and MERS-CoV (Middle East respiratory syndrome (MERS) coronavirus). Coronaviruses can include the genera of alphacoronaviruses, betacoronaviruses, gammacoronaviruses, and deltacoronaviruses. In some embodiments, the antibodies or antigen-binding fragments provided herein can bind to and/or neutralize an alphacoronavirus, a betacoronavirus, a gammacoronavirus, and/or a deltacoronavirus. In certain embodiments, this binding and/or neutralization can be specific for a particular genus of coronavirus or for a particular subgroup of a genus. "Viral infection" refers to the invasion and multiplication of a virus in the body of a subject.

[00091] Coronavirus virions are spherical with diameters of approximately 125 nm. The most prominent feature of coronaviruses is the club-shape spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the virion is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses. SARS-CoV-2, MERS-CoV, and SARS-CoV belong to the coronavirus family. The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The sites of receptor binding domains (RBD) within the S1 region of a coronavirus S protein vary depending on the virus, with some having the RBD at the C-terminus of S1. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Many coronaviruses utilize

peptidases as their cellular receptor. Following receptor binding, the virus must next gain access to the host cell cytosol. This is generally accomplished by acid-dependent proteolytic cleavage of S protein by a cathepsin, TMPRRS2 or another protease, followed by fusion of the viral and cellular membranes.

[00092] The coronaviruses described herein also include variant coronaviruses, which in some embodiments are classified as "variants of interest" or "variants of concern" by the World Health Organization (WHO). Variant coronaviruses can have mutations in their spike glycoprotein, which may change the virus's properties such as severity of COVID-19 or transmissibility. WHO defines a variant of concern as one that is associated with one or more of the following changes from wild-type, to such a degree that it is a matter of global public health significance: 1) increased transmissibility or detrimental change in COVID-19 epidemiology; 2) increased virulence or changed clinical disease presentation; or 3) decreased effectiveness of public health measures and social measures, including available therapeutics, vaccines, and diagnostics. Variants of interest are defined by WHO as SARS-CoV-2 viruses 1) with genetic changes that are predicted or have been demonstrated to affect virus characteristics including immune escape, therapeutic escape, diagnostic escpe, transmissibility, and disease severity; and 2) that have been identified as causing significant community transmission or multiple COVID-19 clusters, in multiple countries and with increasing relative prevalence alongside an increasing number of cases over time, or with other epidemiological impacts that suggest an emerging risk to global public health. As of December 13, 2021, there are five variants of concern as classified by WHO (alpha, beta, gamma, delta, and omicron), and two variants of interest as classified by WHO (lambda and mu). Each variant can be defined by the mutations in its spike glycoprotein as compared to the wild-type spike glycoprotein. For example, the Omicron variant (also classified as B.1.1.529) comprises the following mutations in its spike glycoprotein: A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F (full length omicron spike glycoprotein: SEQ ID NO: 1072). Moreover, these variants may have further lineages that encompass a group of related viruses. For example, as of July 8, 2022, the Omicron variant has BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3, and BA.4/BA.5 lineages. In some embodiments, the antibodies and antigen-binding fragments thereof described herein can bind to any of these

variants and/or lineages. In further embodiments, the antibodies and antigen-binding fragments thereof can neutralize these variants and/or lineages.

Anti-CoV-S Antibodies and Antigen-Binding Fragments

[00093] The present invention provides antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, that specifically bind to CoV spike protein or an antigenic fragment thereof.

[00094] The term "antibody", as used herein, refers to immunoglobulin molecules comprising four polypeptide chains, two heavy chains (HCs) and two light chains (LCs) inter-connected by disulfide bonds (*i.e.*, "full antibody molecules"), as well as multimers thereof (*e.g.* IgM). Exemplary antibodies include, for example, those listed in Table 4. Each heavy chain comprises a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Heavy chain CDRs can also be referred to as HCDRs or CDR-Hs, and numbered as described above (e.g., HCDR1, HCDR2, and HCDR3 or HCDR1, HCDR2, and HCDR3). Likewise, light chain CDRs can be referred to as LCDRs or CDR-Ls, and numbered LCDR1, LCDR2, and LCDR3, or LCDR1, LCDR2, and LCDR3. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) are identical to the human germline sequences, or are naturally or artificially modified. Exemplary human germline sequences include, but are not limited to, VH3-66 and Vk1-33. Thus, the present disclosure provides anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCDR and LCDR sequences of Table 4 within a VH3-66 or Vk1-33 variable heavy chain or light chain region. The present disclosure further provides anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCDR and LCDR sequences of Table 4 within a combination of a light chain selected from IgKV4-1, IgKV 1-5, IgKV1-9, IgKV1-12, IgKV3-15, IgKV1-16,

IgKV1-17, IgKV3-20, IgLV3-21, IgKV2-24, IgKV1-33, IgKV1-39, IgLV1-40, IgLV1-44, IgLV1-51, IgLV3-1, IgKV1-6, IgLV2-8, IgKV3-11, IgLV2-11, IgLV2-14, IgLV2-23, or IgLV6-57, and a heavy chain selected from IgHV1-69, IgHV3-64, IgHV4-59, IgHV3-53, IgHV3-48, IgHV4-34, IgHV3-33, IgHV3-30, IgHV3-23, IgHV3-20, IgHV1-18, IgHV3-15, IgHV3-11, IgHV3-9, IgHV1-8, IgHV3-7, IgHV2-5, IgHV1-2, IgHV2-70, IgHV3-66, IgHV5-51, IgHV1-46, IgHV4-39, IgHV4-31, IgHV3-30-3, IgHV2-26, or IgHV7-4-1. The present disclosure further provides anti-CoV-S antibodies or antigen-binding fragments thereof (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) comprising HCVR and LCVR sequences of Table 4 within a combination of a light chain selected from IgKV4-1, IgKV 1-5, IgKV1-9, IgKV1-12, IgKV3-15, IgKV1-16, IgKV1-17, IgKV3-20, IgLV3-21, IgKV2-24, IgKV1-33, IgKV1-39, IgLV1-40, IgLV1-44, IgLV1-51, IgLV3-1, IgKV1-6, IgLV2-8, IgKV3-11, IgLV2-11, IgLV2-14, IgLV2-23, or IgLV6-57, and a heavy chain selected from IgHV1-69, IgHV3-64, IgHV4-59, IgHV3-53, IgHV3-48, IgHV4-34, IgHV3-33, IgHV3-30, IgHV3-23, IgHV3-20, IgHV1-18, IgHV3-15, IgHV3-11, IgHV3-9, IgHV1-8, IgHV3-7, IgHV2-5, IgHV1-2, IgHV2-70, IgHV3-66, IgHV5-51, IgHV1-46, IgHV4-39, IgHV4-31, IgHV3-30-3, IgHV2-26, or IgHV7-4-1.

[00095] Typically, the variable domains of both the heavy and light immunoglobulin chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. In an embodiment of the invention, the assignment of amino acids to each domain is in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md.; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia, *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia, *et al.*, (1989) Nature 342:878-883.

[00096] The present invention includes monoclonal anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, as well as monoclonal compositions comprising a plurality of isolated monoclonal antigen-binding proteins. The term "monoclonal antibody", as used herein, refers to a population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. A "plurality"

of such monoclonal antibodies and fragments in a composition refers to a concentration of identical (*i.e*., as discussed above, in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts) antibodies and fragments which is above that which would normally occur in nature, *e.g*., in the blood of a host organism such as a mouse or a human.

[00097] In an embodiment of the invention, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment comprises a heavy chain constant domain, *e.g*., of the type IgA (*e.g.*, IgA1 or IgA2), IgD, IgE, IgG (*e.g.*, IgG1, IgG2, IgG3 and IgG4) or IgM. In an embodiment of the invention, an antigen-binding protein, *e.g.*, antibody or antigen-binding fragment comprises a light chain constant domain, *e.g*., of the type kappa or lambda.

[00098] The term "human" antigen-binding protein, such as an antibody, as used herein, includes antibodies having variable and constant regions derived from human germline immunoglobulin sequences whether in a human cell or grafted into a non-human cell, *e.g*., a mouse cell. See *e.g*., US8502018, US6596541 or US5789215. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and, in particular, CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (*e.g.*, mouse) have been grafted onto human FR sequences. The term includes antibodies recombinantly produced in a non-human mammal or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject. See below.

[00099] The present invention includes anti-CoV-S chimeric antigen-binding proteins, *e.g*., antibodies and antigen-binding fragments thereof, and methods of use thereof. As used herein, a "chimeric antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, where the first and second antibodies are from different species. (US4816567; and Morrison *et al.*, (1984) Proc. Natl. Acad. Sci. USA 81: 6851-6855).

[000100] The present invention includes anti-CoV-S hybrid antigen-binding proteins, *e.g*., antibodies and antigen-binding fragments thereof, and methods of use thereof. As used herein, a "hybrid antibody" is an antibody having the variable domain from a first antibody and the constant domain from a second antibody, wherein the first and second antibodies are from

different animals, or wherein the variable domain, but not the constant region, is from a first animal. For example, a variable domain can be taken from an antibody isolated from a human and expressed with a fixed constant region not isolated from that antibody. Exemplary hybrid antibodies are described in Example 1, which refers to antibody heavy chain variable region and light chain variable region derived PCR products that were cloned into expression vectors containing a heavy constant region and a light constant region, respectively. Hybrid antibodies are synthetic and non-natrually occurring because the variable and constant regions they contain are not isolated from a single natural source.

[000101] The term "recombinant" antigen-binding proteins, such as antibodies or antigen-binding fragments thereof, refers to such molecules created, expressed, isolated or obtained by technologies or methods known in the art as recombinant DNA technology which include, *e.g.*, DNA splicing and transgenic expression. The term includes antibodies expressed in a non-human mammal (including transgenic non-human mammals, *e.g.*, transgenic mice), or a cell (*e.g.*, CHO cells) expression system, or a non-human cell expression system, or isolated from a recombinant combinatorial human antibody library. In some embodiments, a recombinant antibody shares a sequence with an antibody isolated from an organism (*e.g.*, a mouse or a human), but has been expressed via recombinant DNA technology. Such antibodies may have post-translational modifications (*e.g.*, glycosylation) that differ from the antibody as isolated from the organism.

[000102] In some embodiments, the antibodies disclosed herein lack fucose in its constant region glycosylation. Methods of measuring fucose in an antibody composition have been described in the art, e.g., U.S. Patent No. 8,409,838 (Regeneron Pharmaceuticals), incorporated herein by reference. In some embodiments, fucose is undetectable in a composition comprising a population of antibody molecules. In some embodiments, an antibody lacking fucose has enhanced ADCC activity.

[000103] In some embodiments, antibodies that lack fucose can be produced using cell lines that are deficient in their ability to fucosylate proteins, i.e., the ability to fucosylate proteins is reduced or eliminated. Fucosylation of glycans requires synthesis of GDP-fucose via the de novo pathway or the salvage pathway, both of which involve sequential function of several enzymes, leading to addition of a fucose molecule to the first N-acetylglucosamine (GlcNAc) moiety of the reducing end of a glycan. The two key enzymes of the de novo pathway

responsible for production of GDP-fucose are GDP-D-mannose-4,6-dehydratase (GMD) and GDP-keto-6-deoxymannose-3,5-epimerase,4-reductase (FX). In the absence of fucose, these two de novo pathway enzymes (GMD and FX) convert mannose and/or glucose to GDP-fucose which is then transported into the Golgi complex where nine fucosyl-transferases (FUT1-9) act in concert to fucosylate the first GlcNAc molecule of a glycan. In the presence of fucose, however, the salvage pathway enzymes, fucose-kinase and GDP-fucose pyrophosphorylase, convert fucose into GDP-fucose.

[000104] Cell lines that are deficient in their ability to fucosylate proteins have been described in the art. In some embodiments, a cell line deficient in its ability to fucosylate proteins is a mammalian cell line (e.g., CHO cell lines, such as CHO K1, DXB-11 CHO, Veggie-CHO) comprising a mutation or genetic modification in one or more of endogenous FUT1 to 9 genes resulting in a lack of one or more functional fucosyl-transferases. In some embodiments, the mammalian cell line comprises a mutation in an endogenous FUT8 gene (e.g., a FUT8 knock-out cell line in which the FUT8 gene has been disrupted resulting in a lack of a functional □1,6-fucosyltransferase in the cell line, as described in US Patent No. 7,214,775 (Kyowa Hakko Kogyo Co., Ltd.) and US Patent 7,737,725 (Kyowa Hakko Kirin Co., Ltd), incorporated herein by reference. In some embodiments, the mammalian cell line comprises a mutation or genetic modification in an endogenous GMD gene resulting in a lack of a functional GMD in the cell line, e.g., a GMD knock-out cell line in which the GMD gene has been disrupted, described in e.g., US Patent 7,737,725 (Kyowa Hakko Kirin Co., Ltd), incorporated herein by reference. In some embodiments, the mammalian cell line comprises a mutation or genetic modification in an endogenous Fx gene resulting in a lack of a functional Fx protein. In some embodiments, the mammalian cell line is an Fx knock-out cell line in which the endogenous Fx gene has been disrupted (see, e.g., US Patent 7,737,725 (Kyowa Hakko Kirin Co., Ltd), incorporated herein by reference). In some embodiments, the mammalian cell line comprises a mutation in an endogenous Fx mutation that confers temperature sensitive phenotypes (as described in, e.g., U.S. Patent No. 8,409,838 (Regeneron Pharmaceuticals), incorporated herein by reference). In some embodiments, the mammalian cell line deficient in its ability to fucosylate proteins is a cell line that has been selected based on resistance to certain lectins, e.g., the Lens culinaris lectin. See, e.g., U.S. Patent No. 8,409,838 (Regeneron Pharmaceuticals), incorporated herein by reference.

[000105] Recombinant anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments, disclosed herein may also be produced in an *E. coli*/T7 expression system. In this embodiment, nucleic acids encoding the anti-CoV-S antibody immunoglobulin molecules of the invention (*e.g.*, as found in Table 4) may be inserted into a pET-based plasmid and expressed in the *E. coli*/T7 system. For example, the present invention includes methods for expressing an antibody or antigen-binding fragment thereof or immunoglobulin chain thereof in a host cell (*e.g.*, bacterial host cell such as *E. coli* such as BL21 or BL21DE3) comprising expressing T7 RNA polymerase in the cell which also includes a polynucleotide encoding an immunoglobulin chain that is operably linked to a T7 promoter. For example, in an embodiment of the invention, a bacterial host cell, such as an *E. coli*, includes a polynucleotide encoding the T7 RNA polymerase gene operably linked to a *lac* promoter and expression of the polymerase and the chain is induced by incubation of the host cell with IPTG (isopropyl-beta-D-thiogalactopyranoside). See US4952496 and US5693489 or Studier & Moffatt, Use of bacteriophage T7 RNA polymerase to direct selective high-level expression of cloned genes, J. Mol. Biol. 1986 May 5;189(1): 113-30.

[000106] There are several methods by which to produce recombinant antibodies which are known in the art. One example of a method for recombinant production of antibodies is disclosed in US4816567.

[000107] Transformation can be by any known method for introducing polynucleotides (e.g., DNA or RNA, including mRNA) into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, lipid nanoparticle technology, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors such as lentivirus or adeno-associated virus. Methods of transforming cells are well known in the art. See, for example, U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461 and 4,959,455. In some embodiments, an antibody or antigen-binding fragment thereof of the present disclosure can be introduced to a subject in nucleic acid form (e.g, DNA or RNA, including mRNA), such that the subject's own cells produce the antibody. The present disclosure further provides modifications to nucleotide sequences encoding the anti-CoV-S antibodies described herein that result in

increased antibody expression, increased antibody stability, increased nucleic acid (e.g., mRNA) stability, or improved affinity or specificity of the antibodies for the CoV spike protein.

[000108] Thus, the present invention includes recombinant methods for making an anti-CoV-S antigen-binding protein, such as an antibody or antigen-binding fragment thereof of the present invention, or an immunoglobulin chain thereof, comprising (i) introducing one or more polynucleotides (*e.g.*, including the nucleotide sequence of any one or more of the sequences of Table 5) encoding light and/or heavy immunoglobulin chains, or CDRs, of the antigen-binding protein, *e.g.*, of Table 4, for example, wherein the polynucleotide is in a vector; and/or integrated into a host cell chromosome and/or is operably linked to a promoter; (ii) culturing the host cell (*e.g.*, CHO or *Pichia* or *Pichia pastoris*) under condition favorable to expression of the polynucleotide and, (iii) optionally, isolating the antigen-binding protein, (*e.g.*, antibody or fragment) or chain from the host cell and/or medium in which the host cell is grown. For example, a polynucleotide can be integrated into a host cell chromosome through targeted insertion with a vector such as adeno-associated virus (AAV), e.g., after cleavage of the chromosome using a gene editing system (e.g., CRISPR (for example, CRISPR-Cas9), TALEN, megaTAL, zinc finger, or Argonaute). Targeted insertions can take place, for example, at host cell loci such as an albumin or immunoglopbulin genomic locus. Alternatively, insertion can be at a random locus, e.g., using a vector such as lentivirus. When making an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment) comprising more than one immunoglobulin chain, *e.g.*, an antibody that comprises two heavy immunoglobulin chains and two light immunoglobulin chains, co-expression of the chains in a single host cell leads to association of the chains, *e.g.*, in the cell or on the cell surface or outside the cell if such chains are secreted, so as to form the antigen-binding protein (*e.g.*, antibody or antigen-binding fragment). The methods include those wherein only a heavy immunoglobulin chain or only a light immunoglobulin chain (*e.g.*, any of those discussed herein including mature fragments and/or variable domains thereof) is expressed. Such chains are useful, for example, as intermediates in the expression of an antibody or antigen-binding fragment that includes such a chain. For example, the present invention also includes anti-CoV-S antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, comprising a heavy chain immunoglobulin (or variable domain thereof or comprising the CDRs thereof) encoded by a polynucleotide comprising a nucleotide sequence set forth in Table 5 and a light chain immunoglobulin (or

variable domain thereof or comprising the CDRs thereof) encoded by a nucleotide sequence set forth in Table 5 which are the product of such production methods, and, optionally, the purification methods set forth herein. For example, in some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising an HCVR comprising an amino acid sequence set forth in Table 4 and an LCVR comprising an amino acid sequence set forth in Table 4, wherein the HCVR and LCVR sequences are selected from a single antibody listed in Table 4. In some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising HCDR1, HCDR2, and HCDR3 comprising amino acid sequences set forth in Table 4 and LCDR1, LCDR2, and LCDR3 comprising amino acid sequences set forth in Table 4, wherein the six CDR sequences are selected from a single antibody listed in Table 4. In some embodiments, the product of the method is an anti-CoV-S antigen-binding protein which is an antibody or fragment comprising a heavy chain comprising an HC amino acid sequence set forth in Table 4 and a light chain comprising an LC amino acid sequence set forth in Table 4.

[000109] Eukaryotic and prokaryotic host cells, including mammalian cells, may be used as hosts for expression of an anti-CoV-S antigen-binding protein. Such host cells are well known in the art and many are available from the American Type Culture Collection (ATCC). These host cells include, *inter alia*, Chinese hamster ovary (CHO) cells, NS0, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, HEK-293 cells and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Other cell lines that may be used are insect cell lines (*e.g.*, *Spodoptera frugiperda* or *Trichoplusia ni*), amphibian cells, bacterial cells, plant cells and fungal cells. Fungal cells include yeast and filamentous fungus cells including, for example, *Pichia pastoris*, *Pichia finlandica*, *Pichia trehalophila*, *Pichia koclamae*, *Pichia membranaefaciens*, *Pichia minuta* (*Ogataea minuta*, *Pichia lindneri*), *Pichia opuntiae*, *Pichia thermotolerans*, *Pichia salictaria*, *Pichia guercuum*, *Pichia pijperi*, *Pichia stiptis*, *Pichia methanolica*, *Pichia* sp., *Saccharomyces cerevisiae*, *Saccharomyces* sp., *Hansenula polymorpha*, *Kluyveromyces* sp., *Kluyveromyces lactis*, *Candida albicans*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus oryzae*, *Trichoderma reesei*, *Chrysosporium lucknowense*, *Fusarium* sp., *Fusarium gramineum*, *Fusarium venenatum*, *Physcomitrella patens* and *Neurospora crassa*. The present invention

includes an isolated host cell (*e.g.*, a CHO cell) comprising an antigen-binding protein, such as those of Table 4; or a polynucleotide encoding such a polypeptide thereof.

[000110] Polynucleotides, as discussed herein, may encode all or a portion of an antibody or antigen-binding fragment as discussed throughout the present disclosure. In some cases, a single polynucleotide may encode both a HCVR and a LCVR (*e.g.*, defined with reference to the CDRs contained within the respective amino acid sequence-defined HCVR and LCVR, defined with reference to the amino acid sequences of the CDRs of the HCVR and LCVR. respectively, or defined with reference to the amino acid sequences of the HCVR and LCVR, respectively) of an antibody or antigen-binding fragment, or the HCVR and LCVR may be encoded by separate polynucleotides (*i.e.*, a pair of polynucleotides). In the latter case, in which the HCVR and LCVR are encoded by separate polynucleotides, the polynucleotides may be combined in a single vector or may be contained in separate vectors (*i.e.*, a pair of vectors). In any case, a host cell used to express the polynucleotide(s) or vector(s) may contain the full complement of component parts to generate the antibody or antigen-binding fragment thereof. For example, a host cell may comprise separate vectors, each encoding a HCVR and a LCVR, respectively, of an antibody or antigen-binding fragment thereof as discussed above or herein. Similarly, the polynucleotide or polynucleotides, and the vector or vectors, may be used to express the full-length heavy chain and full-length light chain of an antibody as discussed above or herein. For example, a host cell may comprise a single vector with polynucleotides encoding both a heavy chain and a light chain of an antibody, or the host cell may comprise separate vectors with polynucleotides encoding, respectively, a heavy chain and a light chain of an antibody as discussed above or herein.

[000111] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 214, 216 and 218 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 213, 215 and 217). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 222, 126 and 224 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 221, 125 and 223). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host

cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 212 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 211). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 220 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 219). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 226 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 225). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 228 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 227). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph, as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb14315 or an antigen-binding fragment thereof.

[000112] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 364, 366 and 368 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 363, 365 and 367). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 372, 106 and 374 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 371, 105 and 373). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 362 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 361). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 370 (*e.g.*, in an

embodiment, the polynucleotide comprises SEQ ID NO: 369). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 376 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 375). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 378 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 377). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph, as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb15160 or an antigen-binding fragment thereof.

[000113] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 495, 497 and 499 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 494, 496 and 498). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 503, 505 and 507 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 502, 504 and 506). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 493 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 492). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 501 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 500). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 509 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 508). In an exemplary embodiment, the present disclosure provides a

polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 511 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 510). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph, as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb14284 or an antigen-binding fragment thereof.

[000114] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 889, 891 and 893 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 888, 890 and 892). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 897, 164 and 899 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 896, 163 and 898). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 887 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 886). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 895 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 894). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 901 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 900). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 903 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 902). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph,

as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb14256 or an antigen-binding fragment thereof.

[000115] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 495, 497 and 499 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 494, 496 and 498). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 503, 505 and 507 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 502, 504 and 506). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 493 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 492). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 501 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 500). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1075 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 1074). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 511 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 510). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph, as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb17090 or an antigen-binding fragment thereof.

[000116] In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the HCDRs of SEQ ID NOs: 364, 366 and 368 (*e.g.*, in an

embodiment, the polynucleotide comprises SEQ ID NOs: 363, 365 and 367). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the LCDRs of SEQ ID NOs: 372, 106 and 374 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NOs: 371, 105 and 373). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a HCVR comprising the amino acid sequence of SEQ ID NO: 362 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 361). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a LCVR comprising the amino acid sequence of SEQ ID NO: 370 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 369). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 1077 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 1076). In an exemplary embodiment, the present disclosure provides a polynucleotide (or a vector comprising the polynucleotide, or a host cell comprising the polynucleotide or the vector) encoding a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 378 (*e.g.*, in an embodiment, the polynucleotide comprises SEQ ID NO: 377). In an embodiment, the present disclosure provides a pair of polynucleotides or a pair of vectors encoding, respectively, a HCVR and a LCVR, or a HC and a LC, as discussed in this paragraph, as well as a host cell containing the pair or polynucleotides and/or the pair of vectors to encode the antibody designated mAb15160_2 or an antigen-binding fragment thereof.

[000117] The term "specifically binds" refers to those antigen-binding proteins (*e.g.*, mAbs) having a binding affinity to an antigen, such as a CoV-S protein (*e.g.*, SARS-CoV-2-S), expressed as K_D, of at least about 10^{-8} M, as measured by real-time, label free bio-layer interferometry assay, for example, at 25ºC or 37ºC, *e.g.*, an Octet® HTX biosensor, or by surface plasmon resonance, *e.g.*, BIACORE™, or by solution-affinity ELISA. The present invention includes antigen-binding proteins that specifically bind to a CoV-S protein.

[000118] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody or antigen-binding protein, and the like, as used herein, include any naturally occurring,

enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.*, as defined in WO08/020079 or WO09/138519) (*e.g.*, monovalent nanobodies, bivalent nanobodies, *etc.*), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein. In an embodiment of the invention, the antigen-binding fragment comprises three or more CDRs of an antibody of Table 4 (*e.g.*, HCDR1, HCDR2 and HCDR3; or LCDR1, LCDR2 and LCDR3).

[000119] An antigen-binding fragment of an antibody will, in an embodiment of the invention, comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H, V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[000120] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may

consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[000121] Antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) may be mono-specific or multi-specific (*e.g.*, bi-specific). Multispecific antigen-binding proteins are discussed further herein.

[000122] In specific embodiments, antibody or antibody fragments of the invention may be conjugated to a moiety such a ligand or a therapeutic moiety ("immunoconjugate"), such as an anti-viral drug, a second anti-influenza antibody, or any other therapeutic moiety useful for treating a viral infection, *e.g.*, influenza viral infection. See below.

[000123] The present invention also provides a complex comprising an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, discussed herein complexed with CoV-S polypeptide or an antigenic fragment thereof and/or with a secondary antibody or antigen-binding fragment thereof (*e.g.*, detectably labeled secondary antibody) that binds specifically to the anti-CoV-S antibody or fragment. In an embodiment of the invention, the antibody or fragment is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is in the body of a subject. In an embodiment of the invention, the CoV-S is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is on the surface of a virus or is in the body of a subject. Immobilized anti-CoV-S antibodies and antigen-binding fragments thereof which are covalently linked to an insoluble matrix material (*e.g.*, glass or polysaccharide such as agarose or sepharose, *e.g.*, a bead or other particle thereof) are also part of the present invention; optionally, wherein the immobilized antibody is complexed with CoV-S or antigenic fragment thereof or a secondary antibody or fragment thereof.

[000124] "Isolated" antigen-binding proteins, antibodies or antigen-binding fragments thereof, polypeptides, polynucleotides and vectors, are at least partially free of other biological molecules from the cells or cell culture from which they are produced. Such biological molecules include nucleic acids, proteins, other antibodies or antigen-binding fragments, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated antibody or antigen-

binding fragment may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof. Generally, the term "isolated" is not intended to refer to a complete absence of such biological molecules or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the antibodies or fragments.

[000125] The term “epitope” refers to an antigenic determinant (*e.g.*, a CoV-S polypeptide) that interacts with a specific antigen-binding site of an antigen-binding protein, *e.g.*, a variable region of an antibody molecule, known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term “epitope” also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may be linear or conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[000126] Methods for determining the epitope of an antigen-binding protein, *e.g.*, antibody or fragment or polypeptide, include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol. Biol. 248: 443-63), peptide cleavage analysis, crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Prot. Sci. 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding protein (*e.g.*, antibody or fragment or polypeptide) (*e.g.*, coversin) interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antigen-binding protein, *e.g.*, antibody or fragment or polypeptide, to the deuterium-labeled protein. Next, the CoV-S protein/ antigen-binding protein complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than

exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/ antigen-binding protein interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antigen-binding protein (*e.g.*, antibody or fragment or polypeptide), the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antigen-binding protein interacts. See, *e.g.*, Ehring (1999) Analytical Biochemistry 267: 252-259; Engen and Smith (2001) Anal. Chem. 73: 256A-265A.

[000127] The term "competes" as used herein, refers to an antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) that binds to an antigen (*e.g.*, CoV-S) and inhibits or blocks the binding of another antigen-binding protein (*e.g.*, antibody or antigen-binding fragment thereof) to the antigen. The term also includes competition between two antigen-binding proteins *e.g.*, antibodies, in both orientations, *i.e.*, a first antibody that binds and blocks binding of second antibody and *vice versa*. In certain embodiments, the first antigen-binding protein (*e.g.*, antibody) and second antigen-binding protein (*e.g.*, antibody) may bind to the same epitope. Alternatively, the first and second antigen-binding proteins (*e.g.*, antibodies) may bind to different, but, for example, overlapping epitopes, wherein binding of one inhibits or blocks the binding of the second antibody, *e.g.*, via steric hindrance. Competition between antigen-binding proteins (*e.g.*, antibodies) may be measured by methods known in the art, for example, by a real-time, label-free bio-layer interferometry assay. Epitope mapping (e.g., via alanine scanning or hydrogen-deuterium exchange (HDX)) can be used to determine whether two or more antibodies are non-competing (e.g., on a spike protein receptor binding domain (RBD) monomer), competing for the same epitope, or competing but with diverse micro-epitopes (e.g., identified through HDX). In an embodiment of the invention, competition between a first and second anti-CoV-S antigen-binding protein (*e.g.*, antibody) is determined by measuring the ability of an immobilized first anti-CoV-S antigen-binding protein (*e.g.*, antibody) (not initially complexed with CoV-S protein) to bind to soluble CoV-S protein complexed with a second anti-CoV-S antigen-binding protein (*e.g.*, antibody). A reduction in the ability of the first anti-CoV-S antigen-binding protein (*e.g.*, antibody) to bind to the complexed CoV-S protein, relative to uncomplexed CoV-S protein, indicates that the first and second anti-CoV-S antigen-binding proteins (*e.g.*, antibodies) compete. The degree of competition can be expressed as a percentage

of the reduction in binding. Such competition can be measured using a real time, label-free bio-layer interferometry assay, *e.g.*, on an Octet RED384 biosensor (Pall ForteBio Corp.), ELISA (enzyme-linked immunosorbent assays) or SPR (surface plasmon resonance).

[000128] Binding competition between anti-CoV-S antigen-binding proteins (*e.g.*, monoclonal antibodies (mAbs)) can be determined using a real time, label-free bio-layer interferometry assay on an Octet RED384 biosensor (Pall ForteBio Corp.). For example, to determine competition between two anti-CoV-S monoclonal antibodies, the anti-CoV-S mAb can be first captured onto anti-hFc antibody coated Octet biosensor tips (Pall ForteBio Corp., # 18-5060) by submerging the tips into a solution of anti-CoV-S mAb (subsequently referred to as "mAb1"). As a positive-control for blocking, the antibody captured biosensor tips can then be saturated with a known blocking isotype control mAb (subsequently referred to as "blocking mAb") by dipping into a solution of blocking mAb. To determine if mAb2 competes with mAb1, the biosensor tips can then be subsequently dipped into a co-complexed solution of CoV-S polypeptide and a second anti-CoV-S mAb (subsequently referred to as "mAb2"), that had been pre-incubated for a period of time and binding of mAb1 to the CoV-S polypeptide can be determined. The biosensor tips can be washed in buffer in between every step of the experiment. The real-time binding response can be monitored during the course of the experiment and the binding response at the end of every step can be recorded.

[000129] For example, in an embodiment of the invention, the competition assay is conducted at 25 ºC and pH about 7, *e.g.*, 7.4, *e.g.*, in the presence of buffer, salt, surfactant and a non-specific protein (*e.g.*, bovine serum albumin).

[000130] Typically, an antibody or antigen-binding fragment of the invention which is modified in some way retains the ability to specifically bind to CoV-S, *e.g.*, retains at least 10% of its CoV-S binding activity (when compared to the parental antibody) when that activity is expressed on a molar basis. Preferably, an antibody or antigen-binding fragment of the invention retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the CoV-S binding affinity as the parental antibody. It is also intended that an antibody or antigen-binding fragment of the invention can include conservative or non-conservative amino acid substitutions (referred to as "conservative variants" or "function conserved variants" of the antibody) that do not substantially alter its biologic activity.

[000131] A "variant" of a polypeptide, such as an immunoglobulin chain (*e.g.*, mAb8021 V_H, V_L, HC, or LC, mAb8028 V_H, V_L, HC, or LC, or mAb8029 V_H, V_L, HC, or LC), refers to a polypeptide comprising an amino acid sequence that is at least about 70-99.9% (*e.g.*, 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.9%) identical or similar to a referenced amino acid sequence that is set forth herein (*e.g.*, SEQ ID NO: 2, 10, 18, 20, 22, 30, 38, 40, 42, 50, 58, or 60); when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 3; max matches in a query range: 0; BLOSUM 62 matrix; gap costs: existence 11, extension 1; conditional compositional score matrix adjustment).

[000132] A "variant" of a polynucleotide refers to a polynucleotide comprising a nucleotide sequence that is at least about 70-99.9% (*e.g.*, at least about 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or 99.9%) identical to a referenced nucleotide sequence that is set forth herein (*e.g.*, SEQ ID NO: 1, 9, 17, 19, 21, 29, 37, 39, 41, 49, 57, or 59); when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences (*e.g.*, expect threshold: 10; word size: 28; max matches in a query range: 0; match/mismatch scores: 1, -2; gap costs: linear).

[000133] Anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof of the present invention, in an embodiment of the invention, include a heavy chain immunoglobulin variable region having at least 70% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) amino acid sequence identity to the HCVR amino acid sequences set forth in Table 4; and/or a light chain immunoglobulin variable region having at least 70% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) amino acid sequence identity to the LCVR amino acid sequences set forth in Table 4.

[000134] In addition, a variant anti-CoV-S antigen-binding protein may include a polypeptide comprising an amino acid sequence that is set forth herein except for one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) mutations such as, for example, missense mutations (*e.g.*, conservative substitutions), non-sense mutations, deletions, or insertions. For example, the present invention includes antigen-binding proteins which include an immunoglobulin light chain variant comprising an LCVR amino acid sequence set forth in Table 4 but having one or more of such

mutations and/or an immunoglobulin heavy chain variant comprising an HCVR amino acid sequence set forth in Table 4 but having one or more of such mutations. In an embodiment of the invention, a variant anti-CoV-S antigen-binding protein includes an immunoglobulin light chain variant comprising LCDR1, LCDR2 and LCDR3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions) and/or an immunoglobulin heavy chain variant comprising HCDR1, HCDR2 and HCDR3 wherein one or more (*e.g.*, 1 or 2 or 3) of such CDRs has one or more of such mutations (*e.g.*, conservative substitutions). Substitutions can be in a CDR, framework, or constant region.

[000135] The invention further provides variant anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof, comprising one or more variant CDRs (*e.g.*, any one or more of LCDR1, LCDR2, LCDR3, HCDR1, HCDR2 and/or HCDR3) that are set forth herein with at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% sequence identity or similarity to, *e.g.*, the heavy chain and light chain CDRs of Table 4.

[000136] Embodiments of the present invention also include variant antigen-binding proteins, *e.g.*, anti-CoV-S antibodies and antigen-binding fragments thereof, that comprise immunoglobulin V_Hs and V_Ls; or HCs and LCs, which comprise an amino acid sequence having 70% or more (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater) overall amino acid sequence identity or similarity to the amino acid sequences of the corresponding V_Hs, V_Ls, HCs or LCs specifically set forth herein, but wherein the LCDR1, LCDR2, LCDR3, HCDR1, HCDR2 and HCDR3 of such immunoglobulins are not variants and comprise CDR amino acid sequence set forth in Table 4. Thus, in such embodiments, the CDRs within variant antigen-binding proteins are not, themselves, variants.

[000137] Conservatively modified variant anti-CoV-S antibodies and antigen-binding fragments thereof are also part of the present invention. A "conservatively modified variant" or a "conservative substitution" refers to a variant wherein there is one or more substitutions of amino acids in a polypeptide with other amino acids having similar characteristics (*e.g.* charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.). Such changes can frequently be made without significantly disrupting the biological activity of the antibody or fragment. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological

activity (see, *e.g.*, Watson *et al.* (1987) Molecular Biology of the Gene, The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to significantly disrupt biological activity.

[000138] Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443 45.

[000139] Function-conservative variants of the anti-CoV-S antibodies and antigen-binding fragments thereof are also part of the present invention. Any of the variants of the anti-CoV-S antibodies and antigen-binding fragments thereof (as discussed herein) may be "function-conservative variants". Such function-conservative variants may, in some cases, also be characterized as conservatively modified variants. "Function-conservative variants," as used herein, refers to variants of the anti-CoV-S antibodies or antigen-binding fragments thereof in which one or more amino acid residues have been changed without significantly altering one or more functional properties of the antibody or fragment. In an embodiment of the invention, a function-conservative variant anti-CoV-S antibody or antigen-binding fragment thereof of the present invention comprises a variant amino acid sequence and exhibits one or more of the following functional properties:

- Inhibits growth of coronavirus (*e.g.*, SARS-CoV-2, SARS-CoV, and/or MERS-CoV) in ACE2- and/or TMPRSS2-expressing cells (*e.g.*, Calu-3 cells);
- Does not significantly bind to MDCK/Tet-on cells which do not express ACE2 and/or TMPRSS2;
- Limits spread of coronavirus infection (*e.g.*, by SARS-CoV-2, SARS-CoV, and/or MERS-CoV) of cells, *e.g.*, Calu-3, *in vitro*; and/or

- Protects a mouse engineered to express the human TMPRSS2 and/or ACE2 protein from death caused by coronavirus infection (*e.g.*, SARS-CoV-2, SARS-CoV, or MERS-CoV), for example, wherein the mice are infected with an otherwise lethal dose of the virus, optionally when combined with a second therapeutic agent.
- Protects a mouse engineered to express the human TMPRSS2 and/or ACE2 protein from weight loss caused by coronavirus infection (*e.g.*, SARS-CoV-2, SARS-CoV, or MERS-CoV), for example, wherein the mice are infected with a dose of the virus that would otherwise cause weighht loss, optionally when combined with a second therapeutic agent.

[000140] A "neutralizing" or "antagonist" anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, refers to a molecule that inhibits an activity of CoV-S to any detectable degree, *e.g.*, inhibits the ability of CoV-S to bind to a receptor such as ACE2, to be cleaved by a protease such as TMPRSS2, or to mediate viral entry into a host cell or viral reproduction in a host cell.

[000141] Table 4 refers to antigen-binding proteins, such as antibodies and antigen-binding fragments thereof, that comprise the heavy chain or V_H (or a variant thereof) and light chain or V_L (or a variant thereof) as set forth below; or that comprise a V_H that comprises the CDRs thereof (HCDR1 (or a variant thereof), HCDR2 (or a variant thereof) and HCDR3 (or a variant thereof)) and a V_L that comprises the CDRs thereof (LCDR1 (or a variant thereof), LCDR2 (or a variant thereof) and LCDR3 (or a variant thereof)), *e.g.*, wherein the immunoglobulin chains, variable regions and/or CDRs comprise the specific amino acid sequences described below.

[000142] The antibodies described herein also include embodiments wherein the V_H is fused to a wild-type IgG4 (*e.g.*, wherein residue 108 is S) or to IgG4 variants (*e.g.*, wherein residue 108 is P).

[000143] Antibodies and antigen-binding fragments of the present invention comprise immunoglobulin chains including the amino acid sequences set forth herein as well as cellular and *in vitro* post-translational modifications to the antibody. For example, the present invention includes antibodies and antigen-binding fragments thereof that specifically bind to CoV-S comprising heavy and/or light chain amino acid sequences set forth herein (*e.g.*, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and/or LCDR3) as well as antibodies and fragments wherein one or more amino acid residues is glycosylated, one or more Asn residues is deamidated, one or

more residues (*e.g.*, Met, Trp and/or His) is oxidized, the N-terminal Gln is pyroglutamate (pyroE) and/or the C-terminal Lysine is missing. The amino acid and nucleotide sequences of exemplary anti-SARS-CoV-2-Spike protein (SARS-CoV-2-S) antibodies are shown in the Table of Exemplary Sequences (Table 1), below.

Table 1: Table of Exemplary Sequences

Antibody Designation	Component Part	Sequence	SEQ ID NO
mAb14256		**Amino Acids**	
	HCVR	QVQLQESGPGLVKPSETLSLTCTVSGGSISSHYW SWIRQPPGKGLEWIGYIYYSGSSNYNPSLKSRVT ISVDTSKNQFSLKLNSVTAADTAVYYCARHYDIL TGFDWFDPWGQGTLVTVSS	887
	HCDR1	GGSISSHY	889
	HCDR2	IYYSGSS	891
	HCDR3	ARHYDILTGFDWFDP	893
	LCVR	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGTHYD VHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSK SGTSASLAITGLQAEDEADYYCQSFDNSLTAPYV FGTGTKVTVL	895
	LCDR1	SSNIGTHYD	897
	LCDR2	GNS	164
	LCDR3	QSFDNSLTAPYV	899
	HC	QVQLQESGPGLVKPSETLSLTCTVSGGSISSHYW SWIRQPPGKGLEWIGYIYYSGSSNYNPSLKSRVT ISVDTSKNQFSLKLNSVTAADTAVYYCARHYDIL TGFDWFDPWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	901
	LC	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGTHYD VHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSK	903

		SGTSASLAITGLQAEDEADYYCQSFDNSLTAPYV FGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTP SKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS	
	Nucleic Acids		
	HCVR	caggtgcagctgcaggagtcgggcccaggactgg tgaagccttcggagaccctgtccctcacctgcac tgtctctggtggctccatcagtagtcactactgg agctggatccggcagcccccagggaagggactgg aatggattgggtatatttattacagcgggagctc caactacaaccctccctcaagagtcgagtcacc atatcagtagacacgtccaagaaccagttctccc tgaaactgaattctgtgaccgccgcagacacggc cgtgtattactgtgcgagacattacgatattttg actggttttgactggttcgacccctggggccagg gaaccctggtcaccgtctcctca	886
	HCDR1	ggtggctccatcagtagtcactac	888
	HCDR2	atttattacagcgggagctcc	890
	HCDR3	gcgagacattacgatattttgactggttttgact ggttcgacccc	892
	LCVR	cagtctgtgctgacgcagccgccctcagtgtcag gggccccagggcagagggtcaccatctcctgcac tgggagcagttccaacatcgggacacattatgat gtacactggtaccaacaacttccaggaacagccc ccaaactcctcatctatggtaacagcaatcggcc ctcaggggtccctgaccgattctctggctccaag tctggcacctcagcctccctggccatcactgggc tccaggctgaggatgaggctgattattactgcca gtcctttgacaacagcctgactgcccttatgtc ttcggaactgggaccaaggtcaccgtccta	894
	LCDR1	agttccaacatcgggacacattatgat	896
	LCDR2	ggtaacagc	163
	LCDR3	cagtcctttgacaacagcctgactgcccttatg tc	898
	HC	caggtgcagctgcaggagtcgggcccaggactgg tgaagccttcggagaccctgtccctcacctgcac tgtctctggtggctccatcagtagtcactactgg agctggatccggcagcccccagggaagggactgg aatggattgggtatatttattacagcgggagctc caactacaaccctccctcaagagtcgagtcacc atatcagtagacacgtccaagaaccagttctccc tgaaactgaattctgtgaccgccgcagacacggc cgtgtattactgtgcgagacattacgatattttg	900

		actggttttgactggttcgacccctggggccagg gaaccctggtcaccgtctcctcagcctccaccaa gggcccatcggtcttccccctggcaccctcctcc aagagcacctctgggggcacagcggccctgggct gcctggtcaaggactacttccccgaaccggtgac ggtgtcgtggaactcaggcgccctgaccagcggc gtgcacaccttcccggctgtcctacagtcctcag gactctactccctcagcagcgtggtgaccgtgcc ctccagcagcttgggcacccagacctacatctgc aacgtgaatcacaagcccagcaacaccaaggtgg acaagaaagttgagcccaaatcttgtgacaaaac tcacacatgcccaccgtgcccagcacctgaactc ctgggggggaccgtcagtcttcctcttcccccaa aacccaaggacaccctcatgatctcccggacccc tgaggtcacatgcgtggtggtggacgtgagccac gaagaccctgaggtcaagttcaactggtacgtgg acggcgtggaggtgcataatgccaagacaaagcc gcgggaggagcagtacaacagcacgtaccgtgtg gtcagcgtcctcaccgtcctgcaccaggactggc tgaatggcaaggagtacaagtgcaaggtctccaa caaagccctcccagcccccatcgagaaaaccatc tccaaagccaaagggcagccccgagaaccacagg tgtacaccctgcccccatcccgggatgagctgac caagaaccaggtcagcctgacctgcctggtcaaa ggcttctatcccagcgacatcgccgtggagtggg agagcaatgggcagccggagaacaactacaagac cacgcctcccgtgctggactccgacggctccttc ttcctctacagcaagctcaccgtggacaagagca ggtggcagcaggggaacgtcttctcatgctccgt gatgcatgaggctctgcacaaccactacacgcag aagtccctctccctgtctccgggtaaatga	
	LC	cagtctgtgctgacgcagccgccctcagtgtcag gggccccagggcagagggtcaccatctcctgcac tgggagcagttccaacatcgggacacattatgat gtacactggtaccaacaacttccaggaacagccc ccaaactcctcatctatggtaacagcaatcggcc ctcaggggtccctgaccgattctctggctccaag tctggcacctcagcctccctggccatcactgggc tccaggctgaggatgaggctgattattactgcca gtcctttgacaacagcctgactgccccttatgtc ttcggaactgggaccaaggtcaccgtcctaggcc agcccaaggccgccccctccgtgaccctgttccc cccctcctccgaggagctgcaggccaacaaggcc accctggtgtgcctgatctccgacttctaccccg gcgccgtgaccgtggcctggaaggccgactcctc ccccgtgaaggccggcgtggagaccaccacccc tccaagcagtccaacaacaagtacgccgcctcct	902

		cctacctgtccctgacccccgagcagtggaagtc ccaccggtcctactcctgccaggtgacccacgag ggctccaccgtggagaagaccgtggcccccaccg agtgctcctga	
mAb14315	**Amino Acids**		
	HCVR	QVQLVQSGAEVKKPGSSVKVSCKASGDTFSTYAI NWVRQAPGQGLEWMGRFIHIFGTANYAQKFQGRV TITADESTSTAYMELRSLRSEDTAVYYCARDGVD YGDYRPDYWGQGTLVTVSS	212
	HCDR1	GDTFSTYA	214
	HCDR2	FIHIFGTA	216
	HCDR3	ARDGVDYGDYRPDY	218
	LCVR	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYL AWYQQKPGQAPRLLIYGASSRATGIPERFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSLYTFGQG TKLEIK	220
	LCDR1	QSVSSNY	222
	LCDR2	GAS	126
	LCDR3	QQYGSSLYT	224
	HC	QVQLVQSGAEVKKPGSSVKVSCKASGDTFSTYAI NWVRQAPGQGLEWMGRFIHIFGTANYAQKFQGRV TITADESTSTAYMELRSLRSEDTAVYYCARDGVD YGDYRPDYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	226
	LC	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYL AWYQQKPGQAPRLLIYGASSRATGIPERFSGSGS GTDFTLTISRLEPEDFAVYYCQQYGSSLYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	228
	Nucleic Acids		

	HCVR	caggtgcagctggtgcagtctggggctgaggtga agaagcctgggtcctcggtgaaggtctcctgcaa ggcttctggagacaccttcagcacctatgctatc aactgggtgcgacaggcccctggacaagggcttg agtggatgggaagattcatccatatctttggtac agcaaactacgcacagaagttccagggcagagtc accattaccgcggacgaatccacgagcacagcct acatggagctgcgcagcctgagatctgaggacac ggccgtttattactgcgcgagagacggagtagac tacggtgactaccgacctgactactggggccagg gaaccctggtcaccgtctcctca	211
	HCDR1	ggagacaccttcagcacctatgct	213
	HCDR2	ttcatccatatctttggtacagca	215
	HCDR3	gcgagagacggagtagactacggtgactaccgac ctgactac	217
	LCVR	gaaattgtgttgacgcagtctccaggcaccctgt ctttgtctccaggggaaagagccaccctctcctg cagggccagtcagagtgttagtagcaactactta gcctggtaccagcagaaacctggccaggctccca gactcctcatctatggtgcatccagcagggccac tggcatcccagagaggttcagtggcagtgggtct gggacagacttcactctcaccatcagcagactgg agcctgaagattttgcagtatattactgtcagca gtatggtagctcgctgtacacttttggccagggg accaagctggagatcaaa	219
	LCDR1	cagagtgttagtagcaactac	221
	LCDR2	ggtgcatcc	125
	LCDR3	cagcagtatggtagctcgctgtacact	223
	HC	caggtgcagctggtgcagtctggggctgaggtga agaagcctgggtcctcggtgaaggtctcctgcaa ggcttctggagacaccttcagcacctatgctatc aactgggtgcgacaggcccctggacaagggcttg agtggatgggaagattcatccatatctttggtac agcaaactacgcacagaagttccagggcagagtc accattaccgcggacgaatccacgagcacagcct acatggagctgcgcagcctgagatctgaggacac ggccgtttattactgcgcgagagacggagtagac tacggtgactaccgacctgactactggggccagg gaaccctggtcaccgtctcctcagcctccaccaa gggcccatcggtcttcccctggcaccctcctcc aagagcacctctgggggcacagcggccctgggct gcctggtcaaggactacttccccgaaccggtgac ggtgtcgtggaactcaggcgccctgaccagcggc gtgcacaccttcccggctgtcctacagtcctcag	225

		gactctactccctcagcagcgtggtgaccgtgcc ctccagcagcttgggcacccagacctacatctgc aacgtgaatcacaagcccagcaacaccaaggtgg acaagaaagttgagcccaaatcttgtgacaaaac tcacacatgcccaccgtgcccagcacctgaactc ctgggggaccgtcagtcttcctcttcccccaa aacccaaggacaccctcatgatctcccggacccc tgaggtcacatgcgtggtggtggacgtgagccac gaagaccctgaggtcaagttcaactggtacgtgg acggcgtggaggtgcataatgccaagacaaagcc gcgggaggagcagtacaacagcacgtaccgtgtg gtcagcgtcctcaccgtcctgcaccaggactggc tgaatggcaaggagtacaagtgcaaggtctccaa caaagccctcccagcccccatcgagaaaaccatc tccaaagccaaagggcagccccgagaaccacagg tgtacaccctgcccccatcccgggatgagctgac caagaaccaggtcagcctgacctgcctggtcaaa ggcttctatcccagcgacatcgccgtggagtggg agagcaatgggcagccggagaacaactacaagac cacgcctcccgtgctggactccgacggctccttc ttcctctacagcaagctcaccgtggacaagagca ggtggcagcaggggaacgtcttctcatgctccgt gatgcatgaggctctgcacaaccactacacgcag aagtccctctccctgtctccgggtaaatga	
	LC	gaaattgtgttgacgcagtctccaggcaccctgt ctttgtctccaggggaaagagccacctctcctg cagggccagtcagagtgttagtagcaactactta gcctggtaccagcagaaacctggccaggctccca gactcctcatctatggtgcatccagcagggccac tggcatcccagagaggttcagtggcagtgggtct gggacagacttcactctcaccatcagcagactgg agcctgaagattttgcagtatattactgtcagca gtatggtagctcgctgtacacttttggccagggg accaagctggagatcaaacgaactgtggctgcac catctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctg ctgaataacttctatcccagagaggccaaagtac agtggaaggtggataacgccctccaatcgggtaa ctcccaggagagtgtcacagagcaggacagcaag gacagcacctacagcctcagcagcaccctgacgc tgagcaaagcagactacgagaaacacaaagtcta cgcctgcgaagtcacccatcagggcctgagctcg cccgtcacaaagagcttcaacaggggagagtgtt ag	227
mAb15151	**Amino Acids**		

	HCVR	QVQLVESGGGVVQPGRSLRLSCAASGFVFNSYGM HWVRQAPGKGLEWVAVLWYEGSKNYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCARHGSG SFFGYYLDYWGQGTLVTVSS	270
	HCDR1	GFVFNSYG	272
	HCDR2	LWYEGSKN	274
	HCDR3	ARHGSGSFFGYYLDY	276
	LCVR	DIQMTQSPSSLSASVGDRVTITCRASHNINDFLN WYQQKPGKAPRLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQESYTTPPTFGQGT KLEIK	278
	LCDR1	HNINDF	280
	LCDR2	AAS	106
	LCDR3	QESYTTPPT	282
	HC	QVQLVESGGGVVQPGRSLRLSCAASGFVFNSYGM HWVRQAPGKGLEWVAVLWYEGSKNYYADSVKGRF TISRDNSKNTLYLQMNSLRAEDTAVYYCARHGSG SFFGYYLDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK	284
	LC	DIQMTQSPSSLSASVGDRVTITCRASHNINDFLN WYQQKPGKAPRLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQESYTTPPTFGQGT KLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	286
	Nucleic Acids		
	HCVR	caggtgcagctggtggagtctgggggaggcgtgg tccagcctgggaggtccctgagactctcctgtgc agcgtctggtttcgtcttcaatagctatggcatg cactgggtccgccaggctccaggcaaggggctgg agtgggtggcagttctatggtatgaaggaagtaa aaattactatgcagactccgtgaagggccgattc accatctccagagacaattccaagaacacactgt	269

		atctgcaaatgaacagcctgagagccgaggacac ggctgtgtattactgtgcgaggcatggttcaggg agtttttttgggtactacttggactactggggcc agggaaccctggtcaccgtctcctca	
	HCDR1	ggtttcgtcttcaatagctatggc	271
	HCDR2	ctatggtatgaaggaagtaaaaat	273
	HCDR3	gcgaggcatggttcagggagtttttttgggtact acttggactac	275
	LCVR	gacatccagatgacccagtctccatcctccctgt ctgcatctgtaggagacagagtcaccatcacttg ccgggcaagtcacaacattaatgacttttttaaat tggtatcagcagaaaccagggaaagcccctaggc tcctgatctatgctgcatccagtttgcaaagtgg ggtcccatcaaggttcagtggcagtggatctggg acagatttcactctcaccatcagcagtctacaac ctgaagattttgcaacttactactgtcaagagag ttacactacccctccgacttttggccaggggacc aagctggagatcaaa	277
	LCDR1	cacaacattaatgacttt	279
	LCDR2	gctgcatcc	105
	LCDR3	caagagagttacactacccctccgact	281
	HC	caggtgcagctggtggagtctgggggaggcgtgg tccagcctgggaggtccctgagactctcctgtgc agcgtctggtttcgtcttcaatagctatggcatg cactgggtccgccaggctccaggcaaggggctgg agtgggtggcagttctatggtatgaaggaagtaa aaattactatgcagactccgtgaagggccgattc accatctccagagacaattccaagaacacactgt atctgcaaatgaacagcctgagagccgaggacac ggctgtgtattactgtgcgaggcatggttcaggg agtttttttgggtactacttggactactggggcc agggaaccctggtcaccgtctcctcagcctccac caagggcccatcggtcttccccctggcaccctcc tccaagagcacctctgggggcacagcggccctgg gctgcctggtcaaggactacttccccgaaccggt gacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcct caggactctactccctcagcagcgtggtgaccgt gccctccagcagcttgggcacccagacctacatc tgcaacgtgaatcacaagcccagcaacaccaagg tggacaagaaagttgagcccaaatcttgtgacaa aactcacacatgcccaccgtgcccagcacctgaa ctcctgggggggaccgtcagtcttcctcttccccc caaaacccaaggacaccctcatgatctcccggac	283

		ccctgaggtcacatgcgtggtggtggacgtgagc cacgaagaccctgaggtcaagttcaactggtacg tggacggcgtggaggtgcataatgccaagacaaa gccgcgggaggagcagtacaacagcacgtaccgt gtggtcagcgtcctcaccgtcctgcaccaggact ggctgaatggcaaggagtacaagtgcaaggtctc caacaaagccctcccagcccccatcgagaaaacc atctccaaagccaaagggcagccccgagaaccac aggtgtacaccctgcccccatcccgggatgagct gaccaagaaccaggtcagcctgacctgcctggtc aaaggcttctatcccagcgacatcgccgtggagt gggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctcc ttcttcctctacagcaagctcaccgtggacaaga gcaggtggcagcaggggaacgtcttctcatgctc cgtgatgcatgaggctctgcacaaccactacacg cagaagtccctctccctgtctccgggtaaatga	
	LC	gacatccagatgacccagtctccatcctccctgt ctgcatctgtaggagacagagtcaccatcacttg ccgggcaagtcacaacattaatgacttttaaat tggtatcagcagaaaccagggaaagcccctaggc tcctgatctatgctgcatccagtttgcaaagtgg ggtcccatcaaggttcagtggcagtggatctggg acagatttcactctcaccatcagcagtctacaac ctgaagattttgcaacttactactgtcaagagag ttacactacccctccgacttttggccaggggacc aagctggagatcaaacgaactgtggctgcaccat ctgtcttcatcttcccgccatctgatgagcagtt gaaatctggaactgcctctgttgtgtgcctgctg aataacttctatcccagaggccaaagtacagt ggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggac agcacctacagcctcagcagcaccctgacgctga gcaaagcagactacgagaaacacaaagtctacgc ctgcgaagtcacccatcagggcctgagctcgccc gtcacaaagagcttcaacaggggagagtgttag	285
mAb14284	**Amino Acids**		
	HCVR	QITLKESGPTLVKPTQTLTLTCTFSGFSFSTSGV GVGWIRQPPGKTLEWLALIYWDDDKRYSPSLKSR LTITKDTSKNQVVLTMTNMDPVDTATYFCAHHGI PTIFGYWGQGALVTVSS	493
	HCDR1	GFSFSTSGVG	495
	HCDR2	IYWDDDK	497
	HCDR3	AHHGIPTIFGY	499

	LCVR	QSALTQPASVSGSPGQSITISCTGTSSDLGVFNY VSWYQQHPGKAPKLMIYEVTNRPSGVSNRFSGSK SGNTASLTISGLQAEDEADYYCSSYTTSSTVFGG GTKLTVL	501
	LCDR1	SSDLGVFNY	503
	LCDR2	EVT	505
	LCDR3	SSYTTSSTV	507
	HC	QITLKESGPTLVKPTQTLTLTCTFSGFSFSTSGV GVGWIRQPPGKTLEWLALIYWDDDKRYSPSLKSR LTITKDTSKNQVVLTMTNMDPVDTATYFCAHHGI PTIFGYWGQGALVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	509
	LC	QSALTQPASVSGSPGQSITISCTGTSSDLGVFNY VSWYQQHPGKAPKLMIYEVTNRPSGVSNRFSGSK SGNTASLTISGLQAEDEADYYCSSYTTSSTVFGG GTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV CLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQ SNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS	511
	Nucleic Acids		
	HCVR	cagatcaccttgaaggagtctggtcctacgctgg tgaaacccacacagaccctcacgctgacctgcac cttctctgggttctcatttagcacttctggagtg ggtgtgggctggatccgtcagccccaggaaaga ccctggagtggcttgcactcatttattgggatga tgataagcgctacagcccatctctgaagagcagg ctcaccattaccaaggacacctccaaaaaccagg tggtccttacaatgaccaacatggaccctgtgga cactgccacatatttctgtgcacaccatggaata cctacgatctttggctactggggccagggagccc tggtcaccgtctcctca	492
	HCDR1	gggttctcatttagcacttctggagtgggt	494
	HCDR2	atttattgggatgatgataag	496
	HCDR3	gcacaccatggaatacctacgatctttggctac	498

	LCVR	cagtctgccctgactcagcctgcctccgtgtctg ggtctcctggacagtcgatcaccatctcctgcac tggaaccagcagtgaccttggtgttttaactat gtctcctggtaccaacagcacccaggcaaagccc ccaaactcatgatttatgaggtcactaatcggcc ctcaggggtttctaatcgcttctctggctccaag tctggcaacacggcctccctgaccatctctgggc tccaggctgaggacgaggctgattattattgcag ctcatatacaaccagcagcactgttttcggcgga gggaccaagctgaccgtccta	500
	LCDR1	agcagtgaccttggtgttttaactat	502
	LCDR2	gaggtcact	504
	LCDR3	agctcatatacaaccagcagcactgtt	506
	HC	cagatcaccttgaaggagtctggtcctacgctgg tgaaacccacacagaccctcacgctgacctgcac cttctctgggttctcatttagcacttctggagtg ggtgtgggctggatccgtcagccccaggaaaga ccctggagtggcttgcactcatttattgggatga tgataagcgctacagcccatctctgaagagcagg ctcaccattaccaaggacacctccaaaaaccagg tggtccttacaatgaccaacatggaccctgtgga cactgccacatatttctgtgcacaccatggaata cctacgatctttggctactggggccagggagccc tggtcaccgtctcctcagcctccaccaagggccc atcggtcttcccctggcaccctcctccaagagc acctctgggggcacagcggccctgggctgcctgg tcaaggactacttccccgaaccggtgacggtgtc gtggaactcaggcgccctgaccagcggcgtgcac accttcccggctgtcctacagtcctcaggactct actccctcagcagcgtggtgaccgtgccctccag cagcttgggcacccagacctacatctgcaacgtg aatcacaagcccagcaacaccaaggtggacaaga aagttgagcccaaatcttgtgacaaaactcacac atgcccaccgtgcccagcacctgaactcctgggg ggaccgtcagtcttcctcttcccccaaaaccca aggacaccctcatgatctcccggaccccctgaggt cacatgcgtggtggtggacgtgagccacgaagac cctgaggtcaagttcaactggtacgtggacggcg tggaggtgcataatgccaagacaaagccgcggga ggagcagtacaacagcacgtaccgtgtggtcagc gtcctcaccgtcctgcaccaggactggctgaatg gcaaggagtacaagtgcaaggtctccaacaaagc cctcccagcccccatcgagaaaaccatctccaaa gccaaagggcagccccgagaaccacaggtgtaca ccctgcccccatcccgggatgagctgaccaagaa	508

		ccaggtcagcctgacctgcctggtcaaaggcttc tatcccagcgacatcgccgtggagtgggagagca atgggcagccggagaacaactacaagaccacgcc tcccgtgctggactccgacggctccttcttcctc tacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgca tgaggctctgcacaaccactacacgcagaagtcc ctctccctgtctccgggtaaatga	
	LC	cagtctgccctgactcagcctgcctccgtgtctg ggtctcctggacagtcgatcaccatctcctgcac tggaaccagcagtgaccttggtgtttttaactat gtctcctggtaccaacagcacccaggcaaagccc ccaaactcatgatttatgaggtcactaatcggcc ctcaggggtttctaatcgcttctctggctccaag tctggcaacacggcctccctgaccatctctgggc tccaggctgaggacgaggctgattattattgcag ctcatatacaaccagcagcactgttttcggcgga gggaccaagctgaccgtcctaggccagcccaagg ccgccccctccgtgaccctgttcccccctcctc cgaggagctgcaggccaacaaggccaccctggtg tgcctgatctccgacttctaccccggcgccgtga ccgtggcctggaaggccgactcctcccccgtgaa ggccggcgtggagaccaccacccccctccaagcag tccaacaacaagtacgccgcctcctcctacctgt ccctgacccccgagcagtggaagtcccaccggtc ctactcctgccaggtgacccacgagggctccacc gtggagaagaccgtggcccccaccgagtgctcct ga	510
mAb15160	**Amino Acids**		
	HCVR	EVQLVESGGGLVQPGGSLRLSCSASGFTFSRYAM YWVRQAPGKGLEYVSAISSDGGSTYDADSVKGRF TISRANSKNTLYLQMSSLRAEDTAVYYCVKGLRE LLYYYYGMDVWGQGTTVTVSS	362
	HCDR1	GFTFSRYA	364
	HCDR2	ISSDGGST	366
	HCDR3	VKGLRELLYYYYGMDV	368
	LCVR	DIQMTQSPSSLSASVGDRVTITCRAGQSISSFLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYITPFTFGPGT KVDIK	370
	LCDR1	QSISSF	372
	LCDR2	AAS	106
	LCDR3	QQSYITPFT	374

	HC	EVQLVESGGGLVQPGGSLRLSCSASGFTFSRYAM YWVRQAPGKGLEYVSAISSDGGSTYDADSVKGRF TISRANSKNTLYLQMSSLRAEDTAVYYCVKGLRE LLYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK	376
	LC	DIQMTQSPSSLSASVGDRVTITCRAGQSISSFLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYITPFTFGPGT KVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	378
	Nucleic Acids		
	HCVR	gaggtgcagctggtggagtctgggggaggcttgg tccagcctgggggtccctgagactctcctgttc agcctctggattcaccttcagtaggtacgctatg tactgggtccgccaggctccagggaagggactgg aatatgtttcagctattagtagtgatgggggtag cacatacgacgcagactccgtgaagggcagattc accatctccagagccaattccaagaacacgctgt accttcaaatgagcagtctgagagctgaggacac ggctgtgtattattgtgtgaaaggtctgcgggag ttactctactactattacggaatggacgtctggg gccaagggactacggtcaccgtctcctca	361
	HCDR1	ggattcaccttcagtaggtacgct	363
	HCDR2	attagtagtgatgggggtagcaca	365
	HCDR3	gtgaaaggtctgcgggagttactctactactatt acggaatggacgtc	367
	LCVR	gacatccagatgacccagtctccatcctccctgt ctgcatctgtaggagacagagtcaccatcacttg ccgggcaggtcagagcattagcagcttttaaat tggtatcagcagaagccagggaaagccccctaagc tcctgatctatgctgcatccagtttgcaaagtgg ggtcccatcaaggttcagtggcagtggatctggg acagatttcactctcaccatcagcagtctccaac ctgaagattttgcaacttactactgtcaacagag	369

		ttacattacccccttcactttcggccctgggacc aaggtggatatcaaa	
	LCDR1	cagagcattagcagcttt	371
	LCDR2	gctgcatcc	105
	LCDR3	caacagagttacattacccccttcact	373
	HC	gaggtgcagctggtggagtctgggggaggcttgg tccagcctgggggtccctgagactctcctgttc agcctctggattcaccttcagtaggtacgctatg tactgggtccgccaggctccagggaagggactgg aatatgtttcagctattagtagtgatgggggtag cacatacgacgcagactccgtgaagggcagattc accatctccagagccaattccaagaacacgctgt accttcaaatgagcagtctgagagctgaggacac ggctgtgtattattgtgtgaaaggtctgcgggag ttactctactactattacggaatggacgtctggg gccaagggactacggtcaccgtctcctcagcctc caccaagggcccatcggtcttccccctggcaccc tcctccaagagcacctctgggggcacagcggccc tgggctgcctggtcaaggactacttccccgaacc ggtgacggtgtcgtggaactcaggcgccctgacc agcggcgtgcacaccttcccggctgtcctacagt cctcaggactctactccctcagcagcgtggtgac cgtgccctccagcagcttgggcacccagacctac atctgcaacgtgaatcacaagcccagcaacacca aggtggacaagaaagttgagcccaaatcttgtga caaaactcacacatgcccaccgtgcccagcacct gaactcctgggggggaccgtcagtcttcctcttcc ccccaaaacccaaggacaccctcatgatctcccg gacccctgaggtcacatgcgtggtggtggacgtg agccacgaagaccctgaggtcaagttcaactggt acgtggacggcgtggaggtgcataatgccaagac aaagccgcgggaggagcagtacaacagcacgtac cgtgtggtcagcgtcctcaccgtcctgcaccagg actggctgaatggcaaggagtacaagtgcaaggt ctccaacaaagccctcccagcccccatcgagaaa accatctccaaagccaaagggcagccccgagaac cacaggtgtacaccctgcccccatcccgggatga gctgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtgg agtgggagagcaatgggcagccggagaacaacta caagaccacgcctcccgtgctggactccgacggc tccttcttcctctacagcaagctcaccgtggaca agagcaggtggcagcaggggaacgtcttctcatg ctccgtgatgcatgaggctctgcacaaccactac	375

		acgcagaagtccctctccctgtctccgggtaaat ga	
	LC	gacatccagatgacccagtctccatcctccctgt ctgcatctgtaggagacagagtcaccatcacttg ccgggcaggtcagagcattagcagcttttaaat tggtatcagcagaagccagggaaagcccctaagc tcctgatctatgctgcatccagtttgcaaagtgg ggtcccatcaaggttcagtggcagtggatctggg acagatttcactctcaccatcagcagtctccaac ctgaagattttgcaacttactactgtcaacagag ttacattacccccttcactttcggccctgggacc aaggtggatatcaaacgaactgtggctgcaccat ctgtcttcatcttcccgccatctgatgagcagtt gaaatctggaactgcctctgttgtgtgcctgctg aataacttctatcccagagaggccaaagtacagt ggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggac agcacctacagcctcagcagcaccctgacgctga gcaaagcagactacgagaaacacaaagtctacgc ctgcgaagtcacccatcagggcctgagctcgccc gtcacaaagagcttcaacaggggagagtgttag	377

Administration of Antibodies

[000144] The present invention provides methods for administering an anti-CoV-S antigen-binding protein of the present invention, *e.g.*, those of Table 4, comprising introducing the antigen-binding protein into the body of a subject (*e.g.*, a human). For example, the method comprises piercing the body of the subject with a needle of a syringe and injecting the antigen-binding protein into the body of the subject, *e.g.*, into the vein, artery, tumor, muscular tissue or subcutis of the subject.

[000145] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising an anti-CoV-S antigen-binding protein of the present invention, *e.g.*, those of Table 4.

[000146] The present invention also provides an injection device comprising one or more antigen-binding proteins (*e.g.,* antibody or antigen-binding fragment) that bind specifically to CoV-S, *e.g.*, those of Table 4, or a pharmaceutical composition thereof. The injection device may be packaged into a kit. An injection device is a device that introduces a substance into the body of a subject via a parenteral route, *e.g.*, intramuscular, subcutaneous or intravenous. For

example, an injection device may be a syringe (*e.g.*, pre-filled with the pharmaceutical composition, such as an auto-injector) which, for example, includes a cylinder or barrel for holding fluid to be injected (*e.g.*, comprising the antibody or fragment or a pharmaceutical composition thereof), a needle for piecing skin and/or blood vessels for injection of the fluid; and a plunger for pushing the fluid out of the cylinder and through the needle bore. In an embodiment of the invention, an injection device that comprises an antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment thereof, from a combination of the present invention, or a pharmaceutical composition thereof is an intravenous (IV) injection device. Such a device can include the antigen-binding protein or a pharmaceutical composition thereof in a cannula or trocar/needle which may be attached to a tube which may be attached to a bag or reservoir for holding fluid (*e.g.*, saline) introduced into the body of the subject through the cannula or trocar/needle. The antibody or fragment or a pharmaceutical composition thereof may, in an embodiment of the invention, be introduced into the device once the trocar and cannula are inserted into the vein of a subject and the trocar is removed from the inserted cannula. The IV device may, for example, be inserted into a peripheral vein (*e.g.*, in the hand or arm); the superior *vena cava* or inferior *vena cava*, or within the right atrium of the heart (*e.g.*, a central IV); or into a subclavian, internal jugular, or a femoral vein and, for example, advanced toward the heart until it reaches the superior vena cava or right atrium (*e.g.*, a central venous line). In an embodiment of the invention, an injection device is an autoinjector; a jet injector or an external infusion pump. A jet injector uses a high-pressure narrow jet of liquid which penetrate the epidermis to introduce the antibody or fragment or a pharmaceutical composition thereof to a subject's body. External infusion pumps are medical devices that deliver the antibody or fragment or a pharmaceutical composition thereof into a subject's body in controlled amounts. External infusion pumps may be powered electrically or mechanically. Different pumps operate in different ways, for example, a syringe pump holds fluid in the reservoir of a syringe, and a moveable piston controls fluid delivery, an elastomeric pump holds fluid in a stretchable balloon reservoir, and pressure from the elastic walls of the balloon drives fluid delivery. In a peristaltic pump, a set of rollers pinches down on a length of flexible tubing, pushing fluid forward. In a multi-channel pump, fluids can be delivered from multiple reservoirs at multiple rates.

Preparation of Human Antibodies

[000147] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to CoV-S. An immunogen comprising any one of the following can be used to generate antibodies to CoV-S. In certain embodiments of the invention, the antibodies of the invention are obtained from mice immunized with a full length, native CoV-S, or with a live attenuated or inactivated virus, or with DNA encoding the protein or fragment thereof. Alternatively, the CoV-S protein or a fragment thereof may be produced using standard biochemical techniques and modified and used as immunogen. In one embodiment of the invention, the immunogen is a recombinantly produced CoV-S protein or fragment thereof. In certain embodiments of the invention, the immunogen may be a CoV-S polypeptide vaccine. In certain embodiments, one or more booster injections may be administered. In certain embodiments, the immunogen may be a recombinant CoV-S polypeptide expressed in *E. coli* or in any other eukaryotic or mammalian cells such as Chinese hamster ovary (CHO) cells.

[000148] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to CoV-S can be initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[000149] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of

the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[000150] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, *etc.* The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Anti-Coronavirus Spike Protein Antibodies Comprising Fc Variants

[000151] According to certain embodiments of the present invention, anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, are provided comprising an Fc domain comprising one or more mutations, which, for example, enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH. For example, the present invention includes anti-CoV-S antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.*, in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (*e.g.*, E or Q); 250 and 428 (*e.g.*, L or F); 252 (*e.g.*, L/Y/F/W or T), 254 (*e.g.*, S or T), and 256 (*e.g.*, S/R/Q/E/D or T); or a modification at position 428 and/or 433 (*e.g.*, H/L/R/S/P/Q or K) and/or 434 (*e.g.*, A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.*, 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.*, M428L) and 434S (*e.g.*, N434S) modification; a 428L, 259I (*e.g.*, V259I), and 308F (*e.g.*, V308F) modification; a 433K (*e.g.*, H433K) and a 434 (*e.g.*, 434Y) modification; a 252, 254, and 256 (*e.g.*, 252Y, 254T, and 256E) modification; a 250Q and 428L modification (*e.g.*, T250Q and

M428L); and a 307 and/or 308 modification (*e.g.*, 308F or 308P). In yet another embodiment, the modification comprises a 265A (*e.g.*, D265A) and/or a 297A (*e.g.*, N297A) modification.

[000152] For example, the present invention includes anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.*, T250Q and M248L); 252Y, 254T and 256E (*e.g.*, M252Y, S254T and T256E); 428L and 434S (*e.g.*, M428L and N434S); 257I and 311I (*e.g.*, P257I and Q311I); 257I and 434H (*e.g.*, P257I and N434H); 376V and 434H (*e.g.*, D376V and N434H); 307A, 380A and 434A (*e.g.*, T307A, E380A and N434A); and 433K and 434F (*e.g.*, H433K and N434F). In particular, antibodies designated mAb17090 and mAb15160_2 each contain M252Y, S254T and T256E modifications in the heavy chain constant region as compared to mAb14286 and mAb15160, respectively.

[000153] Anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, that comprise a V_H and/or V_L as set forth herein comprising any possible combinations of the foregoing Fc domain mutations, are contemplated within the scope of the present invention.

[000154] The present invention also includes anti-CoV-S antigen-binding proteins, antibodies or antigen-binding fragments, comprising a V_H set forth herein and a chimeric heavy chain constant (C_H) region, wherein the chimeric C_H region comprises segments derived from the C_H regions of more than one immunoglobulin isotype. For example, the antibodies of the invention may comprise a chimeric C_H region comprising part or all of a C_H2 domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a C_H3 domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the invention comprise a chimeric C_H region having a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence (amino acid residues from positions 228 to 236 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric C_H region as described herein may, in certain

embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (See, *e.g.,* WO2014/022540).

Immunoconjugates

[000155] The invention encompasses an anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, conjugated to another moiety, *e.g.*, a therapeutic moiety (an "immunoconjugate"), such as a toxoid or an anti-viral drug to treat influenza virus infection. In an embodiment of the invention, an anti-CoV-S antibody or fragment is conjugated to any of the further therapeutic agents set forth herein. As used herein, the term "immunoconjugate" refers to an antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment, which is chemically or biologically linked to a radioactive agent, a cytokine, an interferon, a target or reporter moiety, an enzyme, a peptide or protein or a therapeutic agent. The antigen-binding protein may be linked to the radioactive agent, cytokine, interferon, target or reporter moiety, enzyme, peptide or therapeutic agent at any location along the molecule so long as it is able to bind its target (CoV-S). Examples of immunoconjugates include antibody-drug conjugates and antibody-toxin fusion proteins. In one embodiment of the invention, the agent may be a second, different antibody that binds specifically to CoV-S. The type of therapeutic moiety that may be conjugated to the anti-CoV-S antigen-binding protein (*e.g.*, antibody or fragment) will take into account the condition to be treated and the desired therapeutic effect to be achieved. See, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", Monoclonal Antibodies 1984: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62: 119-58 (1982).

Multi-specific Antibodies

[000156] The present invention includes anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof, as well as methods of use thereof and methods of making such antigen-binding proteins. The term "anti-CoV-S" antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments, includes multispecific (*e.g.*, bispecific or biparatopic) molecules that include at least one first antigen-binding domain that specifically binds to CoV-S (*e.g.*, an antigen-binding domain from an antibody of Table 4) and at least one second antigen-binding domain that binds to a different antigen or to an epitope in CoV-S which is different from that of the first antigen-binding domain. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are both selected from the antigen-binding domains of Table 4. In an embodiment of the invention, the first and second epitopes overlap. In another embodiment of the invention, the first and second epitopes do not overlap. For example, in an embodiment of the invention, a multispecific antibody is a bispecific IgG antibody (*e.g.*, IgG1 or IgG4) that includes a first antigen-binding domain that binds specifically to CoV-S including the heavy and light immunoglobulin chain of an antibody of Table 4, and a second antigen-binding domain that binds specifically to a different epitope of CoV-S. In some embodiments, a bispecific IgG antibody (*e.g.*, IgG1 or IgG4) includes a first antigen-binding domain that binds specifically to CoV-S and a second binding domain that binds to a host cell protein, e.g., ACE2 or TMPRSS2.

[000157] The antibodies of Table 4 include multispecific molecules, *e.g.*, antibodies or antigen-binding fragments, that include the CDR-Hs and CDR-Ls, V_H and V_L, or HC and LC of those antibodies, respectively (including variants thereof as set forth herein).

[000158] In an embodiment of the invention, an antigen-binding domain that binds specifically to CoV-S, which may be included in a multispecific molecule, comprises:

(1)

(i) a heavy chain variable domain sequence that comprises HCDR1, HCDR2, and HCDR3 amino acid sequences set forth in Table 4, and

(ii) a light chain variable domain sequence that comprises LCDR1, LCDR2, and LCDR3 amino acid sequences set forth in Table 4;

or,

(2)

(i) a heavy chain variable domain sequence comprising an amino acid sequence set forth in Table 4, and

(ii) a light chain variable domain sequence comprising an amino acid sequence set forth in Table 4;

or,

(3)

(i) a heavy chain immunoglobulin sequence comprising an amino acid sequence set forth in Table 4, and

(ii) a light chain immunoglobulin sequence comprising an amino acid sequence set forth in Table 4.

[000159] In an embodiment of the invention, the multispecific antibody or fragment includes more than two different binding specificities (*e.g.*, a trispecific molecule), for example, one or more additional antigen-binding domains which are the same or different from the first and/or second antigen-binding domain.

[000160] In one embodiment of the invention, a bispecific antigen-binding fragment comprises a first scFv (*e.g.*, comprising V_H and V_L sequences of Table 4) having binding specificity for a first epitope (*e.g.*, CoV-S) and a second scFv having binding specificity for a second, different epitope. For example, in an embodiment of the invention, the first and second scFv are tethered with a linker, *e.g.*, a peptide linker (*e.g.*, a GS linker such as $(GGGGS)_n$ (SEQ ID NO: 834) wherein n is, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10). Other bispecific antigen-binding fragments include an $F(ab)_2$ of a bispecific IgG antibody which comprises the heavy and light chain CDRs of Table 4 and of another antibody that binds to a different epitope.

Therapeutic Methods

[000161] The present invention provides methods for treating or preventing viral infection (*e.g.*, coronavirus infection) by administering a therapeutically effective amount of anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment, (*e.g.*, of Table 4) to a subject (*e.g.*, a human) in need of such treatment or prevention.

[000162] Coronavirus infection may be treated or prevented, in a subject, by administering an anti-CoV-S antigen-binding protein of the present invention to a subject. Exemplary

coronaviruses include SARS-CoV-2, which may further include variants such as alpha, beta, gamma, delta, and omicron.

[000163] An effective or therapeutically effective dose of anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment (*e.g.*, of Table 4), for treating or preventing a viral infection refers to the amount of the antibody or fragment sufficient to alleviate one or more signs and/or symptoms of the infection in the treated subject, whether by inducing the regression or elimination of such signs and/or symptoms or by inhibiting the progression of such signs and/or symptoms. The dose amount may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. In an embodiment of the invention, an effective or therapeutically effective dose of antibody or antigen-binding fragment thereof of the present invention, for treating or preventing viral infection, *e.g.*, in an adult human subject, is about 0.01 to about 200 mg/kg, *e.g.*, up to about 150 mg/kg. In an embodiment of the invention, the dosage is up to about 10.8 or 11 grams (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 grams). Depending on the severity of the infection, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antigen-binding protein of the present invention can be administered at an initial dose, followed by one or more secondary doses. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of antibody or antigen-binding fragment thereof in an amount that can be approximately the same or less than that of the initial dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

[000164] In some embodiments, mAb10933 and mAb10987 (casirivimab and imdevimab, respectively) can be administered to a subject in a method of prophylaxis, e.g., pre-exposure prophylaxis, against symptomatic COVID-19. In some embodiments, the subject is immunocompromised, e.g., has an immunodeficiency such as a primary or secondary immunodeficiency. In some embodiments, the subject has not mounted an effective response to COVID-19 vaccination. Exemplary criteria associated with immune compromise include: active or recent treatment for solid tumor and hematologic malignancies; receipt of solid-organ or recent hematopoietic stem cell transplants; severe primary immunodeficiency; advanced or

untreated HIV infection; active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory; and chronic medical conditions such as asplenia and chronic renal disease, in which some patients with these conditions may be associated with varying degrees of immune deficit. In some embodiments, a subject meets ≥ 1 of the following criteria:

a. Solid organ transplant (SOT) or hematopoietic blood cell transplant (HSCT) recipients receiving any immunosuppressive medication
b. Active hematologic malignancies or that have completed therapy within 3 months
c. Solid organ malignancies receiving active treatment with T cell or B cell immunosuppressive therapy
d. Moderate or severe primary immunodeficiency (such as hypogammaglobulinemia, Common variable immune deficiency, severe combined immunodeficiency)
e. HIV and CD4 <200 cells/microliter
f. Patients with rheumatologic disease, autoimmune disease, or multiple sclerosis receiving immunosuppressive therapy that modulates Th1, Th17 or B cell responses
g. Receiving any of the following immunosuppressant drugs for more than 3 weeks:
   - T cell suppressing agents (eg, ≥5 mg prednisone equivalent/day during >3 weeks), proteasome inhibitors (such as bortezomib, lenalidomide), alemtuzumab, anti-thymocyte globulin, CAR-T therapy, calcineurin inhibitors)
   - Alkylating agents
   - Purine analogs, such as fludarabine or cladribine
   - B cell depleting agents, such as rituximab and ocrelizumab
   - mTOR inhibitors
   - Antimetabolites, such as mycophenolate
   - JAK inhibitors.

[000165] Exemplary dosing regimens include:

- Co-administration of mAb10933 and mAb10987 combination therapy, 1200 mg (600 mg per mAb) on day 1, then 600 mg (300 mg per mAb) subcutaneous (SC) every four weeks (Q4W) ;

- Co-administration of mAb10933 and mAb10987 combination therapy, 300 mg (150 mg per mAb) SC Q4W; and
- Co-administration of mAb10933 and mAb10987 combination therapy, 300 mg (150 mg per mAb) SC Q12W.

[000166] As used herein, the term "subject" refers to a mammal (*e.g.*, rat, mouse, cat, dog, cow, pig, sheep, horse, goat, rabbit), preferably a human, for example, in need of prevention and/or treatment of a disease or disorder such as viral infection or cancer. The subject may have a viral infection, *e.g.*, an influenza infection, or be predisposed to developing an infection. Subjects predisposed to developing an infection, or subjects who may be at elevated risk for contracting an infection (*e.g.*, of coronavirus or influenza virus), include subjects with compromised immune systems because of autoimmune disease, subjects receiving immunosuppressive therapy (for example, following organ transplant), subjects afflicted with human immunodeficiency syndrome (HIV) or acquired immune deficiency syndrome (AIDS), subjects with forms of anemia that deplete or destroy white blood cells, subjects receiving radiation or chemotherapy, or subjects afflicted with an inflammatory disorder. Additionally, subjects of very young (*e.g.*, 5 years of age or younger) or old age (*e.g.*, 65 years of age or older) are at increased risk. Moreover, a subject may be at risk of contracting a viral infection due to proximity to an outbreak of the disease, *e.g.* subject resides in a densely-populated city or in close proximity to subjects having confirmed or suspected infections of a virus, or choice of employment, *e.g.* hospital worker, pharmaceutical researcher, traveler to infected area, or frequent flier.

[000167] "Treat" or "treating" means to administer an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment of the present invention (*e.g.*, of Table 4), to a subject having one or more signs or symptoms of a disease or infection, *e.g.*, viral infection, for which the antigen-binding protein is effective when administered to the subject at an effective or therapeutically effective amount or dose (as discussed herein).

[000168] The present invention also encompasses prophylactically administering an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 4), to a subject who is at risk of viral infection so as to prevent such infection. Passive antibody-based immunoprophylaxis has proven an effective strategy for preventing subject from viral infection. See *e.g.*, Berry *et al.*, Passive broad-spectrum influenza

immunoprophylaxis. Influenza Res Treat. 2014; 2014:267594. Epub 2014 Sep 22; and Jianqiang *et al.*, Passive immune neutralization strategies for prevention and control of influenza A infections, Immunotherapy. 2012 February; 4(2): 175–186; Prabhu *et al.*, Antivir Ther. 2009;14(7):911-21, Prophylactic and therapeutic efficacy of a chimeric monoclonal antibody specific for H5 hemagglutinin against lethal H5N1 influenza. "Prevent" or "preventing" means to administer an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment of the present invention (*e.g.*, of Table 4), to a subject to inhibit the manifestation of a disease or infection (*e.g.*, viral infection) in the body of a subject, for which the antigen-binding protein is effective when administered to the subject at an effective or therapeutically effective amount or dose (as discussed herein). As used herein, prophylaxis can be pre-exposure prophylaxis (e.g., administration of an antibody or antigen-binding fragment described herein to an individual prior to exposure to the SARS-CoV-2 virus), or post-exposure prophylaxis (e.g., administration of an antibody or antigen-binding fragment described herein to an individual prior to exposure to the SARS-CoV-2 virus). In some embodimenbts, post-exposure prophylaxis can prevent one or more symptoms of COVID-19 despite infection with SARS-CoV-2.

[000169] In an embodiment of the invention, a sign or symptom of a viral infection in a subject is survival or proliferation of virus in the body of the subject, *e.g.*, as determined by viral titer assay (*e.g.*, coronavirus propagation in embryonated chicken eggs or coronavirus spike protein assay). Other signs and symptoms of viral infection are discussed herein.

[000170] As noted above, in some embodiments the subject may be a non-human animal, and the antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments) discussed herein may be used in a veterinary context to treat and/or prevent disease in the non-human animals (*e.g.*, cats, dogs, pigs, cows, horses, goats, rabbits, sheep, and the like).

[000171] The present invention provides a method for treating or preventing viral infection (*e.g.*, coronavirus infection) or for inducing the regression or elimination or inhibiting the progression of at least one sign or symptom of viral infection such as:

- fever or feeling feverish/chills;
- cough;
- sore throat;
- runny or stuffy nose;
- sneezing;

- muscle or body aches;
- headaches;
- fatigue (tiredness);
- vomiting;
- diarrhea;
- respiratory tract infection;
- chest discomfort;
- shortness of breath;
- bronchitis; and/or
- pneumonia,

which sign or symptom is secondary to viral infection, in a subject in need thereof (*e.g.*, a human), by administering a therapeutically effective amount of anti-CoV-S antigen-binding protein (*e.g.*, of Table 4) to the subject, for example, by injection of the protein into the body of the subject.

Combinations and Pharmaceutical Compositions

[000172] To prepare pharmaceutical compositions of the anti-CoV-S antigen-binding proteins, *e.g.*, antibodies and antigen-binding fragments thereof (*e.g.*, of Table 4), antigen-binding protein is admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.*, Remington's Pharmaceutical Sciences and U.S. Pharmacopeia: National Formulary, Mack Publishing Company, Easton, Pa. (1984); Hardman, *et al.* (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y.; Gennaro (2000) Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y.; Avis, *et al.* (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY; Weiner and Kotkoskie (2000) Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y. In an embodiment of the invention, the pharmaceutical composition is sterile. Such compositions are part of the present invention.

[000173] The scope of the present invention includes desiccated, *e.g.*, freeze-dried, compositions comprising an anti-CoV-S antigen-binding proteins, *e.g.*, antibody or antigen-

binding fragment thereof (*e.g.*, of Table 4), or a pharmaceutical composition thereof that includes a pharmaceutically acceptable carrier but substantially lacks water.

[000174] In a further embodiment of the invention, a further therapeutic agent that is administered to a subject in association with an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, of Table 4), disclosed herein is administered to the subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (Nov. 1, 2002)).

[000175] The mode of administration can vary. Routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal or intra-arterial.

[000176] The present invention provides methods for administering an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof (*e.g.*, of Table 4), comprising introducing the protein into the body of a subject. For example, the method comprises piercing the body of the subject with a needle of a syringe and injecting the antigen-binding protein into the body of the subject, *e.g.*, into the vein, artery, tumor, muscular tissue or subcutis of the subject.

[000177] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising any of the anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof (*e.g.*, of Table 4), polypeptides (*e.g.*, an HC, LC, V_H or V_L of Table 4) or polynucleotides (*e.g.*, of Table 5) or vectors set forth herein or a pharmaceutical composition thereof comprising a pharmaceutically acceptable carrier.

[000178] In an embodiment of the present disclosure, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 4), is administered in association with one or more further therapeutic agents. A further therapeutic agent includes, but is not limited to: an anti-inflammatory agent, an antimalarial agent, a second antibody or antigen-binding fragment thereof that specifically binds TMPRSS2, and a second antibody or antigen-binding fragment thereof that specifically binds to CoV-S (e.g., an antibody described herein, or described in U.S. Patent No. 10,787,501 which is hereby specifically incorporated by reference in its entirety). In some embodiments, an antimalarial agent is

chloroquine or hydroxychloroquine. In some embodiments, an anti-inflammatory agent is an antibody such as sarilumab, tocilizumab, or gimsilumab. In some embodiments, the further therapeutic agent is a second antibody or antigen-binding fragment disclosed herein, *e.g.*, of Table 4. In some cases, the antibody that binds to CoV-S is casirivimab or imdevimab, In certain embodiments, one, two, three, four, or more antibodies, or antigen-binding fragments thereof, of Table 4 can be administered in combination (e.g., concurrently or sequentially). In particular, combinations of antibodies can be selected such that the antibodies do not cross-compete, as described in Example 7. In some embodiments, mAb14256 is administered in combination with mAb14315. In some embodiments, mAb15151 is administered in combination with mAb14315. In some embodiments, an antibody (e.g., one antibody or two antibodies) of the present disclosure can be combined with an antibody (e.g., one antibody or two antibodies) described in U.S. Patent 10,787,501 ("the '501 patent"). In certain embodiments, mAb10987 of the '501 patent is administered in combination with mAb14256 and/or mAb15151 of the present disclosure. In certain embodiments, mAb10933 and mAb10987 of the '501 patent are administered in combination with mAb14256 of the present disclosure. In certain embodiments, mAb10985 and mAb10987 of the '501 patent are administered in combination with mAb15151 of the present disclosure. In certain embodiments, mAb10985 of the '501 patent is administered in combination with mAb14315 and/or mAb15151 of the present disclosure. In certain embodiments, mAb15160 of the present disclosure is administered in combination with mAb10987 of the '501 patent. In certain embodiments, mAb15160 of the present disclosure is administered in combination with mAb10985 of the '501 patent. In certain embodiments, mAb15160 of the present disclosure is administered in combination with mAb10985 and mAb10987 of the '501 patent. In certain embodiments, mAb15160 of the present disclosure is administered in combination with any one, two, or three of mAb14256, mAb14315, and mAb15151, optionally further administered with mAb10987 and/or mAb10985. In certain embodiments, any one of, two of, three of, of four of mAb14256, mAb14315, mAb15151, and mAb15160 is administered in combination with i) mAb10933, ii) mAb10987, or iii) mAb10933 and mAb10987. In certain embodiments, any combination of one, two, three, four, five, six, or seven of mAb10933, mAb10987, mAb10985, mAb14256, mAb1435, mAb15151, and mAb15160 is administered in combination. In certain embodiments, an antibody or antigen-binding fragment thereof selected from mAb10987, mAb14284, mAb14315 and mAb17090 is

combined with an antibody or antigen-binding fragment thereof seleted from mAb10933, mAb14256, mAb15160 and mAb15160_2. In certain embodiments, the combination comprises mAb10987 and mAb10933. In certain embodiments, the combination comprises mAb10987 and mAb14256. In certain embodiments, the combination comprises mAb10987 and mAb15160. In certain embodiments, the combination comprises mAb10987 and mAb15160_2. In certain embodiments, the combination comprises mAb14284 and mAb10933. In certain embodiments, the combination comprises mAb14284 and mAb14256. In certain embodiments, the combination comprises mAb14284 and mAb15160. In certain embodiments, the combination comprises mAb14284 and mAb15160_2. In certain embodiments, the combination comprises mAb14315 and mAb10933. In certain embodiments, the combination comprises mAb14315 and mAb14256. In certain embodiments, the combination comprises mAb14315 and mAb15160. In certain embodiments, the combination comprises mAb14315 and mAb15160_2. In certain embodiments, the combination comprises mAb17090 and mAb10933. In certain embodiments, the combination comprises mAb17090 and mAb14256. In certain embodiments, the combination comprises mAb17090 and mAb15160. In certain embodiments, the combination comprises mAb17090 and mAb15160_2. In any of the combinations discussed above or herein, the antibody or antigen-binding fragment may be defined by the CDRs contained within the HCVR and LCVR sequences identified in Table 4, by the heavy and light chain CDR sequences identified in Table 4, by the HCVR and LCVR sequences identified in Table 4, or by the full-length heavy and light chain sequences identified in Table 4, and each of these specific combinations is encompassed within the present disclosure. Certain exemplary combinations of two antibodies are shown below. In some embodiments, an antibody that specifically binds TMPRSS2 is H1H7017N, as described in International Patent Pub. No. WO/2019/147831.

Table 2: Exemplary Combinations of Two Antibodies

mAb / Combination No.	mAb 10933	mAb 10985	mAb 10987	mAb 14256	mAb 14315	mAb 15151	mAb 14284	mAb 17090	mAb 15160	mAb 15160_2
mAb10933	X	1	2	3	4	5	6	7	8	9
mAb10985	10	X	11	12	13	14	15	16	17	18
mAb10987	19	20	X	21	22	23	24	25	26	27
mAb14256	28	29	30	X	31	32	33	34	35	36
mAb14315	37	38	39	40	X	41	42	43	44	45
mAb15151	46	47	48	49	50	X	51	52	53	54

mAb14284	55	56	57	58	59	60	X	61	62	63
mAb17090	64	65	66	67	68	69	70	X	71	72
mAb15160	73	74	75	76	77	78	79	80	X	81
mAb15160_2	82	83	84	85	86	87	88	89	90	X

Table 3: Exemplary Sequences from U.S. Patent 10,787,501

Antibody Designation	Component Part	Sequence	SEQ ID NO
mAb10933		**Amino Acids**	
	HCVR	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYM SWIRQAPGKGLEWVSYITYSGSTIYYADSVKGRF TISRDNAKSSLYLQMNSLRAEDTAVYYCARDRGT TMVPFDYWGQGTLVTVSS	1010
	HCDR1	GFTFSDYY	1012
	HCDR2	ITYSGSTI	1014
	HCDR3	ARDRGTTMVPFDY	1016
	LCVR	DIQMTQSPSSLSASVGDRVTITCQASQDITNYLN WYQQKPGKAPKLLIYAASNLETGVPSRFSGSGSG TDFTFTISGLQPEDIATYYCQQYDNLPLTFGGGT KVEIK	1018
	LCDR1	QDITNY	1020
	LCDR2	AAS	1022
	LCDR3	QQYDNLPLT	1024
	HC	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYM SWIRQAPGKGLEWVSYITYSGSTIYYADSVKGRF TISRDNAKSSLYLQMNSLRAEDTAVYYCARDRGT TMVPFDYWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	1026
	LC	DIQMTQSPSSLSASVGDRVTITCQASQDITNYLN WYQQKPGKAPKLLIYAASNLETGVPSRFSGSGSG	1028

		TDFTFTISGLQPEDIATYYCQQYDNLPLTFGGGT KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	
	Nucleic Acids		
	HCVR	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTGACTACTACATG AGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTTCATACATTACTTATAGTGGTAGTAC CATATACTACGCAGACTCTGTGAAGGGCCGATTC ACCATCTCCAGGGACAACGCCAAGAGCTCACTGT ATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC GGCCGTGTATTACTGTGCGAGAGATCGCGGTACA ACTATGGTCCCCTTTGACTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCA	1009
	HCDR1	GGATTCACCTTCAGTGACTACTAC	1011
	HCDR2	ATTACTTATAGTGGTAGTACCATA	1013
	HCDR3	GCGAGAGATCGCGGTACAACTATGGTCCCCTTTG ACTAC	1015
	LCVR	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTACCAACTATTTAAAT TGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGC TCCTGATCTACGCTGCATCCAATTTGGAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCGGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGTA TGATAATCTCCCTCTCACTTTCGGCGGAGGGACC AAGGTGGAGATCAAA	1017
	LCDR1	CAGGACATTACCAACTAT	1019
	LCDR2	GCTGCATCC	1021
	LCDR3	CAACAGTATGATAATCTCCCTCTCACT	1023
	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTGACTACTACATG AGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGG AGTGGGTTTCATACATTACTTATAGTGGTAGTAC CATATACTACGCAGACTCTGTGAAGGGCCGATTC ACCATCTCCAGGGACAACGCCAAGAGCTCACTGT ATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC GGCCGTGTATTACTGTGCGAGAGATCGCGGTACA ACTATGGTCCCCTTTGACTACTGGGGCCAGGGAA	1025

		CCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACA AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT ACACCCTGCCCCCATCCCGGGATGAGCTGACCAA GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAG TCCCTCTCCCTGTCTCCGGGTAAATGA	
	LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGT CTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCAGGCGAGTCAGGACATTACCAACTATTTAAAT TGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGC TCCTGATCTACGCTGCATCCAATTTGGAAACAGG GGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGG ACAGATTTTACTTTCACCATCAGCGGCCTGCAGC CTGAAGATATTGCAACATATTACTGTCAACAGTA TGATAATCTCCCTCTCACTTTCGGCGGAGGGACC AAGGTGGAGATCAAACGAACTGTGGCTGCACCAT CTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGT GGAAGGTGGATAACGCCCTCCAATCGGGTAACTC CCAGGAGAGTGTCACAGAGCAGGACAGCAAGGAC AGCACCTACAGCCTCAGCAGCACCCTGACGCTGA GCAAAGCAGACTACGAGAAACACAAAGTCTACGC	1027

		CTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCC GTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG	
mAb10987	**Amino Acids**		
	HCVR	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYAM YWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRF TISRDNSKNTLYLQMNSLRTEDTAVYYCASGSDY GDYLLVYWGQGTLVTVSS	1030
	HCDR1	GFTFSNYA	1032
	HCDR2	ISYDGSNK	1034
	HCDR3	ASGSDYGDYLLVY	1036
	LCVR	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNY VSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSK SGNTASLTISGLQSEDEADYYCNSLTSISTWVFG GGTKLTVL	1038
	LCDR1	SSDVGGYNY	1040
	LCDR2	DVS	1042
	LCDR3	NSLTSISTWV	1044
	HC	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYAM YWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRF TISRDNSKNTLYLQMNSLRTEDTAVYYCASGSDY GDYLLVYWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	1046
	LC	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNY VSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSK SGNTASLTISGLQSEDEADYYCNSLTSISTWVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS	1048
	Nucleic Acids		
	HCVR	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTAACTATGCTATG	1029

		TACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGG AGTGGGTGGCAGTTATATCATATGATGGAAGTAA TAAATACTATGCAGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCAAGAACACGCTGT ATCTGCAAATGAACAGCCTGAGAACTGAGGACAC GGCTGTGTATTACTGTGCGAGTGGCTCCGACTAC GGTGACTACTTATTGGTTTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCA	
	HCDR1	GGATTCACCTTCAGTAACTATGCT	1031
	HCDR2	ATATCATATGATGGAAGTAATAAA	1033
	HCDR3	GCGAGTGGCTCCGACTACGGTGACTACTTATTGG TTTAC	1035
	LCVR	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTGGTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTATGATGTCAGTAAGCGGCC CTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGTCTGAGGACGAGGCTGATTATTACTGCAA CTCTTTGACAAGCATCAGCACTTGGGTGTTCGGC GGAGGGACCAAGCTGACCGTCCTA	1037
	LCDR1	AGCAGTGACGTTGGTGGTTATAACTAT	1039
	LCDR2	GATGTCAGT	1041
	LCDR3	AACTCTTTGACAAGCATCAGCACTTGGGTG	1043
	HC	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTCAGTAACTATGCTATG TACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGG AGTGGGTGGCAGTTATATCATATGATGGAAGTAA TAAATACTATGCAGACTCCGTGAAGGGCCGATTC ACCATCTCCAGAGACAATTCCAAGAACACGCTGT ATCTGCAAATGAACAGCCTGAGAACTGAGGACAC GGCTGTGTATTACTGTGCGAGTGGCTCCGACTAC GGTGACTACTTATTGGTTTACTGGGGCCAGGGAA CCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC TGGTCAAGGACTACTTCCCCGAACCGGTGACGGT GTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTG CACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACA	1045

		AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTGAACTCCTG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAAC CCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT ACACCCTGCCCCCATCCCGGGATGAGCTGACCAA GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAG TCCCTCTCCCTGTCTCCGGGTAAATGA	
	LC	CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTG GGTCTCCTGGACAGTCGATCACCATCTCCTGCAC TGGAACCAGCAGTGACGTTGGTGGTTATAACTAT GTCTCCTGGTACCAACAACACCCAGGCAAAGCCC CCAAACTCATGATTTATGATGTCAGTAAGCGGCC CTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAG TCTGGCAACACGGCCTCCCTGACCATCTCTGGGC TCCAGTCTGAGGACGAGGCTGATTATTACTGCAA CTCTTTGACAAGCATCAGCACTTGGGTGTTCGGC GGAGGGACCAAGCTGACCGTCCTAGGCCAGCCCA AGGCCGCCCCCTCCGTGACCCTGTTCCCCCCCTC CTCCGAGGAGCTGCAGGCCAACAAGGCCACCCTG GTGTGCCTGATCTCCGACTTCTACCCCGGCGCCG TGACCGTGGCCTGGAAGGCCGACTCCTCCCCCGT GAAGGCCGGCGTGGAGACCACCACCCCCTCCAAG CAGTCCAACAACAAGTACGCCGCCTCCTCCTACC TGTCCCTGACCCCCGAGCAGTGGAAGTCCCACCG GTCCTACTCCTGCCAGGTGACCCACGAGGGCTCC ACCGTGGAGAAGACCGTGGCCCCCACCGAGTGCT CCTGA	1047
	Amino Acids		
mAb10985	HCVR	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAM HWVRQAPGKGLEWVSGISWNRGSIGYADSVKGRF TISRDNAKNSLYLQMSSLRAEDTALYYCAKDGER WDSVVVPSARNGMDVWGQGTTVTVSS	1050

	HCDR1	GFTFDDYA	1052
	HCDR2	ISWNRGSI	1054
	HCDR3	AKDGERWDSVVVPSARNGMDV	1056
	LCVR	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYD VHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSK SGTSASLAITGLQAEDEADYYCQSYDSSLSGSYV FGTGTKVTVL	1058
	LCDR1	SSNIGAGYD	1060
	LCDR2	GNS	1062
	LCDR3	QSYDSSLSGSYV	1064
	HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAM HWVRQAPGKGLEWVSGISWNRGSIGYADSVKGRF TISRDNAKNSLYLQMSSLRAEDTALYYCAKDGER WDSVVVPSARNGMDVWGQGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK	1066
	LC	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYD VHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSK SGTSASLAITGLQAEDEADYYCQSYDSSLSGSYV FGTGTKVTVLGQPKAAPSVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTP SKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS	1068
	Nucleic Acids		
	HCVR	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTTGATGATTATGCCATG CACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGG AGTGGGTCTCAGGTATTAGTTGGAATAGGGGTAG CATAGGCTATGCGGACTCTGTGAAGGGCCGATTC ACCATCTCCAGAGACAACGCCAAGAACTCCCTGT ATCTGCAAATGAGCAGTCTGAGAGCTGAGGACAC GGCCTTGTATTACTGCGCAAAAGATGGCGAGAGA TGGGATAGTGTAGTAGTACCATCTGCTAGGAACG	1049

		GTATGGACGTCTGGGGCCAAGGGACCACGGTCAC CGTCTCCTCA	
	HCDR1	GGATTCACCTTTGATGATTATGCC	1051
	HCDR2	ATTAGTTGGAATAGGGGTAGCATA	1053
	HCDR3	GCAAAAGATGGCGAGAGATGGGATAGTGTAGTAG TACCATCTGCTAGGAACGGTATGGACGTC	1055
	LCVR	CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTG GGGCCCCAGGGCAGAGGGTCACCATCTCCTGCAC TGGGAGCAGCTCCAACATCGGGGCAGGTTATGAT GTACATTGGTACCAGCAGCTTCCAGGAACAGCCC CCAAACTCCTCATCTATGGTAACAGCAATCGGCC CTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAG TCTGGCACCTCAGCCTCCCTGGCCATCACTGGGC TCCAGGCTGAGGATGAGGCTGATTATTACTGCCA GTCCTATGACAGCAGCCTGAGTGGCTCTTATGTC TTCGGAACTGGGACCAAGGTCACCGTCCTA	1057
	LCDR1	AGCTCCAACATCGGGGCAGGTTATGAT	1059
	LCDR2	GGTAACAGC	1061
	LCDR3	CAGTCCTATGACAGCAGCCTGAGTGGCTCTTATG TC	1063
	HC	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGG TACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGC AGCCTCTGGATTCACCTTTGATGATTATGCCATG CACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGG AGTGGGTCTCAGGTATTAGTTGGAATAGGGGTAG CATAGGCTATGCGGACTCTGTGAAGGGCCGATTC ACCATCTCCAGAGACAACGCCAAGAACTCCCTGT ATCTGCAAATGAGCAGTCTGAGAGCTGAGGACAC GGCCTTGTATTACTGCGCAAAAGATGGCGAGAGA TGGGATAGTGTAGTAGTACCATCTGCTAGGAACG GTATGGACGTCTGGGGCCAAGGGACCACGGTCAC CGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTC TTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTG GGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCGTGGAAC TCAGGCGCCCTGACCAGCGGCGTGCACACCTTCC CGGCTGTCCTACAGTCCTCAGGACTCTACTCCCT CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG GGCACCCAGACCTACATCTGCAACGTGAATCACA AGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA GCCCAAATCTTGTGACAAAACTCACACATGCCCA CCGTGCCCAGCACCTGAACTCCTGGGGGGACCGT CAGTCTTCCTCTTCCCCCCAAAACCCAAGGACAC CCTCATGATCTCCCGGACCCCTGAGGTCACATGC GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG	1065

		TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAG TACAACAGCACGTACCGTGTGGTCAGCGTCCTCA CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGA GTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGATGAGCTGACCAAGAACCAGGTC AGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCA GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA GCCGGAGAACAACTACAAGACCACGCCTCCCGTG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCA AGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGG GAACGTCTTCTCATGCTCCGTGATGCATGAGGCT CTGCACAACCACTACACGCAGAAGTCCCTCTCCC TGTCTCCGGGTAAATGA	
	LC	CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTG GGGCCCCAGGGCAGAGGGTCACCATCTCCTGCAC TGGGAGCAGCTCCAACATCGGGGCAGGTTATGAT GTACATTGGTACCAGCAGCTTCCAGGAACAGCCC CCAAACTCCTCATCTATGGTAACAGCAATCGGCC CTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAG TCTGGCACCTCAGCCTCCCTGGCCATCACTGGGC TCCAGGCTGAGGATGAGGCTGATTATTACTGCCA GTCCTATGACAGCAGCCTGAGTGGCTCTTATGTC TTCGGAACTGGGACCAAGGTCACCGTCCTAGGCC AGCCCAAGGCCGCCCCCTCCGTGACCCTGTTCCC CCCCTCCTCCGAGGAGCTGCAGGCCAACAAGGCC ACCCTGGTGTGCCTGATCTCCGACTTCTACCCCG GCGCCGTGACCGTGGCCTGGAAGGCCGACTCCTC CCCCGTGAAGGCCGGCGTGGAGACCACCACCCCC TCCAAGCAGTCCAACAACAAGTACGCCGCCTCCT CCTACCTGTCCCTGACCCCCGAGCAGTGGAAGTC CCACCGGTCCTACTCCTGCCAGGTGACCCACGAG GGCTCCACCGTGGAGAAGACCGTGGCCCCCACCG AGTGCTCCTGA	1067

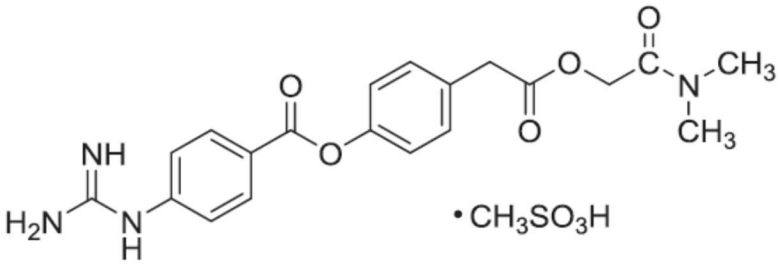
[000179] In some embodiments, anti-CoV-S antigen-binding proteins (*e.g.*, anti-SARS-CoV-2-S antibodies or antigen-binding fragments thereof) from different human donors may be combined. The present invention includes a composition comprising two (or more) anti-SARS-CoV-2-S antibodies or antigen-binding fragments comprising variable domains from human subjects, wherein the two (or more) antibodies or antigen-binding fragments are derived from different subjects (*e.g.*, two different human subjects). Antibody variable regions derived from

human B cells are discussed, *e.g.*, in Examples 1 and 2 (Table 6), which describes that variable domains cloned from such B cells are combined with a constant region not from those B cells to produce hybrid antibodies.

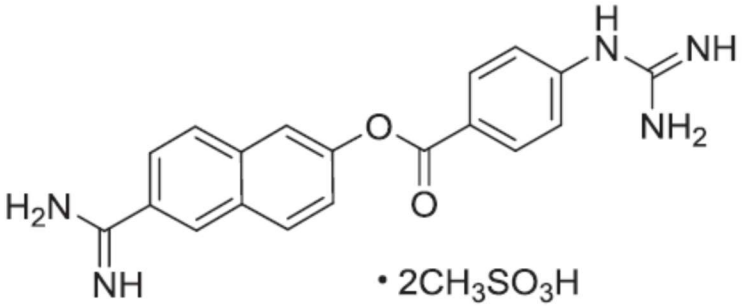
[000180] In some embodiments, the further therapeutic agent is an anti-viral drug and/or a vaccine. As used herein, the term "anti-viral drug" refers to any anti-infective drug or therapy used to treat, prevent, or ameliorate a viral infection in a subject. The term "anti-viral drug" includes, but is not limited to a cationic steroid antimicrobial, leupeptin, aprotinin, ribavirin, or interferon-alpha2b. Methods for treating or preventing virus (*e.g.*, coronavirus) infection in a subject in need of said treatment or prevention by administering an antibody or antigen-binding fragment of Table 4 in association with a further therapeutic agent are part of the present invention.

[000181] For example, in an embodiment of the invention, the further therapeutic agent is a vaccine, *e.g.*, a coronavirus vaccine. In an embodiment of the invention, a vaccine is an inactivated/killed virus vaccine, a live attenuated virus vaccine or a virus subunit vaccine.

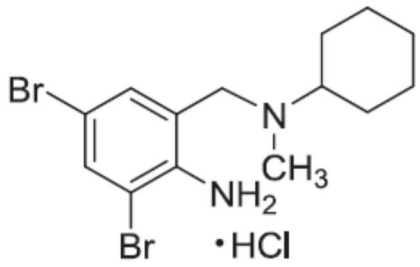
[000182] For example, in an embodiment of the invention, the further therapeutic agent is:



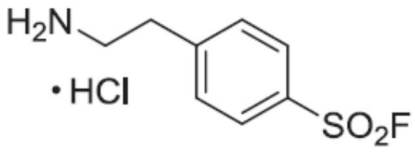
(camostat mesylate);



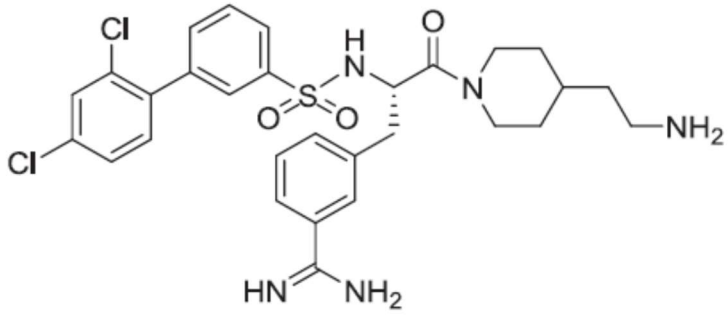
(nafamostat mesylate);



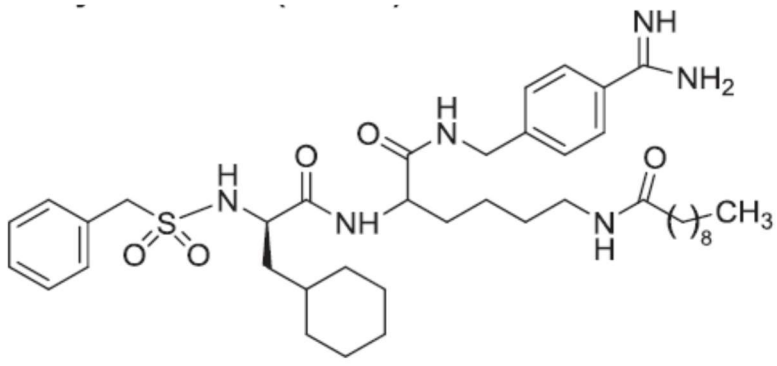
(bromhexine hydrochloride (BHH));



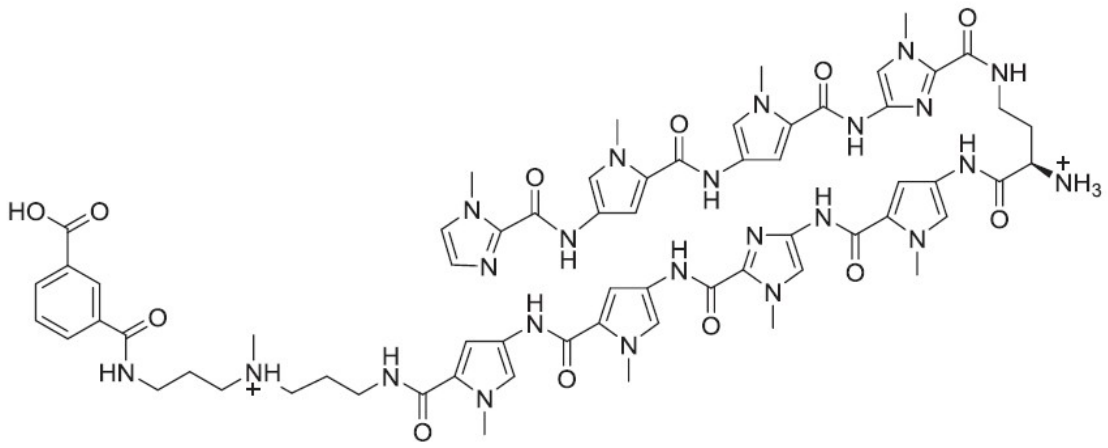
(4-(2-aminomethyl)benzenesulfonyl fluoride hydrochloride (AEBSF));



;



; or



(polyamide). See Shen *et al.* Biochimie 142: 1-10 (2017).

[000183] In an embodiment of the invention, the anti-viral drug is an antibody or antigen-binding fragment that binds specifically to coronavirus, *e.g.*, SARS-CoV-2, SARS-CoV, or MERS-CoV. Exemplary anti-CoV-S antibodies include, but are not limited to: H4sH15188P; H1H15188P; H1H15211P; H1H15177P; H4sH15211P; H1H15260P2; H1H15259P2; H1H15203P; H4sH15260P2; H4sH15231P2; H1H15237P2; H1H15208P; H1H15228P2; H1H15233P2; H1H15264P2; H1H15231P2; H1H15253P2; H1H15215P; and H1H15249P2, as set forth in International patent application publication no. WO/2015/179535, or an antigen-binding fragment thereof, *e.g.*, wherein the antibody or fragment comprises a light chain immunoglobulin that includes LCDR1, LCDR2 and LCDR3 (*e.g.*, the V_L or light chain thereof); and a heavy chain that includes HCDR1, HCDR2 and HCDR3 (*e.g.*, the V_H or heavy chain thereof) of any of the foregoing anti-CoV-S antibodies.

[000184] In a certain embodiment of the invention, the further therapeutic agent is not aprotinin, leupeptin, a cationic steroid antimicrobial, an influenza vaccine (*e.g.*, killed, live, attenuated whole virus or subunit vaccine), or an antibody against influenza virus (*e.g.*, an anti-hemagglutinin antibody).

[000185] The term "in association with" indicates that the components, an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention, along with another agent, can be formulated into a single composition, *e.g.*, for simultaneous delivery, or formulated separately into two or more compositions (*e.g.*, a kit). Each component can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously (*e.g.*,

separately or sequentially) at intervals over a given period of time. Moreover, the separate components may be administered to a subject by the same or by a different route (*e.g.*, wherein an anti-CoV-S antibody or antigen-binding fragment thereof.

Kits

[000186] Further provided are kits comprising one or more components that include, but are not limited to, an anti-CoV-S antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment as discussed herein (*e.g.*, of Table 4), in association with one or more additional components including, but not limited to, a further therapeutic agent, as discussed herein. The antigen-binding protein and/or the further therapeutic agent can be formulated as a single composition or separately in two or more compositions, *e.g.*, with a pharmaceutically acceptable carrier, in a pharmaceutical composition.

[000187] In one embodiment of the invention, the kit includes an anti-CoV-S antigen-binding protein, *e.g.*, an antibody or antigen-binding fragment thereof of the invention (*e.g.*, of Table 4), or a pharmaceutical composition thereof in one container (*e.g.*, in a sterile glass or plastic vial) and a further therapeutic agent in another container (*e.g.*, in a sterile glass or plastic vial).

[000188] In another embodiment, the kit comprises a combination of the invention, including an anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the invention (*e.g.*, of Table 4), or pharmaceutical composition thereof in combination with one or more further therapeutic agents formulated together, optionally, in a pharmaceutical composition, in a single, common container.

[000189] If the kit includes a pharmaceutical composition for parenteral administration to a subject, the kit can include a device (*e.g.*, an injection device) for performing such administration. For example, the kit can include one or more hypodermic needles or other injection devices as discussed above containing the anti-CoV-S antigen-binding protein, *e.g.*, antibody or antigen-binding fragment thereof of the present invention (*e.g.*, of Table 4).

[000190] The kit can include a package insert including information concerning the pharmaceutical compositions and dosage forms in the kit. Generally, such information aids patients and physicians in using the enclosed pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding a combination of the invention may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies,

efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdosage, proper dosage and administration, how supplied, proper storage conditions, references, manufacturer/distributor information and patent information.

Diagnostic Uses of the Antibodies

[000191] The anti-CoV-S antigen-binding proteins, *e.g.*, antibodies or antigen-binding fragments thereof of the present invention (*e.g.*, of Table 4), may be used to detect and/or measure CoV-S in a sample. Exemplary assays for CoV-S may include, *e.g.*, contacting a sample with an anti-CoV-S antigen-binding protein of the invention, wherein the anti-CoV-S antigen-binding protein is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate CoV-S from samples. The presence of an anti-CoV-S antigen-binding protein complexed with CoV-S indicates the presence of CoV-S in the sample. Alternatively, an unlabeled anti-CoV-S antibody can be used in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure CoV-S in a sample include neutralization assays, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS). Thus, the present invention includes a method for detecting the presence of spike protein polypeptide in a sample comprising contacting the sample with an anti-CoV-S antigen-binding protein and detecting the presence of a CoV-S/anti-CoV-S antigen-binding protein wherein the presence of the complex indicates the presence of CoV-S.

[000192] An anti-CoV-S antigen-binding protein of the invention (*e.g.*, of Table 4) may be used in a Western blot or immune-protein blot procedure for detecting the presence of CoV-S or a fragment thereof in a sample. Such a procedure forms part of the present invention and includes the steps of *e.g.*:

- providing a membrane or other solid substrate comprising a sample to be tested for the presence of CoV-S, *e.g.*, optionally including the step of transferring proteins from a sample to be tested for the presence of CoV-S (*e.g.*, from a PAGE or SDS-PAGE electrophoretic separation of the proteins in the sample) onto a membrane or other solid substrate using a method

known in the art (*e.g.*, semi-dry blotting or tank blotting); and contacting the membrane or other solid substrate to be tested for the presence of CoV-S or a fragment thereof with an anti-CoV-S antigen-binding protein of the invention.

[000193] Such a membrane may take the form, for example, of a nitrocellulose or vinyl-based (*e.g.*, polyvinylidene fluoride (PVDF)) membrane to which the proteins to be tested for the presence of CoV-S in a non-denaturing PAGE (polyacrylamide gel electrophoresis) gel or SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) gel have been transferred (*e.g.*, following electrophoretic separation in the gel). Before contacting the membrane with the anti-CoV-S antigen-binding protein, the membrane is optionally blocked, *e.g.*, with non-fat dry milk or the like so as to bind non-specific protein binding sites on the membrane.

(2) washing the membrane one or more times to remove unbound anti-CoV-S antigen-binding protein and other unbound substances; and

(3) detecting the bound anti-CoV-S antigen-binding protein.

[000194] Detection of the bound antigen-binding protein indicates that the CoV-S protein is present on the membrane or substrate and in the sample. Detection of the bound antigen-binding protein may be by binding the antigen-binding protein with a secondary antibody (an anti-immunoglobulin antibody) which is detectably labeled and, then, detecting the presence of the secondary antibody label.

[000195] The anti-CoV-S antigen-binding proteins (*e.g.*, antibodies and antigen-binding fragments (*e.g.*, of Table 4)) disclosed herein may also be used for immunohistochemistry. Such a method forms part of the present invention and comprises, *e.g.*,

- contacting tissue to be tested for the presence of CoV-S protein with an anti-CoV-S antigen-binding protein of the invention; and
- detecting the antigen-binding protein on or in the tissue.

[000196] If the antigen-binding protein itself is detectably labeled, it can be detected directly. Alternatively, the antigen-binding protein may be bound by a detectably labeled secondary antibody wherein the label is then detected.

EXAMPLES

[000197] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and

compositions of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, *etc.*) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, room temperature is about 25°C, and pressure is at or near atmospheric.

Example 1: Generation of human antibodies to SARS-CoV-2 spike protein (SARS-CoV-2-S)

[000198] Human antibodies to SARS-CoV-2-Spike protein (SARS-CoV-2-S) were generated in a VELOCIMMUNE® mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions or human immunoglobulin heavy and lambda light chain variable regions. Each mouse was immunized with a vector expressing the SARS-CoV-2-S receptor binding domain (RBD) (amino acids 1-1273 of NCBI accession number (MN908947.3), SEQ ID NO: 1008), followed by a booster with a SARS-CoV-2-S vector or a SARS-CoV-2-S protein. The antibody immune response was monitored by a SARS-CoV-2-S-specific immunoassay. Anti-SARS-CoV-2-S antibodies were isolated directly from antigen-positive mouse B cells without fusion to myeloma cells, as described in U.S. Patent 7582298, herein specifically incorporated by reference in its entirety. Using this method, fully human anti-SARS-CoV-2-S antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained.

[000199] Antibody variable regions were also isolated from human blood samples. Whole blood was received from patients 6-8 weeks after a laboratory-confirmed PCR positive test for SARS-CoV- 2 and symptomatic COVID-19 disease. Red blood cells were lysed using an ammonium chloride based lysis buffer (Life Technologies) and B cells were enriched by negative selection. Single B cells that bound the SARS-CoV-2 spike protein were isolated by fluorescent-activated cell sorting (FACS). Isolated B cells were single-well plated and mixed with antibody light and heavy variable region-specific PCR primers. cDNAs for each single B cell were synthesized via a reverse transcriptase (RT) reaction. Each resulting RT product was then split and transferred into two corresponding wells for subsequent antibody heavy and light chain PCRs. One set of the resulting RT products was first amplified by PCR using a 5' degenerate primer specific for antibody heavy variable region leader sequence or a 5' degenerate primer specific for antibody light chain variable region leader sequence and a 3' primer specific

for antibody constant region, to form an amplicon. The amplicons were then amplified again by PCR using a 5' degenerate primer specific for antibody heavy variable region framework 1 or a 5' degenerate primer specific for antibody light chain variable region framework 1 and a 3' primer specific for antibody constant region, to generate amplicons for cloning. The antibody heavy chain and light chain derived PCR products were cloned into expression vectors containing heavy constant region and light constant region, respectively, thereby producing expression vectors for hybrid antibodies. The expression vectors expressing full-length heavy and light chain pairs were transfected into CHO cells to produce antibody proteins for testing.

[000200] The biological properties of exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2: Heavy and light chain variable region amino acid and nucleotide sequences

[000201] Table 4 sets forth the amino acid sequence identifiers of the heavy and light chain variable regions and CDRs, as well as the heavy chain and light chain sequences, of exemplary anti-SARS-CoV-2-S antibodies. The corresponding nucleic acid sequence identifiers are set forth in Table 5.

Table 4: Amino Acid Sequence Identifiers

SEQ ID NOs										
mAb	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**	**HC**	**LC**
mAb15163	2	4	6	8	10	12	14	16	18	20
mAb15164	22	24	26	28	30	32	34	36	38	40
mAb15165	42	44	26	47	49	51	34	36	54	56
mAb15166	58	60	62	64	66	51	68	36	70	72
mAb15167	74	76	78	80	82	84	86	88	90	92
mAb15170	94	96	98	100	102	104	106	108	110	112
mAb14296	114	116	118	120	122	124	126	128	130	132
mAb14297	134	136	138	140	142	144	126	146	148	150
mAb14312	152	154	156	158	160	162	164	166	168	170
mAb14313	172	174	176	178	180	182	184	186	188	190
mAb14314	192	194	196	198	200	202	204	206	208	210
mAb14315	212	214	216	218	220	222	126	224	226	228
mAb14316	230	232	234	236	238	240	242	244	246	248
mAb15150	250	252	254	256	258	260	262	264	266	268
mAb15151	270	272	274	276	278	280	106	282	284	286
mAb15156	288	290	292	294	296	298	300	302	304	306

mAb15157	308	310	312	314	316	318	320	322	324	326
mAb15158	328	330	332	334	336	338	106	340	342	344
mAb15159	346	96	98	350	352	354	106	356	358	360
mAb15160	362	364	366	368	370	372	106	374	376	378
mAb15161	380	382	384	386	388	390	392	394	396	398
mAb15162	400	402	98	405	407	409	242	411	413	415
mAb14280	417	419	421	423	425	427	14	429	431	433
mAb14281	435	437	138	440	442	444	446	448	450	452
mAb14282	454	456	458	460	462	84	465	467	469	471
mAb14283	473	475	477	479	481	483	485	487	489	491
mAb14284	493	495	497	499	501	503	505	507	509	511
mAb14285	513	515	517	519	521	523	525	36	527	529
mAb14286	531	533	535	537	539	483	542	544	546	548
mAb14287	550	552	554	556	558	84	14	560	562	564
mAb14288	566	568	570	572	574	576	578	580	582	584
mAb14289	586	588	590	592	594	596	126	598	600	602
mAb14290	604	606	608	610	612	614	126	616	618	620
mAb14291	622	624	626	628	630	632	634	636	638	640
mAb14292	642	644	646	648	650	652	634	655	657	659
mAb14293	661	663	665	667	669	124	126	671	673	675
mAb14295	677	679	78	682	684	686	126	688	690	692
mAb13459	694	696	698	700	702	704	706	708	710	712
mAb14230	714	696	716	718	720	722	126	724	726	728
mAb14231	730	732	734	736	738	740	106	742	744	746
mAb14232	748	750	497	752	754	756	505	758	760	762
mAb14233	764	766	768	770	772	774	776	778	780	782
mAb14234	784	786	788	790	792	794	796	798	800	802
mAb14235	804	806	497	808	810	812	505	814	816	818
mAb14247	820	822	497	825	827	756	14	829	831	833
mAb14248	835	837	839	841	843	845	847	849	851	853
mAb14249	855	857	859	861	863	865	106	867	869	871
mAb14255	873	76	876	878	880	84	86	36	883	885
mAb14256	887	889	891	893	895	897	164	899	901	903
mAb14257	905	154	908	910	912	914	916	166	918	920
mAb14258	922	924	926	928	930	576	933	935	937	939
mAb14259	941	943	945	947	949	951	634	655	953	955
mAb14260	957	959	961	963	965	967	969	971	973	975
mAb13457	694	696	698	700	977	704	706	979	710	981
mAb13458	694	696	698	700	983	704	706	985	710	987
mAb14294	989	991	993	995	997	999	1001	1003	1005	1007
mAb17090	493	495	497	499	501	503	505	507	1075	511

mAb15160_2	362	364	366	368	370	372	106	374	1077	378

Table 5: Nucleic Acid Sequence Identifiers

SEQ ID NOs										
mAb	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**	**HC**	**LC**
mAb15163	1	3	5	7	9	11	13	15	17	19
mAb15164	21	23	25	27	29	31	33	35	37	39
mAb15165	41	43	45	46	48	50	33	52	53	55
mAb15166	57	59	61	63	65	50	67	52	69	71
mAb15167	73	75	77	79	81	83	85	87	89	91
mAb15170	93	95	97	99	101	103	105	107	109	111
mAb14296	113	115	117	119	121	123	125	127	129	131
mAb14297	133	135	137	139	141	143	125	145	147	149
mAb14312	151	153	155	157	159	161	163	165	167	169
mAb14313	171	173	175	177	179	181	183	185	187	189
mAb14314	191	193	195	197	199	201	203	205	207	209
mAb14315	211	213	215	217	219	221	125	223	225	227
mAb14316	229	231	233	235	237	239	241	243	245	247
mAb15150	249	251	253	255	257	259	261	263	265	267
mAb15151	269	271	273	275	277	279	105	281	283	285
mAb15156	287	289	291	293	295	297	299	301	303	305
mAb15157	307	309	311	313	315	317	319	321	323	325
mAb15158	327	329	331	333	335	337	105	339	341	343
mAb15159	345	347	348	349	351	353	105	355	357	359
mAb15160	361	363	365	367	369	371	105	373	375	377
mAb15161	379	381	383	385	387	389	391	393	395	397
mAb15162	399	401	403	404	406	408	241	410	412	414
mAb14280	416	418	420	422	424	426	13	428	430	432
mAb14281	434	436	438	439	441	443	445	447	449	451
mAb14282	453	455	457	459	461	463	464	466	468	470
mAb14283	472	474	476	478	480	482	484	486	488	490
mAb14284	492	494	496	498	500	502	504	506	508	510
mAb14285	512	514	516	518	520	522	524	52	526	528
mAb14286	530	532	534	536	538	540	541	543	545	547
mAb14287	549	551	553	555	557	83	13	559	561	563
mAb14288	565	567	569	571	573	575	577	579	581	583
mAb14289	585	587	589	591	593	595	125	597	599	601
mAb14290	603	605	607	609	611	613	125	615	617	619
mAb14291	621	623	625	627	629	631	633	635	637	639
mAb14292	641	643	645	647	649	651	653	654	656	658

mAb14293	660	662	664	666	668	123	125	670	672	674
mAb14295	676	678	680	681	683	685	125	687	689	691
mAb13459	693	695	697	699	701	703	705	707	709	711
mAb14230	713	695	715	717	719	721	125	723	725	727
mAb14231	729	731	733	735	737	739	105	741	743	745
mAb14232	747	749	496	751	753	755	504	757	759	761
mAb14233	763	765	767	769	771	773	775	777	779	781
mAb14234	783	785	787	789	791	793	795	797	799	801
mAb14235	803	805	496	807	809	811	504	813	815	817
mAb14247	819	821	823	824	826	755	13	828	830	832
mAb14248	834	836	838	840	842	844	846	848	850	852
mAb14249	854	856	858	860	862	864	105	866	868	870
mAb14255	872	874	875	877	879	83	85	881	882	884
mAb14256	886	888	890	892	894	896	163	898	900	902
mAb14257	904	906	907	909	911	913	915	165	917	919
mAb14258	921	923	925	927	929	931	932	934	936	938
mAb14259	940	942	944	946	948	950	633	654	952	954
mAb14260	956	958	960	962	964	966	968	970	972	974
mAb13457	693	695	697	699	976	703	705	978	709	980
mAb13458	693	695	697	699	982	703	705	984	709	986
mAb14294	988	990	992	994	996	998	1000	1002	1004	1006
mAb17090	492	494	496	498	500	502	504	506	1074	510
mAb15160_2	361	363	365	367	369	371	105	373	1076	377

[000202] Antibodies disclosed herein have fully human variable regions but can have mouse constant regions (e.g., a mouse IgG1 Fc or a mouse IgG2 Fc (a or b isotype)) or human constant regions (e.g., a human IgG1 Fc or a human IgG4 Fc). As will be appreciated by a person of ordinary skill in the art, an antibody having a particular Fc isotype can be converted to an antibody with a different Fc isotype (*e.g.*, an antibody with a mouse IgG1 Fc can be converted to an antibody with a human IgG4, etc.), but in any event, the variable domains (including the CDRs) – which are indicated by the numerical identifiers shown in Tables 4 and 5 will remain the same, and the binding properties to antigen are expected to be identical or substantially similar regardless of the nature of the constant domain.

[000203] As described above, the antibodies were obtained by direct isolation from antigen-positive VELOCIMMUNE® mouse B cells or derived from variable regions cloned from antigen-positive human B cells. A summary of these sources is shown in Table 6.

Table 6: Antibody/Variable Region sources

mAb	Source
mAb13457	mouse B cells
mAb13458	mouse B cells
mAb13459	mouse B cells
mAb14230	human B cells
mAb14231	human B cells
mAb14232	human B cells
mAb14233	human B cells
mAb14234	human B cells
mAb14235	human B cells
mAb14247	human B cells
mAb14248	human B cells
mAb14249	human B cells
mAb14255	mouse B cells
mAb14256	mouse B cells
mAb14257	mouse B cells
mAb14258	mouse B cells
mAb14259	human B cells
mAb14260	mouse B cells
mAb14280	human B cells
mAb14281	human B cells
mAb14282	human B cells
mAb14283	human B cells

mAb14284	human B cells
mAb14285	human B cells
mAb14286	human B cells
mAb14287	human B cells
mAb14288	human B cells
mAb14290	human B cells
mAb14289	human B cells
mAb14291	human B cells
mAb14292	human B cells
mAb14293	human B cells
mAb14294	human B cells
mAb14295	human B cells
mAb14296	human B cells
mAb14297	human B cells
mAb14312	mouse B cells
mAb14313	mouse B cells
mAb14314	mouse B cells
mAb14315	human B cells
mAb14316	human B cells
mAb15156	mouse B cells
mAb15157	mouse B cells
mAb15158	human B cells
mAb15159	human B cells
mAb15160	human B cells

mAb15161	human B cells
mAb15162	human B cells
mAb15163	human B cells
mAb15164	human B cells
mAb15165	human B cells
mAb15166	human B cells
mAb15167	human B cells
mAb15170	human B cells
mAb15150	human B cells
mAb15151	human B cells

Example 3: Biacore binding kinetics of purified anti-SARS-CoV-2-S monoclonal antibodies

[000204] Equilibrium dissociation constant (K_D) for different SARS-COV-2 RBD reagents binding to purified CHOt anti-SARS-COV-2 monoclonal antibodies (mAbs) were determined using a real-time surface plasmon resonance based Biacore T200/Biacore 8K biosensor. All binding studies were performed in 10mM HEPES, 150mM NaCl, 3mM EDTA, and 0.05% v/v Surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25 °C and 37 °C. The Biacore CM5 sensor chip surface was first derivatized by amine coupling with either mouse anti-human Fc specific mAb (Regeneron, mAb2567) to capture anti-SARS-COV-2 mAbs. Binding studies were performed on human SARS-COV-2 RBD extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (SARS-COV-2 RBD-mmH) (monomeric RBD) (SEQ ID NO: 1069), SARS-COV-2 RBD extracellular domain expressed with a C-terminal mouse IgG2a Fc (SARS-COV-2 RBD mFc) (dimeric RBD) (SEQ ID NO: 1070), and SARS-CoV2 Spike ecto foldon Trimer expressed with a C-terminal myc-myc-hexahistidine (SARS-CoV2 Spike ECD foldon) (trimeric RBD). Use of these reagents allowed for the testing of the antibodies' ability to bind monomeric, dimeric, and trimeric RBD peptides, respectively.

[000205] Three concentrations, 50nM, 12.5nM and 3.12 nM ,of hSARS-COV-2 RBD-mmH, SARS-COV-2 RBD mFc and SARS-CoV2 Spike ECD foldon prepared in HBS-ET running

buffer, were injected for 1.5-3 minutes at a flow rate of 50µL/min while the dissociation of mAb bound different SARS-COV-2 RBD reagents was monitored for 5-8 minutes in HBS-ET running buffer. At the end of each cycle, the SARS-COV-2 RBD mAb capture surface was regenerated using either 12sec injection of 20mM phosphoric acid for mouse anti-human Fc specific mAb surface. The association rate (k_a) and dissociation rate (k_d) were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using BiaEvaluation software v3.1 or Biacore Insight Evaluation software v2.0. or curve-fitting software. Binding dissociation equilibrium constant (K_D) and dissociative half-life (t½) were calculated from the kinetic rates as:

$$K_D\ (M) = \frac{kd}{ka}, \quad \text{and} \quad t½\ (min) = \frac{\ln(2)}{60 * kd}$$

[000206] Binding kinetics parameters for different anti-SARS-COV-2 mAbs binding to monomeric, dimeric, and trimeric SARS-COV-2 RBD reagents of the invention at 25 °C and 37 °C are shown in Tables 7 through 12, respectively. An isotype control, mAb1932, was also used as a control.

Table 7: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to Monomeric SARS-COV-2 RBD-mmH (SEQ ID NO: 1069) at 25°C.

mAb Captured	mAb Capture Level (RU)	RBD monomer bound at 50nM (RU)	k_a (1/Ms)	k_d (1/s)	KD (M)	t½ (min)
mAb14312	468.6±4.6	190.8	1.53E+06	9.29E-04	6.06E-10	12.4
mAb14260	415.3±1.6	173.5	1.87E+06	1.38E-03	7.38E-10	8.4
mAb14284	731.1±1.2	236.5	6.66E+05	5.49E-04	8.24E-10	21.0
mAb14258	423.9±0.4	180.2	1.89E+06	1.61E-03	8.54E-10	7.2

mAb14294	408.7±2.0	138.3	6.00E+05	5.48E-04	9.14E-10	21.1
mAb14283	410.1±8.9	171.9	1.46E+06	1.58E-03	1.08E-09	7.3
mAb14235	340.0±4.0	117.1	7.89E+05	1.05E-03	1.33E-09	11.0
mAb14289	395.1±1.1	151	1.16E+06	1.58E-03	1.36E-09	7.3
mAb13458	435.7±4.4	158.4	9.09E+05	1.39E-03	1.53E-09	8.3
mAb14313	532.2±1.9	218.2	1.42E+06	2.17E-03	1.53E-09	5.3
mAb14247	179.0±0.5	63.3	8.38E+05	1.63E-03	1.94E-09	7.1
mAb14315	465.8±0.9	127.1	4.07E+05	1.02E-03	2.49E-09	11.4
mAb13459	665.7±4.5	219.3	6.93E+05	1.74E-03	2.51E-09	6.6
mAb13457	412.5±7.4	148.4	7.74E+05	2.05E-03	2.65E-09	5.6
mAb14257	518.6±1.0	215.1	3.40E+06	9.52E-03	2.80E-09	1.2
mAb14255	432.4±4.8	180.4	1.75E+06	4.99E-03	2.84E-09	2.3
mAb14286	394.6±5.2	158.5	3.23E+06	1.04E-02	3.22E-09	1.1
mAb14282	414.4±4.7	170.1	1.93E+06	9.57E-03	4.97E-09	1.2
mAb14281	423.6±0.4	157.8	1.10E+06	5.54E-03	5.02E-09	2.1

mAb14230	315.0±0.3	113.6	1.13E+06	8.52E-03	7.51E-09	1.4
mAb14256	440.5±3.6	175.4	1.11E+06	9.27E-03	8.32E-09	1.2
mAb14285	443.1±0.6	157.9	1.80E+06	2.11E-02	1.17E-08	0.5
mAb14280	474.3±0.5	177.3	1.66E+06	2.55E-02	1.54E-08	0.5
mAb14234	458.8±0.9	152.8	5.50E+05	1.13E-02	2.05E-08	1.0
mAb14232	71.6±1.4	18.8	1.12E+06	3.50E-02	3.12E-08	0.3
mAb14292	431.3±0.7	11.1	4.17E+05	1.71E-02	4.09E-08	0.7
mAb14314	597.8±0.8	11.6	IC	IC	IC	IC
mAb14248	400.8±1.6	269.5	7.06E+05	2.05E-05	2.90E-11	564.0
mAb14295	441.5±3.7	59.8	3.01E+05	≤1.00E-05	3.32E-11	≥1155.0
mAb14233	492.8±3.4	85.7	4.94E+05	3.66E-05	7.41E-11	315.5
mAb14287	419.8±0.3	91.9	3.10E+05	4.59E-05	1.48E-10	251.4
mAb14293	432.5±0.6	119.8	2.43E+05	8.10E-05	3.33E-10	142.6
mAb14291	391.3±3.3	47.8	IC	IC	IC	IC
mAb14249	407.5±1.0	42.3	IC	IC	IC	IC
mAb14316	264.7±1.6	40	IC	IC	IC	IC
mAb14296	529.6±0.7	32.3	IC	IC	IC	IC

mAb14231	407.0±2.2	27.3	IC	IC	IC	IC
mAb14288	458.5±2.3	24.7	IC	IC	IC	IC
mAb14297	444.0±1.4	13.7	IC	IC	IC	IC
mAb14290	378.1±1.2	12	IC	IC	IC	IC
mAb14259	335.8±2.8	7.8	IC	IC	IC	IC
mAb15156	427.3±17.1	91	2.89E+05	1.21E-03	4.18E-09	9.6
mAb15157	291.6±11.5	20.3	2.78E+05	1.25E-03	4.49E-09	9.3
mAb15158	317.3±6.6	26.3	1.04E+05	8.12E-05	7.79E-10	142.2
mAb15159	286.3±16.0	62	4.89E+04	1.30E-04	2.66E-09	88.8
mAb15160	304.2±8.3	9.3	IC	IC	IC	IC
mAb15161	250.6±15.3	40.3	1.73E+05	2.34E-04	1.35E-09	49.3
mAb15162	287.1±12.2	49.6	1.16E+05	8.50E-04	7.30E-09	13.6
mAb15163	358.2±12.8	51	2.18E+05	1.67E-05	7.79E-11	693.3
mAb15164	315.8±11.1	41.2	2.28E+05	3.49E-04	1.53E-09	33.1
mAb15165	271.1±13.8	33.9	5.39E+05	2.12E-04	3.93E-10	54.6
mAb15166	249.2±11.0	13.3	2.46E+05	5.35E-03	2.17E-08	2.2
mAb15167	329.5±10.9	21.8	2.65E+05	4.14E-03	1.56E-08	2.8

mAb15170	278.8±9.9	21.8	2.00E+05	1.53E-05	1.00E-10	756.4
mAb15150	276.5±9.6	33.3	7.74E+05	4.61E-05	5.94E-11	250.8
mAb15151	354.8±13.2	63.4	2.00E+05	7.78E-04	3.89E-09	14.8
mAb1932	790.6±9.6	0.6	NB	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

≤ 1.00E-05 indicates that no dissociation was observed under the current experimental conditions and the k_d value was manually fixed at 1.00E-05 s^{-1} while fitting the real time binding sensorgrams.

Table 8: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to Monomeric SARS-COV-2 RBD-mmH (SEQ ID NO: 1069) at 37°C.

mAb Captured	**mAb Capture Level (RU)**	**RBD monomer bound at 50nM (RU)**	**k_a (1/Ms)**	**k_d (1/s)**	**KD (M)**	**t½ (min)**
mAb14312	543	221.2	1.57E+06	9.88E-04	6.31E-10	11.7
mAb14260	525.5	219.6	1.95E+06	1.44E-03	7.41E-10	8.0
mAb14284	867.3	345.3	6.44E+05	6.05E-04	9.40E-10	19.1
mAb14258	521	215.5	2.14E+06	1.70E-03	7.96E-10	6.8

mAb14294	465.5	185.9	6.00E+05	5.90E-04	9.84E-10	19.6
mAb14283	531.3	217.1	1.54E+06	1.79E-03	1.17E-09	6.4
mAb14235	388.4	153.8	7.93E+05	1.09E-03	1.37E-09	10.6
mAb14289	461.9	185.8	1.20E+06	1.76E-03	1.46E-09	6.5
mAb13458	550.6	212.8	9.07E+05	1.39E-03	1.54E-09	8.3
mAb14313	676	272.8	2.81E+06	2.59E-03	9.21E-10	4.5
mAb14247	222.1	91.2	8.32E+05	1.63E-03	1.95E-09	7.1
mAb14315	581.1	193	4.35E+05	9.85E-04	2.26E-09	11.7
mAb13459	822.4	299	7.86E+05	2.04E-03	2.60E-09	5.7
mAb13457	472.1	180.3	8.01E+05	2.34E-03	2.92E-09	4.9
mAb14257	600.6	242.3	3.26E+06	7.62E-03	2.34E-09	1.5
mAb14255	518.4	206	1.94E+06	5.35E-03	2.76E-09	2.2
mAb14286	436.6	169.1	3.38E+06	1.04E-02	3.07E-09	1.1
mAb14282	492.7	186.2	1.98E+06	1.06E-02	5.37E-09	1.1
mAb14281	486.7	182	1.12E+06	5.82E-03	5.20E-09	2.0

mAb14230	369.8	133.2	1.15E+06	8.76E-03	7.61E-09	1.3
mAb14256	555.8	193.4	1.40E+06	1.15E-02	8.24E-09	1.0
mAb14285	543.5	165.6	2.09E+06	2.74E-02	1.31E-08	0.4
mAb14280	586	176.2	1.53E+06	2.48E-02	1.62E-08	0.5
mAb14234	565.9	162	5.34E+05	1.19E-02	2.23E-08	1.0
mAb14232	98.1	21.1	4.69E+06	3.72E-02	7.92E-09	0.3
mAb14292	507.6	10.4	3.59E+05	2.18E-02	6.07E-08	0.5
mAb14314	693.8	12.5	4.79E+05	1.15E-02	2.39E-08	1.0
mAb14248	509.5	491.7	7.02E+05	1.90E-05	2.71E-11	607.3
mAb14295	558.8	196.2	5.78E+05	≤1.00E-05	1.73E-11	≥1155.0
mAb14233	561.8	276.8	3.20E+05	3.38E-05	1.06E-10	341.7
mAb14287	528.8	154.9	7.04E+05	4.63E-05	6.58E-11	249.4
mAb14293	531	166.7	9.62E+05	8.69E-05	9.03E-11	132.9
mAb14291	516.4	224.5	3.08E+05	4.46E-05	1.45E-10	258.9
mAb14249	482.5	143	2.38E+05	5.34E-05	2.25E-10	216.5

mAb14316	304.6	132.1	8.05E+05	≤1.00E-05	1.24E-11	≥1155.0
mAb14296	672.2	91.3	1.33E+05	≤1.00E-05	7.55E-11	≥1155.0
mAb14231	490.1	54.7	3.18E+05	1.57E-04	4.94E-10	73.5
mAb14288	576.6	72.9	1.06E+05	5.85E-05	5.54E-10	197.5
mAb14297	529.3	32.1	3.01E+05	2.09E-04	6.94E-10	55.3
mAb14290	457.9	32.9	2.34E+05	1.09E-05	4.66E-11	1057.7
mAb14259	395.2	9	NB	NB	NB	NB
mAb15156	463.2±0.7	106.9	3.73E+05	5.35E-03	1.44E-08	2.2
mAb15157	309.1±1	65.7	3.44E+05	3.99E-03	1.16E-08	2.9
mAb15158	298±0.5	44.3	1.26E+05	2.07E-04	1.65E-09	55.7
mAb15159	293.3±1.9	42	1.46E+05	1.76E-04	1.21E-09	65.6
mAb15160	400.6±1.2	79.3	2.50E+05	1.94E-03	7.79E-09	5.9
mAb15161	283.9±0.9	61.1	2.63E+05	8.66E-04	3.29E-09	13.3
mAb15162	322.4±2.9	38.9	1.03E+05	2.99E-03	2.92E-08	3.9
mAb15163	343.6±1.7	72.7	2.18E+05	3.87E-04	1.78E-09	29.9

mAb15164	385±1.1	93.4	2.83E+05	1.79E-03	6.33E-09	6.5
mAb15165	276.1±2.3	82.5	4.75E+05	1.47E-03	3.10E-09	7.9
mAb15166	266.8±0.3	19.7	3.50E+05	3.34E-02	9.53E-08	0.3
mAb15167	405.3±0.6	46.8	3.52E+05	1.95E-02	5.55E-08	0.6
mAb15170	299.4±1.4	56.3	2.83E+05	8.36E-05	2.97E-10	138.1
mAb15150	248.5±1.2	64.9	4.93E+05	7.84E-05	1.58E-10	147.4
mAb15151	595.8±1.6	141.4	1.80E+05	4.42E-03	2.46E-08	2.6
mAb1932	921.8±2	1.3	NB	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

≤ 1.00E-05 indicates that no dissociation was observed under the current experimental conditions and the k_d value was manually fixed at 1.00E-05 s^{-1} while fitting the real time binding sensorgrams.

Table 9: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to Dimeric SARS-COV-2 RBD mFc (SEQ ID NO: 1070) at 25°C.

mAb Captured	**mAb Capture Level (RU)**	**RBD mFc dimer bound at 50nM**	***k_a*** **(1/Ms)**	***k_d*** **(1/s)**	**KD (M)**	**t½ (min)**

mAb14312	465.2±3.8	349.2	1.68E+06	5.60E-05	3.34E-11	206.4
mAb14260	416.5±2.2	327.4	1.96E+06	8.70E-05	4.43E-11	132.8
mAb14284	732.9±0.5	482.2	8.31E+05	2.12E-05	2.55E-11	544.6
mAb14258	420.7±1	332.8	3.56E+04	1.09E-04	3.04E-09	106.5
mAb14294	404.3±5.6	291.4	9.11E+05	2.68E-05	2.94E-11	430.3
mAb14283	417.5±0.6	319.6	1.55E+06	8.14E-05	5.24E-11	141.9
mAb14235	338.6±2.2	242.7	1.10E+06	6.89E-05	6.27E-11	167.6
mAb14289	393.3±2.8	295.3	1.43E+06	8.95E-05	6.28E-11	129.1
mAb13458	439.8±2.5	326.7	1.18E+06	7.55E-05	6.40E-11	153.1
mAb14313	528.5±10.9	407.4	2.36E+06	9.97E-05	4.22E-11	115.9
mAb14247	177.9±0.7	135.5	1.19E+06	1.56E-04	1.31E-10	73.9
mAb14315	455.9±5.0	303.7	7.99E+05	6.26E-05	7.84E-11	184.4
mAb13459	670.8±2.4	465.4	1.05E+06	4.35E-05	4.15E-11	265.6
mAb13457	410.1±7	308.2	1.33E+06	8.59E-05	6.45E-11	134.5
mAb14257	519.6±2.1	403.1	2.81E+06	2.54E-04	9.07E-11	45.4

mAb14255	437.3±0.4	340.7	2.19E+06	1.59E-04	7.26E-11	72.6
mAb14286	393.5±1.5	296.8	2.95E+06	6.55E-04	2.22E-10	17.6
mAb14282	418.3±0.9	326.3	2.17E+06	4.03E-04	1.86E-10	28.7
mAb14281	424.2±0.6	305.1	1.46E+06	2.13E-04	1.46E-10	54.3
mAb14230	315.5±0.6	240.6	2.00E+06	2.86E-04	1.42E-10	40.5
mAb14256	440.9±5.5	331.9	2.84E+06	1.81E-04	6.38E-11	63.7
mAb14285	435.9±1	318.7	5.78E+06	5.02E-04	8.68E-11	23
mAb14280	476.4±0.9	358.2	3.02E+06	3.70E-04	1.23E-10	31.2
mAb14234	458.2±5	328.7	1.02E+06	1.21E-04	1.19E-10	95.2
mAb14232	71.7±1.4	52.4	1.97E+06	1.73E-03	8.78E-10	6.7
mAb14292	431.8±1.4	76.8	1.04E+06	3.51E-02	3.36E-08	0.3
mAb14314	601.8±1.1	173.6	2.22E+06	5.60E-02	2.53E-08	0.2
mAb14248	404.4±1.8	4.9	NB	NB	NB	NB
mAb14295	441.3±4.7	8.4	NB	NB	NB	NB
mAb14233	491.0±2.3	2.3	NB	NB	NB	NB
mAb14287	424.9±3.8	9.4	NB	NB	NB	NB
mAb14293	440.5±0.3	5.8	NB	NB	NB	NB

mAb14291	391.0±4.3	3.3	NB	NB	NB	NB
mAb14249	412.7±1.1	4.6	NB	NB	NB	NB
mAb14316	266.4±1.7	11.4	IC	IC	IC	IC
mAb14296	529.8±1.7	4.6	NB	NB	NB	NB
mAb14231	407.8±1	4.8	NB	NB	NB	NB
mAb14288	462.8±1.2	4	NB	NB	NB	NB
mAb14297	443.5±1.2	6.8	NB	NB	NB	NB
mAb14290	382.1±3.6	7.7	NB	NB	NB	NB
mAb14259	339.7±0.5	8.3	NB	NB	NB	NB
mAb15156	914.2±2.1	493.4	1.41E+06	5.22E-05	3.69E-11	221.2
mAb15157	543.7±0.5	294.3	3.57E+05	6.67E-05	1.87E-10	173.2
mAb15158	573.9±1.8	175.4	4.53E+05	1.00E-05	2.21E-11	1,155.0
mAb15159	519.6±0.8	224.5	6.91E+05	1.19E-05	1.72E-11	971.4
mAb15160	610.1±1.6	268.3	2.58E+05	1.05E-05	4.06E-11	1,101.0
mAb15161	547.4±0.5	328.4	1.06E+06	1.26E-05	1.19E-11	913.8
mAb15162	771.1±0.3	354.1	1.29E+06	2.30E-04	1.79E-10	50.2
mAb15163	529.5±1.1	164.2	9.30E+05	1.00E-05	1.08E-11	1,155.0
mAb15164	719.6±0.5	308.8	3.72E+05	2.12E-05	5.69E-11	545.6

mAb15165	644.5±6.2	222.6	3.01E+05	3.88E-05	1.29E-10	297.5
mAb15166	715.6±4.0	334.4	1.02E+06	1.62E-05	1.60E-11	713.0
mAb15167	501.7±2.5	241.5	4.81E+05	1.05E-04	2.17E-10	110.3
mAb15170	608.7±2.3	237.5	3.39E+05	1.00E-05	2.95E-11	1,155.0
mAb15150	433.3±2.1	235.9	5.07E+05	1.00E-05	1.97E-11	1,155.0
mAb15151	1143±2.6	491.7	9.24E+06	3.12E-05	3.38E-12	369.7
mAb1932	1775.9±2.3	6.8	NB	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Table 10: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to dimeric SARS-COV-2 RBD mFc (SEQ ID NO: 1070) at 37°C.

mAb Captured	**mAb Capture Level (RU)**	**RBD mFc dimer bound at 50nM**	k_a **(1/Ms)**	k_d **(1/s)**	**KD (M)**	**t½ (min)**
mAb14312	550.3	422.3	1.67E+06	5.80E-05	3.47E-11	199.1
mAb14260	521.7	408.3	1.93E+06	1.04E-04	5.40E-11	110.6

mAb14284	872	659.3	8.30E+05	2.24E-05	2.70E-11	516.1
mAb14258	271.5	392.5	IC	IC	IC	IC
mAb14294	467.7	370.4	9.06E+05	3.50E-05	3.86E-11	330.1
mAb14283	534.6	414.9	1.52E+06	9.59E-05	6.31E-11	120.5
mAb14235	393.8	308.2	1.09E+06	6.68E-05	6.12E-11	173
mAb14289	467.8	372.3	1.41E+06	1.28E-04	9.07E-11	90.1
mAb13458	548.4	425.4	1.16E+06	9.12E-05	7.84E-11	126.7
mAb14313	703.3	538	2.52E+06	1.46E-04	5.82E-11	78.9
mAb14247	223	191.8	1.18E+06	1.50E-04	1.27E-10	77
mAb14315	577.7	416.2	8.77E+05	7.91E-05	9.03E-11	145.9
mAb13459	830	613.1	9.85E+05	9.24E-05	9.39E-11	125
mAb13457	467.7	357.9	1.26E+06	1.17E-04	9.35E-11	98.5
mAb14257	597.6	482	2.81E+06	3.39E-04	1.21E-10	34.1
mAb14255	523	407.4	2.12E+06	2.50E-04	1.18E-10	46.2
mAb14286	433.2	336.7	2.94E+06	5.28E-04	1.80E-10	21.9

mAb14282	493.7	393.8	2.21E+06	5.46E-04	2.47E-10	21.1
mAb14281	481.8	370.1	1.34E+06	3.65E-04	2.71E-10	31.7
mAb14230	374	294.6	1.82E+06	4.90E-04	2.68E-10	23.6
mAb14256	573.9	430.4	1.78E+06	4.73E-04	2.67E-10	24.4
mAb14285	537	386.8	4.45E+06	1.03E-03	2.31E-10	11.2
mAb14280	589.2	444.9	2.92E+06	7.72E-04	2.64E-10	15
mAb14234	571.3	414.8	9.80E+05	4.02E-04	4.10E-10	28.8
mAb14232	103.7	69	2.10E+06	1.88E-03	8.93E-10	6.1
mAb14292	503.4	97.9	1.86E+06	6.44E-02	3.46E-08	0.2
mAb14314	700.2	167.3	1.48E+06	3.57E-02	2.41E-08	0.3
mAb14248	506.9	8.1	NB	NB	NB	NB
mAb14295	555.3	13.8	NB	NB	NB	NB
mAb14233	559.6	3.9	NB	NB	NB	NB
mAb14287	528.2	19.8	NB	NB	NB	NB
mAb14293	532.7	9.1	NB	NB	NB	NB
mAb14291	529.1	6.1	NB	NB	NB	NB
mAb14249	481	6.6	NB	NB	NB	NB
mAb14316	303.8	14.5	NB	NB	NB	NB

mAb14296	667.7	7.6	NB	NB	NB	NB
mAb14231	494.9	8	NB	NB	NB	NB
mAb14288	572.7	8.4	NB	NB	NB	NB
mAb14297	525.8	12.4	NB	NB	NB	NB
mAb14290	450.6	10.3	NB	NB	NB	NB
mAb14259	395.4	9.4	NB	NB	NB	NB
mAb15156	1206.3±2.9	672.7	1.78E+05	1.12E-04	6.30E-10	103.2
mAb15157	689.3±1.8	411.9	9.22E+05	1.07E-04	1.16E-10	107.9
mAb15158	699.6±1.7	279.4	1.71E+05	2.90E-05	1.70E-10	398.3
mAb15159	756.1±1.1	314.8	2.20E+05	2.99E-05	1.35E-10	386.3
mAb15160	913.9±1.3	440.3	4.36E+05	7.90E-05	1.81E-10	146.2
mAb15161	674.7±0.6	352.5	1.05E+06	4.90E-05	4.69E-11	235.7
mAb15162	835.4±2.9	322.7	2.00E+05	1.01E-04	5.00E-10	114.8
mAb15163	778.3±3.3	407	4.16E+05	2.50E-05	6.01E-11	462.0
mAb15164	937.9±2.2	466.3	1.82E+06	9.40E-05	5.18E-11	122.9
mAb15165	716.1±0	191.1	1.00E+05	4.55E-05	4.50E-10	254.0
mAb15166	616.1±2.1	350.6	7.81E+05	9.80E-05	1.26E-10	117.9

mAb15167	993.3±3.2	499.8	1.40E+06	1.24E-04	8.90E-11	93.1
mAb15170	779.1±2.9	374.2	2.60E+05	2.41E-05	9.10E-11	480.0
mAb15150	554±1.8	338.7	9.46E+05	2.80E-05	2.96E-11	412.5
mAb15151	1452±4.1	653.6	3.70E+06	3.10E-03	8.50E-10	3.7
mAb1932	2129.7±4	20.6	NB	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Table 11: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to Trimeric SARS-CoV2 Spike ECD foldon Fusion Protein at 25°C.

mAb Captured	**mAb Capture Level (RU)**	**Spike trimer.his bound at 50nM**	k_a **(1/Ms)**	k_d **(1/s)**	**KD (M)**	**t½ (min)**
mAb14312	463.3±4.0	393.4	1.93E+06	5.24E-05	2.72E-11	220.5
mAb14260	411.6±6.6	378.1	1.52E+06	5.87E-05	3.86E-11	196.6
mAb14284	729.9±1.8	469.4	8.12E+05	1.31E-05	1.61E-11	883
mAb14258	420±1.7	406.3	2.12E+06	4.91E-05	2.32E-11	235.3

mAb14294	400.7±3.8	341.7	6.97E+05	2.29E-05	3.29E-11	503.7
mAb14283	417.4±5.5	352.5	1.61E+06	8.66E-05	5.39E-11	133.3
mAb14235	336.9±1.2	297.5	7.79E+05	3.69E-05	4.74E-11	312.9
mAb14289	387.0±3.9	345.3	9.12E+05	6.35E-05	6.96E-11	182
mAb13458	436.2±3.7	340.8	1.21E+06	4.26E-05	3.51E-11	271.3
mAb14313	528.7±2.2	462	2.00E+06	1.13E-04	5.65E-11	102.1
mAb14247	172±4.9	143.3	9.44E+05	4.91E-05	5.21E-11	235
mAb14315	458.4±1.1	335.4	6.52E+05	3.15E-05	4.83E-11	366.2
mAb13459	668.9±8.1	483.2	1.41E+06	5.46E-05	3.89E-11	211.5
mAb13457	405.4±4.6	358.2	7.68E+05	5.52E-05	7.18E-11	209.2
mAb14257	518.4±1.3	535.3	2.45E+06	1.07E-04	4.34E-11	108.5
mAb14255	431.9±3.2	454.1	1.96E+06	1.38E-04	7.06E-11	83.5
mAb14286	389.5±2.0	425	2.63E+06	8.71E-05	3.31E-11	132.6
mAb14282	413.2±3.4	421.7	2.14E+06	1.33E-04	6.24E-11	86.6
mAb14281	415±5.6	310.7	8.34E+05	8.09E-05	9.70E-11	142.8

mAb14230	313.1±2.6	340	1.51E+06	6.09E-05	4.04E-11	189.8
mAb14256	441.9±6.3	356.7	1.47E+06	1.89E-04	1.29E-10	61
mAb14285	435.7±1.6	486.2	2.34E+06	3.98E-05	1.70E-11	290.4
mAb14280	472.8±1.3	458.7	1.99E+06	2.69E-05	1.36E-11	428.7
mAb14234	455.7±5.8	365.5	7.07E+05	5.48E-05	7.75E-11	210.7
mAb14232	69.7±1	72.8	7.63E+05	1.49E-04	1.95E-10	77.7
mAb14292	429.2±0.5	138.4	5.84E+05	4.21E-03	7.21E-09	2.7
mAb14314	600.4±1.7	184	4.92E+05	4.21E-03	8.56E-09	2.7
mAb14248	403.3±0.4	1.4	NB	NB	NB	NB
mAb14295	446.7±2.3	2.4	NB	NB	NB	NB
mAb14233	488.5±2.0	0.3	NB	NB	NB	NB
mAb14287	421.9±3.0	0.9	NB	NB	NB	NB
mAb14293	448.8±0.4	2.4	NB	NB	NB	NB
mAb14291	396.1±4.2	0.3	NB	NB	NB	NB
mAb14249	413.5±1.6	-0.1	NB	NB	NB	NB
mAb14316	269.1±1.4	3.9	NB	NB	NB	NB
mAb14296	528.3±1.5	1.1	NB	NB	NB	NB
mAb14231	410.9±1.7	0.2	NB	NB	NB	NB
mAb14288	459.0±0.8	1.9	NB	NB	NB	NB

mAb14297	451.0±0.8	1.4	NB	NB	NB	NB
mAb14290	379.4±6.1	3.8	NB	NB	NB	NB
mAb14259	340.6±0.2	1.9	NB	NB	NB	NB
mAb15156	447.5±29.5	204.7	3.42E+05	6.61E-05	1.93E-10	174.6
mAb15157	303.7±13.3	42.5	3.02E+05	9.28E-05	3.08E-10	124.5
mAb15158	328.2±11.9	55.1	9.15E+04	1.40E-05	1.53E-10	825.0
mAb15159	307.7±25.7	147.1	8.75E+04	2.02E-05	2.31E-10	571.5
mAb15160	318.2±10.2	55.8	3.04E+05	3.10E-05	1.02E-10	372.6
mAb15161	272±25.5	127	2.80E+05	1.38E-05	4.90E-11	840.0
mAb15162	303.6±18	115.1	1.05E+05	6.79E-05	6.48E-10	170.0
mAb15163	373.8±15.3	97.6	2.14E+05	1.15E-05	5.62E-11	1,002.6
mAb15164	331.2±15.7	107.4	2.98E+05	2.58E-05	8.65E-11	448.0
mAb15165	286.2±19.5	103.9	3.91E+05	1.09E-05	2.79E-11	1,058.7
mAb15166	264.4±15.1	87	2.76E+05	1.74E-04	6.30E-10	66.3
mAb15167	348.2±20.2	114.1	3.36E+05	1.59E-04	4.72E-10	72.8
mAb15170	290±10.6	48.4	1.20E+05	1.29E-05	1.10E-10	893.3

mAb15150	290.2±16	87.6	3.17E+05	1.00E-05	3.15E-11	1,155.0
mAb15151	375.4±21.7	144.9	3.35E+05	6.26E-05	1.87E-10	184.5
mAb1932	806.9±10.9	2.6	NB	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Table 12: Kinetic Binding Parameters of the Interaction of Anti-SARS-COV-2 Monoclonal Antibodies to Trimeric SARS-CoV2 Spike ECD foldon Fusion Protein at 37°C.

Mab Captured	**mAb Capture Level (RU)**	**Spike trimer.his bound at 50nM**	k_a **(1/Ms)**	k_d **(1/s)**	**KD (M)**	**t½ (min)**
mAb14312	541.7	500	9.66E+05	5.44E-05	5.63E-11	212.4
mAb14260	519.4	495.3	9.49E+05	5.73E-05	6.04E-11	201.5
mAb14284	865.5	631.1	8.14E+05	2.05E-05	2.51E-11	564.8
mAb14258	518	523.9	1.02E+06	7.93E-05	7.76E-11	145.7
mAb14294	463.8	440.6	6.94E+05	2.29E-05	3.30E-11	503.9
mAb14283	535.5	470	8.65E+05	7.32E-05	8.47E-11	157.8
mAb14235	386.4	396.9	7.35E+05	3.80E-05	5.17E-11	304

mAb14289	463.7	455.7	9.11E+05	6.63E-05	7.28E-11	174.3
mAb13458	548.9	466	8.15E+05	4.08E-05	5.00E-11	283.2
mAb14313	687.8	610.7	1.01E+06	9.94E-05	9.84E-11	116.2
mAb14247	221.2	247	6.74E+05	4.72E-05	7.01E-11	244.6
mAb14315	576.2	457.2	7.43E+05	3.25E-05	4.37E-11	355.7
mAb13459	826.8	632.1	7.94E+05	4.76E-05	5.99E-11	242.9
mAb13457	468.9	452.4	7.67E+05	5.98E-05	7.79E-11	193.3
mAb14257	602.9	684.6	1.17E+06	1.65E-04	1.41E-10	70.1
mAb14255	516.8	575.4	1.03E+06	1.61E-04	1.55E-10	71.9
mAb14286	437.5	539.2	2.59E+06	1.41E-04	5.44E-11	82
mAb14282	497	566.5	1.05E+06	1.71E-04	1.62E-10	67.7
mAb14281	488.8	429.8	8.34E+05	1.16E-04	1.39E-10	99.7
mAb14230	372.3	435.6	9.06E+05	8.97E-05	9.91E-11	128.7
mAb14256	570.7	509.1	7.96E+05	2.42E-04	3.04E-10	47.7
mAb14285	533.8	647.3	1.16E+06	4.18E-05	3.59E-11	276.3

mAb14280	594.3	650.1	9.85E+05	2.86E-05	2.90E-11	403.7
mAb14234	564.5	473.8	6.99E+05	7.16E-05	1.02E-10	161.4
mAb14232	104.1	119.6	7.51E+05	1.33E-04	1.77E-10	87.1
mAb14292	504.7	236.7	5.92E+05	6.82E-03	1.15E-08	1.7
mAb14314	697.7	259.4	4.59E+05	6.48E-03	1.41E-08	1.8
mAb14248	505.9	2	NB	NB	NB	NB
mAb14295	558.8	6.1	NB	NB	NB	NB
mAb14233	558.6	1.5	NB	NB	NB	NB
mAb14287	523.6	5.2	NB	NB	NB	NB
mAb14293	537.9	3.5	NB	NB	NB	NB
mAb14291	511.8	1.1	NB	NB	NB	NB
mAb14249	478.6	2.7	NB	NB	NB	NB
mAb14316	306.5	4.8	NB	NB	NB	NB
mAb14296	660.5	2.5	NB	NB	NB	NB
mAb14231	489.4	2	NB	NB	NB	NB
mAb14288	571.6	2.9	NB	NB	NB	NB
mAb14297	530.7	2.5	NB	NB	NB	NB
mAb14290	457.4	4.3	NB	NB	NB	NB
mAb14259	395.1	3	NB	NB	NB	NB
mAb15156	463.7±4.1	474.1	1.89E+06	2.12E-04	1.12E-10	54.5

mAb15157	307.2±1.0	298.2	1.70E+06	2.40E-04	1.41E-10	48.2
mAb15158	295.7±1.3	224.5	7.58E+05	4.07E-05	5.41E-11	283.6
mAb15159	293.3±2.0	196.2	4.67E+05	3.22E-05	6.86E-11	359.1
mAb15160	400.3±1.4	301.9	1.26E+06	1.67E-04	1.32E-10	69.2
mAb15161	283.7±0.9	281.6	1.48E+06	9.14E-05	6.16E-11	126.4
mAb15162	323.0±1.5	205.5	4.40E+05	1.87E-04	4.25E-10	61.7
mAb15163	343.6±1.3	323.9	1.35E+06	4.85E-05	3.64E-11	238.1
mAb15164	387.4±1.5	379.2	1.78E+06	1.38E-04	7.77E-11	84.0
mAb15165	279.2±1.5	318.7	2.12E+06	1.15E-04	5.42E-11	100.2
mAb15166	265.2±0.5	282.8	1.54E+06	8.32E-05	5.40E-11	138.8
mAb15167	406.6±1.0	446.1	1.76E+06	9.78E-05	5.57E-11	118.1
mAb15170	303.3±1.4	221.3	8.46E+05	1.00E-05	1.18E-11	1,155.0
mAb15150	249.8±1.8	246.8	1.68E+06	3.42E-05	2.02E-11	337.6
mAb15151	595.2±0.8	372.7	1.92E+06	2.48E-04	1.29E-10	46.6
mAb1932	926.9±3.8	11.4	NB	NB	NB	NB

hBST: human B-cell Sorting Technology

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Example 4: Neutralization of SARS-CoV-2 wild-type and variant spike proteins

[000207] To test whether anti-SARS-CoV-2 spike protein antibodies can neutralize SARS-CoV-2 variants, these antibodies were screened against a panel of VSV pseudotype viruses expressing wild-type and variant spike proteins.

Generation of recombinant VSV

[000208] Non-replicative pseudoparticles were generated using a VSV genome encoding the firefly luciferase and GFP genes instead of the native viral glycoprotein (VSV-G). Infectious particles complemented with VSV-G (VSV-ΔG-Fluc-2A-GFP/VSV-G) were recovered and produced using standard techniques with minor modifications. HEK293T cells (ATCC CRL-3216) were plated on poly-lysine treated plates and incubated overnight in DMEM without glutamine (Life Technologies), 10% fetal bovine serum (Life Technologies) and 1% Penicillin/Streptomycin/L-glutamine (Life Technologies). The following day, the cells were transfected with the VSV genomic clone driven by a T7 promoter and helper plasmids expressing the VSV-N, VSV-P, VSV-G, VSV-L, and T7 RNA polymerase with Lipofectamine LTX reagent (Life Technologies). After 48 hours, the transfected cells were co-cultured with BHK-21 cells (ATCC CCL-10) transfected with VSV-G using the SE cell Line 4D-Nucleofector X Kit L (Lonza) in DMEM without glutamine (Life Technologies), 3% fetal bovine serum (Life Technologies) and 1% Penicillin/Streptomycin/L-glutamine (Life Technologies). Cells were monitored for GFP expression or cytopathic effect (CPE) indicative of virus replication. Virus was then plaque purified, expanded, and titered in BHK-21 cells transiently expressing VSV-G. Fully replicative VSV-SARS-CoV-2-S virus was generated by replacing the VSV glycoprotein with the native SARS-CoV-2 sequences encoding residues 1-1255 of the spike protein (NCBI Accession No. MN908947.3). VSV-SARS-CoV-2-Spike virus was recovered as described above but the HEK293T cells were instead cocultured with BHK-21 cells transfected with both VSV-G and hACE2. VSV-SARS-CoV-2-S virus was plaque-purified and titered in Vero cells (ATCC CCL-81) and expanded in Vero E6 cells (ATCC CRL-1586). After collection, stocks of both

viruses were centrifuged at 3000xg for 5 minutes to clarify, sucrose cushioned to concentrate 10-fold, aliquoted, and frozen at -80C.

Pseudotyping of VSV

[000209] Non-replicative pseudoparticles were generated as previously described (Baum et al., *Science* 2020). Human codon-optimized SARS-CoV-2 spike (NCBI Accession No. MN908947.3) was cloned into an expression plasmid. A total of 1.2 x 107 HEK293T cells (ATCC CRL-3216) were seeded overnight in 15-cm dishes in DMEM without glutamine (Life Technologies) containing 10% heat-inactivated fetal bovine serum (Life Technologies), and Penicillin- Streptomycin-L-Glutamine (Life Technologies). The following day, the cells were transfected with 15μg spike expression plasmid with Lipofectamine LTX (Life Technologies) following the manufacturer's protocol. At 24 hours post transfection, the cells were washed with phosphate buffered saline (PBS) and infected at a MOI of 1 with the VSV-ΔG-Fluc-2A-GFP/VSV-G virus diluted in 10mL Opti-MEM (Life Technologies). The cells were incubated 1 hour at 37C with 5% CO2. Cells were washed three times with PBS to remove residual input virus and overlaid with DMEM with glutamine (Life Technologies) with 0.7% IgG-free BSA (Sigma), sodium pyruvate (Life Technologies), and Gentamicin (Life Technologies). After 24 hours at 37 °C with 5% CO_2, the supernatant containing pseudoparticles was collected, centrifuged at 3000xg for 5 minutes to clarify, aliquoted, and frozen at -80 °C. Variants were cloned into the spike expression plasmid using site-directed mutagenesis and pseudoparticles were produced as described above.

Neutralization assays with VSV based pseudoparticles.

[000210] Vero cells (ATCC: CCL-81) were seeded in 96-well black, clear bottom tissue culture treated plated (Corning: 3904) at 20,000 cells/well in DMEM media without glutamine (Life Technologies) containing 10% heat-inactivated fetal bovine serum (Life Technologies), and 1X Penicillin/Streptomycin/L-Glutamine (Life Technologies) 24 hours prior to assay. Cells were allowed to reach approximately 85% confluence before use in assay. Antibodies were diluted in Infection Media containing DMEM with glutamine (Life Technologies), 0.7% Low IgG BSA (Sigma), 1X Sodium Pyruvate (Life Technologies), and 0.5% Gentamicin (Life Technologies) to 2X assay concentration and diluted 3-fold down in Infection media, for an 11-point dilution curve in the assay beginning at 3 μg/mL (20 nM). Antibody dilutions were mixed 1:1 with pseudoparticles for 30 minutes at room temperature prior to addition onto Vero cells.

Cells were incubated at 37 °C, 5% CO_2 for 24 hours. Supernatant was removed from cells prior to lysis with 100 µL Glo Lysis Buffer (Promega). 100 µL resuspended Bright Glo substrate (Promega) was then added and luminescence was read on a Spectramax i3x (Molecular Devices). Exported values were analyzed using GraphPad Prism (v8.4.1).

[000211] Individual monoclonal antibody half maximal inhibitory concentration (IC50) against VSV-SARS-CoV-2 spike protein (S)-expressing pseudovirus encoding the Wuhan-Hu-1 (NCBI Accession Number MN908947.3) sequence of spike protein (S-wt) or the D614G spike protein variant (SEQ ID NO: 1071) were determined in Vero cells (Table 13). The majority of antibodies displayed neutralization potency in the picomolar range (pM), with some exhibiting neutralization potency in nanomolar (nM) range, and some non-neutralizing. In addition, IC50s were measured for individual monolonal antibodies tested against certain variant of concern/interest VSV-SARS-CoV-2 spike protein (S)-expressing pseudoviruses (Table 14), including the Omicron variant (individual mutations contained in Omicron in Table 15; complete set of Omicron mutations in Table 16, and comparison to and combination with mAb10933 and mAb10987 in Table 17). In the Omicron neutralization assay, mAb15160 was unaffected, while mAb14315 had a marginally decreased neutralization. Based on these results, a mAb14315/mAb15160 combination and a mAb15160/mAb14256 combination maintain effective neutralization of the Omicron variant. In addition, mAb14284, mAb14235, and mAb14287 were potent neutralizers and were unaffected by the Omicron variants, while mAb15151 had a half-log decrease in neutralization of the Omicron variant but maintained potency nonetheless based on its strong neutralization properties. As shown in the tables, the lower the fold change from wt or D614G, the less impact the Omicron mutations have on neutralization. Additional mAb15160 and mAb14284 neutralization data is presented in Tables 18 and 19, showing that these antibodies are potent neutralizers of different variants, including Omicron lineages.

Table 13: mAb neutralization potency (IC50 (M)) against the wild-type or D614G strain of VSV-SARS-CoV-2-S pseudoparticles in Vero cells

mAb	IC50 (M)

mAb13457	2.48E-11
mAb13458	2.61E-11
mAb13459	3.66E-11
mAb14230	2.41E-11
mAb14231	1.02E-09
mAb14232	6.35E-11
mAb14233	5.42E-11
mAb14234	3.98E-11
mAb14235	3.38E-11
mAb14247	5.80E-11
mAb14248	6.20E-11
mAb14249	1.62E-10
mAb14255	3.43E-11
mAb14256	5.47E-11
mAb14257	2.91E-11
mAb14258	5.57E-11
mAb14259	3.72E-11
mAb14260	9.28E-11
mAb14280	2.86E-11
mAb14281	3.35E-11
mAb14282	3.27E-11
mAb14283	5.49E-11
mAb14284	3.14E-11
mAb14285	3.25E-11

mAb14286	~ 2.616E11
mAb14287	1.99E-10
mAb14288	1.38E-09
mAb14289	4.02E-11
mAb14290	1.20E-09
mAb14291	1.23E-10
mAb14292	5.77E-11
mAb14293	1.10E-09
mAb14294	5.67E-11
mAb14295	1.95E-10
mAb14296	5.26E-10
mAb14297	3.85E-10
mAb14312	4.66E-11
mAb14313	2.72E-10
mAb14314	no activity
mAb14315	4.76E-11
mAb14316	1.29E-10
mAb15156	2.09E-11
mAb15157	3.72E-11
mAb15158	1.24E-10
mAb15159	5.78E-11
mAb15160	4.58E-11
mAb15161	4.91E-11
mAb15162	1.11E-10

mAb15163	6.28E-11
mAb15164	2.48E-11
mAb15165	2.96E-11
mAb15166	1.61E-11
mAb15167	2.95E-11
mAb15170	1.22E-10
mAb15150	6.21E-11
mAb15151	7.09E-12

Underlined IC50 values determined using D614G spike protein.

Table 14: Pseudoparticle neutralization IC50 (M) of variants of concern/interest (VOCs/VOIs) variants in Vero cells

mAb	B.1.1.7		B.1.351		P.1		E484K		L452R	
	IC50	FC	IC50	FC	IC50	FC	IC50	FC	IC50	FC
mAb 14255	1.8E-11	1.2	3.9E-11	1.9	4.1E-11	1.7	4.5E-11	2.8	2.9E-11	1.4
mAb 14256	4.3E-11	1.0	1.5E-11	0.4	1.3E-11	0.3	1.6E-11	0.8	2.8E-11	0.7
mAb 14257	1.1E-11	1.6	1.7E-08	>48988	ND	ND	NA	>2640	ND	ND
mAb 14258	1.0E-10	1.5	NA	>1754	ND	ND	NA	>794	ND	ND
mAb 14312	ND	ND	2.9E-10	9.3	ND	ND	ND	ND	7E-11	2.2
mAb 14315	8.0E-11	2.7	9.8E-12	0.3	4.1E-11	0.6	1.5E-11	0.5	4.2E-11	1.0
mAb 15156	3.1E-11	1.5	4.8E-12	0.2	ND	ND	ND	ND	3.7E-11	1.4
mAb 15157	5.7E-11	1.5	1.4E-11	0.4	ND	ND	ND	ND	ND	ND
mAb 15158	1.1E-10	0.9	2.1E-08	172	ND	ND	ND	ND	ND	ND
mAb 15159	7.7E-11	1.3	2.6E-11	0.5	ND	ND	ND	ND	ND	ND
mAb 15160	5.3E-11	1.2	1.1E-11	0.2	ND	ND	ND	ND	5.8E-11	1.6
mAb 15161	7.2E-11	1.5	1.5E-11	0.3	ND	ND	ND	ND	5.9E-11	1.1
mAb 15162	7.5E-11	0.7	4.2E-11	0.4	ND	ND	ND	ND	ND	ND
mAb 15163	6.5E-11	1.0	2.5E-10	4.0	ND	ND	ND	ND	ND	ND
mAb 15164	2.7E-11	1.1	2.6E-11	1.0	ND	ND	ND	ND	3.0E-11	2.0
mAb 15165	2.9E-11	1.0	1.6E-11	0.6	ND	ND	ND	ND	2.9E-11	2.2

mAb 15166	2.4E-11	1.5	1.9E-10	12.0	ND	ND	ND	ND	ND	ND
mAb 15167	2.9E-11	1.0	3.1E-10	10.4	ND	ND	ND	ND	ND	ND
mAb 15170	9.5E-11	0.8	8.9E-11	0.7	ND	ND	ND	ND	ND	ND
mAb 15150	8.3E-11	1.3	5.7E-12	0.1	ND	ND	ND	ND	ND	ND
mAb 15151	1.1E-11	1.0	5.4E-12	0.8	ND	ND	2.3E-11	2.1	2E-11	0.9

Full B.1.1.7 (H69del, V70del, Y145del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), B.1.351 (D80Y, D215Y, L241del, L242del, A243del, L242del, K417N, E484K, N501Y, D614G, A701V), and P.1 (L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F) variants were assessed. Key RBD residues from B.1.429 (L452R) and B.1.526 (E484K) lineages were assessed.

Fold-decrease in potency (FC) was calculated relative to wt or D614G control from same assay
NA: No Activity
ND: Not determined

Table 15: Pseudoparticle neutralization IC50 (M) and fold-change of variants in Vero cells

Spike protein	**mAb14256**	**mAb14315**	**mAb15160**	**mAb10985**
WT/D614G (IC50)	*2.606E-11*	*2.95E-11*	*4.58E-11*	*2.17E-10*
K417N (FC)	1.46	0.66	0.86	1.38
N440K (FC)	2.51	0.94	ND	1.41
S477N (FC)	1.01	0.60	1.01	1.32
T478K (FC)	0.81	0.96	1.98	0.98
Q493R (FC)	0.86	0.45	ND	0.38
N501Y (FC)	1.06	ND	1.81	1.28

Italics: IC50 values for each antibody against wt or D614G control spike protein
Fold-decrease in potency (FC) was calculated relative to wt or D614G control from the same assay
ND: Not determined

Table 16: Pseudoparticle neutralization IC50 (M), IC90 (M), and IC50 fold-change of Omicron variant SARS-CoV-2 in Vero cells

SARS-CoV-2 spike glycoprotein	mAb14256	mAb14315	mAb15160	mAb15160 + mAb14315	mAb14256 + mAb15160
D614G (control) IC50 (IC90, where provided)	5.33E-11 (4.08E-10)	4.97E-11	2.95E-11	4.76E-11	4.84E-11
Omicron IC50 (IC90, where provided)	NC (NC)	1.45E-10	1.71E-11	6.47E-11	1.02E-10
D614G (control) IC50 FC (log10 FC)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Omicron IC50 FC (log10 FC)	**375.38 (2.57)**	2.91 (0.46)	0.58 (-0.24)	1.36 (0.13)	2.10 (0.32)

Table 16 (cont'd)

SARS-CoV-2 spike glycoprotein	mAb14284	mAb14235	mAb14294	mAb14234	mAb14312
D614G (control)	8.25E-12	3.79E-12	5.00E-12	2.38E-12	1.00E-12
Omicron	1.03E-11	6.84E-12	6.67E-12	2.62E-12	7.94E-13
D614G (control) IC50 FC (log10 FC)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Omicron IC50 FC (log10 FC)	1.25 (0.10)	1.81 (0.26)	1418.80 (3.15)	21.82 (1.34)	5287.59 (3.72)

Table 16 (cont'd)

SARS-CoV-2 spike glycoprotein	mAb15170	mAb15162	mAb15150	mAb15151	mAb15159	mAb15161
D614G (control)	6.41E-12	4.31E-12	8.52E-13	7.78E-13	4.34E-12	1.92E-12
Omicron	6.11E-12	7.25E-12	1.23E-12	2.44E-12	5.05E-12	1.08E-12
D614G (control) IC50 FC (log10 FC)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Omicron IC50 FC (log10 FC)	37.20 (1.57)	27.88 (1.45)	392.47 (2.59)	3.14 (0.50)	214.77 (2.33)	160.43 (2.21)

SARS-CoV-2 spike glycoprotein	mAb15157	mAb15156	mAb14287	mAb14297
D614G (control)	1.01E-12	4.62E-13	2.18E-12	9.72E-12
Omicron	1.15E-12	4.96E-13	4.42E-12	NC
D614G (control) IC50 FC (log10 FC)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Omicron IC50 FC (log10 FC)	**19841.27 (4.30)**	74.72 (1.87)	0.20 (-0.69)	**2058.67 (3.31)**

Omicron spike protein used comprises SEQ ID NO: 1073 the following mutations: A67V, Δ69-70, T95I, G142D/Δ143-145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

NC: No IC50 calculated due to no activity

FC: Fold change calculated relative to D614G control

Values in bold and underlined: Fold change is at least this value, calculated as highest assay concentration/D614G IC50; highest concentration in assay was 2.00E-08

Table 17: Pseudoparticle neutralization IC50 (M) and IC50 fold-change of Omicron variant (B.1.1.529/BA.1) SARS-CoV-2 in Vero cells

	mAb10933 + mAb10987		mAb15160		mAb15160 + mAb10933 + mAb10987 2:1:1 (inferred values)	
Variant[a]	**IC_{50}(M)**	**Fold Decrease in IC_{50} over Ref Virus[b]**	**IC_{50}(M)**	**Fold Decrease in IC_{50} over Ref Virus[b]**	**IC_{50}(M)**	**Fold Decrease in IC_{50} over Ref Virus[b]**
D614G control	9.91E-12	1.0	1.92E-11	1.0	3.84E-11	1.0
B.1.1.529/BA.1 (Omicron)	NC	>2018.98[c]	3.18E-11	1.65	6.36E-11	3.3

[a] Amino acid substitutions versus Wuhan lineage S protein: **B.1.1.529/BA.1** (A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F)

[b] Fold decrease relative to reference (ref) D614G virus was calculated by dividing the IC_{50} value generated by the antibody(ies) in the presence of a particular variant by the IC_{50} value generated by the antibody(ies) in the presence of reference virus from the same assay.

[c] Where an IC_{50} value could not be accurately calculated, the change in mAb potency in the presence of each mutant was calculated by dividing the maximum antibody concentration tested (20nM) by the IC_{50} value calculated for the reference D614G VLP. The actual fold change is at least that of the indicated value.

Abbreviations: NC, not calculated due to poor or lack of neutralization

Table 18: IC_{50} and IC_{90} Values for mAb15160-Mediated Neutralization of Entry of pVSV-Luc-SARS-CoV-2-S Pseudotyped with S Protein Variants into Vero Cells

SARS-CoV-2 S Protein Variant	mAb15160			mAb10933 (Casirivimab)			mAb10987 (Imdevimab)			Casirivimab+Imdevimab		
	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
Full Sequences or Key Residues of Variants under Surveillance[a] and Other Multi-Variant Lineages												
B.1.1.7 (Alpha)	5.28E-11	2.21E-10	1.15	2.26E-11	2.23E-10	0.69	1.71E-11	9.31E-11	0.41	1.11E-11	9.09E-11	0.46
B.1.351 (Beta)	1.07E-11	1.70E-10	0.23	2.87E-09	2.68E-08	87.97	2.12E-11	4.43E-11	0.51	2.67E-11	2.54E-10	1.11
P.1 (Gamma)	1.02E-11	6.55E-11	0.48	7.52E-09	3.16E-07	167.54	4.58E-12	6.46E-11	0.18	1.01E-11	7.63E-11	1.16
B.1.617.2 (Delta)	2.80E-11	1.55E-10	3.07	4.32E-12	4.23E-11	0.55	1.04E-11	2.11E-10	1.26	7.45E-12	5.02E-11	1.06
K417N+L452R+T478K (AY.1 [Delta])	5.61E-12	1.04E-10	0.16	1.81E-11	5.01E-10	1.23	8.08E-12	1.46E-10	0.58	7.50E-12	5.53E-11	0.55
L145H+A222V+L452R+T478K (AY4.2 [Delta])	2.32E-11	1.82E-10	1.73	1.15E-11	8.27E-11	0.70	3.60E-11	6.57E-10	1.94	1.55E-11	7.38E-11	1.51
L452R (B.1.427/B.1.429 [Epsilon])	5.83E-11	2.24E-10	1.55	5.60E-11	3.17E-10	0.76	7.83E-11	7.26E-10	1.03	4.96E-11	1.64E-10	1.15
E484K (B.1.526 [Iota])	5.97E-11	4.83E-10	2.84	2.49E-10	3.53E-09	5.55	2.62E-11	4.30E-10	1.01	3.20E-11	1.60E-10	3.67
B.1.617.1 (Kappa)	2.98E-11	1.76E-10	2.98	1.14E-10	1.06E-09	22.12	1.51E-11	1.63E-10	1.68	2.45E-11	9.08E-11	3.07
F490S+L452Q (C.37 [Lambda])	2.64E-11	2.35E-10	0.73	1.37E-11	1.73E-10	0.93	4.23E-11	5.72E-10	3.05	1.53E-11	1.23E-10	1.12
R346K+E484K+N501Y (B.1.621 [Mu])	2.52E-11	2.95E-10	1.71	2.10E-10	1.74E-09	19.22	9.03E-12	1.00E-10	0.60	1.44E-11	1.54E-10	1.29
BA.1 (Omicron)	1.84E-11	1.80E-10	1.05	NC	NC	>1731.60[b]	NC	NC	>754.43[b]	NC	NC	>1012.66[b]
BA.1.1 (Omicron)	2.26E-11	1.57E-10	0.96	NC	NC	>1336.01[b]	NC	NC	>1108.65[b]	NC	NC	>1460.92[b]
BA.2 (Omicron)	1.46E-11	1.53E-10	2.08	6.80E-09	8.04E-08	461.82	2.19E-09	1.99E-08	158.12	2.60E-09	1.82E-08	190.26
BA.2.12.1 (Omicron)	5.63E-11	4.67E-10	2.22	NC	NC	>702.26	3.18E-09	1.79E-08	137.46	4.77E-09	1.71E-08	275.13

SARS-CoV-2 S Protein Variant	mAb15160			mAb10933 (Casirivimab)			mAb10987 (Imdevimab)			Casirivimab+Imdevimab		
	IC_{50} [M]	**IC_{90} [M]**	**Fold Change in IC_{50} over Ref Virus**	**IC_{50} [M]**	**IC_{90} [M]**	**Fold Change in IC_{50} over Ref Virus**	**IC_{50} [M]**	**IC_{90} [M]**	**Fold Change in IC_{50} over Ref Virus**	**IC_{50} [M]**	**IC_{90} [M]**	**Fold Change in IC_{50} over Ref Virus**
BA.3 (Omicron)	6.06E-11	1.16E-09	3.34	NC	NC	1258.65	NC	NC	899.69	NC	NC	1456.66
BA.4/BA.5 (Omicron)	NC	NC	>701.48	NC	NC	652.76	1.38E-09	1.10E-08	54.10	3.67E-09	1.91E-08	200.81
N439K+E484K (AV.1)	3.57E-11	4.00E-10	3.92	1.22E-10	1.98E-09	15.58	NC	NC	>2417.79 [b]	4.23E-10	2.99E-09	60.04
N440K+E484K (B.1.619, B.1.619.1, B.1.625)	3.25E-11	4.37E-10	3.57	2.03E-10	2.41E-09	25.89	1.85E-09	1.07E-07	223.53	2.76E-10	1.60E-09	39.20
C.1.2	3.75E-11	2.03E-10	2.79	1.76E-10	1.22E-09	10.69	8.62E-12	8.51E-11	0.46	1.57E-11	8.03E-11	1.53
All Single-Mutation Variants												
Y145H	1.88E-11	1.03E-10	1.40	1.61E-11	7.83E-11	0.98	2.13E-11	1.51E-10	1.15	1.46E-11	4.36E-11	1.43
W152C	1.24E-11	1.60E-10	0.34	4.99E-12	1.37E-10	0.34	9.60E-12	1.05E-10	0.69	8.86E-12	1.01E-10	0.65
V308L	2.86E-11	2.58E-10	0.79	1.39E-11	1.46E-10	0.95	1.62E-11	1.60E-10	1.17	1.23E-11	1.05E-10	0.90
G339D	5.47E-11	2.42E-10	1.46	2.54E-11	2.26E-10	0.94	2.52E-11	1.98E-10	1.00	2.22E-11	9.66E-11	1.43
E340A	2.16E-11	2.02E-10	0.74	2.36E-11	1.10E-10	0.78	2.13E-11	2.26E-10	0.59	1.48E-11	1.02E-10	1.22
E340K	2.54E-11	1.81E-10	0.86	1.98E-11	1.95E-10	0.65	1.63E-11	4.20E-10	0.45	1.13E-11	1.36E-10	0.93
R346K	3.95E-11	2.56E-10	2.99	2.45E-11	1.48E-10	1.44	2.90E-11	1.85E-10	2.51	2.10E-11	8.42E-11	2.39
R346S	3.21E-11	1.65E-10	1.36	2.31E-11	1.34E-10	1.54	2.76E-11	2.28E-10	1.53	1.90E-11	8.63E-11	1.39
S371L	2.62E-10	1.01E-09	7.00	1.37E-10	3.99E-10	5.07	1.78E-10	6.48E-10	7.07	9.21E-11	2.52E-10	5.96
A372T	3.00E-12	1.57E-10	0.16	2.01E-13	7.46E-12	0.05	4.09E-12	8.55E-11	0.35	3.46E-12	4.35E-11	0.35
S373P	3.58E-11	1.66E-10	0.96	1.90E-11	1.07E-10	0.71	1.88E-11	1.16E-10	0.74	1.26E-11	7.11E-11	0.82
S375F	1.72E-11	7.65E-11	0.46	8.68E-12	1.13E-10	0.32	7.45E-12	2.75E-11	0.30	5.17E-12	4.04E-11	0.33
D389Y	6.90E-12	6.82E-11	0.17	2.24E-12	3.73E-11	0.12	5.74E-12	8.36E-11	0.41	4.69E-12	3.96E-11	0.24
D405N	3.26E-11	2.10E-10	1.38	3.06E-11	2.69E-10	2.04	1.29E-11	1.78E-10	0.71	1.73E-11	7.98E-11	1.27
E406D	1.91E-11	2.51E-10	1.91	5.69E-10	5.05E-09	110.30	2.08E-11	4.32E-10	2.31	3.67E-11	4.50E-10	4.60
E406Q	2.05E-11	1.72E-10	2.07	1.07E-09	6.74E-09	255.89	1.12E-11	1.63E-10	2.32	2.10E-11	2.99E-10	11.37
K417N	2.47E-11	2.29E-10	1.27	8.96E-11	1.15E-09	8.74	6.22E-12	7.65E-11	1.35	1.35E-11	5.16E-11	1.54
K417R [c]	5.04E-12	1.96E-11	2.37	4.10E-09	2.96E-08	61.23	2.92E-11	2.92E-10	1.70	1.24E-10	6.59E-10	2.45
N439K	2.13E-11	1.06E-10	0.57	4.47E-11	4.31E-10	0.60	1.77E-08	1.12E-07	231.51	7.25E-11	2.50E-10	1.69
N440D	5.41E-11	3.94E-10	2.28	1.69E-11	2.09E-10	1.04	1.92E-09	1.42E-08	119.13	6.71E-11	4.36E-10	4.90
N440K	2.44E-11	2.06E-10	1.26	1.02E-11	1.22E-10	0.99	1.34E-09	1.57E-08	291.40	1.88E-11	3.28E-10	2.15
V445T	2.23E-11	1.85E-10	0.94	2.27E-11	1.82E-10	1.52	7.25E-09	6.14E-08	401.72	4.86E-11	4.00E-10	3.55

SARS-CoV-2 S Protein Variant	mAb15160			mAb10933 (Casirivimab)			mAb10987 (Imdevimab)			Casirivimab+Imdevimab		
	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
G446D	1.58E-11	2.80E-10	0.44	1.75E-11	1.79E-10	1.19	7.66E-09	3.38E-08	553.07	3.52E-11	2.71E-10	2.58
G446R	2.59E-11	1.72E-10	1.09	1.09E-11	1.05E-10	0.68	4.41E-09	4.26E-08	273.91	4.36E-11	2.74E-10	3.18
G446S	1.13E-11	1.74E-10	0.58	8.70E-12	7.95E-11	0.85	4.24E-09	1.61E-08	920.25	1.95E-11	2.24E-10	2.23
Y449F	2.03E-11	2.25E-10	0.64	8.48E-12	6.34E-11	0.59	1.07E-11	9.56E-11	0.96	6.23E-12	4.90E-11	0.82
Y449H	3.68E-11	2.12E-10	1.26	2.74E-11	1.56E-10	0.91	3.11E-12	6.68E-11	0.09	1.42E-11	1.43E-10	1.17
Y449N	2.68E-11	2.64E-10	1.13	1.23E-11	1.16E-10	0.82	5.14E-12	3.84E-11	0.28	7.83E-12	3.38E-11	0.57
N450K	4.75E-11	2.88E-10	0.83	4.40E-11	1.97E-10	0.91	2.95E-11	1.60E-10	0.84	3.18E-11	1.07E-10	0.91
L452R	5.83E-11	2.24E-10	1.55	5.60E-11	3.17E-10	0.76	7.83E-11	7.26E-10	1.03	4.96E-11	1.64E-10	1.15
L455F	3.15E-11	3.00E-10	0.78	7.69E-09	9.21E-08	426.00	1.93E-11	1.05E-10	1.39	2.73E-11	2.94E-10	1.39
K458N	4.50E-11	2.76E-10	1.86	1.76E-11	1.89E-10	1.14	1.92E-11	1.38E-10	1.60	1.39E-11	7.82E-11	2.58
K458R	2.20E-11	1.94E-10	2.77	7.59E-12	1.09E-10	1.36	7.71E-12	1.57E-10	0.96	6.58E-12	9.08E-11	1.28
A475V	1.47E-11	1.09E-10	0.61	1.48E-11	1.49E-10	0.96	1.05E-11	8.96E-11	0.88	8.43E-12	5.26E-11	1.56
S477N	3.78E-11	1.47E-10	1.01	9.78E-11	4.22E-10	1.32	6.54E-11	4.44E-10	0.86	4.15E-11	1.68E-10	0.97
S477R	3.87E-11	2.16E-10	1.60	1.29E-11	1.14E-10	0.84	3.19E-11	1.70E-10	2.67	1.19E-11	6.78E-11	2.19
T478I	4.19E-11	2.76E-10	1.73	2.44E-11	1.84E-10	1.58	2.42E-11	1.73E-10	2.02	1.58E-11	9.96E-11	2.93
T478K	2.45E-11	1.87E-10	1.26	7.11E-12	9.04E-11	0.69	1.23E-11	2.96E-10	2.66	6.28E-12	6.43E-11	0.72
P479S	2.63E-11	1.88E-10	1.09	2.31E-11	1.76E-10	1.50	2.12E-11	1.56E-10	1.77	1.03E-11	6.23E-11	1.90
E484A	5.09E-11	2.73E-10	1.36	1.03E-10	7.12E-10	3.83	1.10E-11	1.04E-10	0.43	1.87E-11	1.04E-10	1.21
E484K	5.97E-11	4.83E-10	2.84	2.49E-10	3.53E-09	5.55	2.62E-11	4.30E-10	1.01	3.20E-11	1.60E-10	3.67
G485S	2.30E-11	1.31E-10	0.97	4.24E-11	3.46E-10	2.83	1.23E-11	1.10E-10	0.68	1.93E-11	6.01E-11	1.41
F486V	NC	NC	>531.21[b]	NC	NC	>269.61[b]	5.75E-11	2.40E-10	0.75	9.85E-11	3.68E-10	2.29
Y489H	2.53E-09	6.61E-09	121.48	NC	NC	>2311.60[b]	3.55E-12	7.16E-11	0.35	2.15E-11	2.42E-10	2.57
F490L	5.68E-11	2.08E-10	1.94	2.96E-11	1.69E-10	0.98	2.37E-11	1.51E-10	0.65	1.43E-11	1.53E-10	1.18
F490S	1.76E-11	2.69E-10	0.60	2.53E-11	1.45E-10	0.84	7.24E-12	4.51E-10	0.20	1.65E-11	1.81E-10	1.36
F490Y	1.86E-11	1.67E-10	0.79	9.70E-12	1.47E-10	0.65	1.33E-11	1.51E-10	0.74	1.62E-11	7.39E-11	1.18
Q493E	8.85E-12	6.10E-11	1.11	NC	NC	>3588.73[b]	1.34E-11	8.69E-11	1.67	3.05E-11	2.69E-10	5.95
Q493K	4.57E-11	6.68E-10	3.40	6.25E-09	1.31E-07	378.67	1.77E-11	1.53E-10	0.95	4.22E-11	3.40E-10	4.11
Q493R	9.47E-11	5.79E-10	4.88	8.68E-10	8.94E-09	84.71	1.76E-11	1.12E-10	3.82	2.79E-11	2.56E-10	3.18

SARS-CoV-2 S Protein Variant	mAb15160			mAb10933 (Casirivimab)			mAb10987 (Imdevimab)			Casirivimab+Imdevimab		
	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
G496S	4.53E-11	1.72E-10	1.21	2.25E-11	1.07E-10	0.83	1.28E-10	9.49E-10	5.08	2.66E-11	9.64E-11	1.72
Q498R	4.72E-11	2.55E-10	1.26	1.89E-11	2.02E-10	0.70	1.93E-11	2.00E-10	0.77	1.53E-11	7.85E-11	0.99
T500A	1.18E-12	6.09E-10	0.12	3.74E-12	3.45E-10	0.90	4.91E-11	4.77E-10	10.21	9.85E-12	1.05E-10	5.32
T500F	8.35E-12	1.97E-10	0.84	2.76E-12	8.39E-11	0.66	1.70E-12	2.56E-11	0.35	2.54E-12	1.90E-11	1.37
N501Y	5.40E-11	2.79E-10	2.78	2.13E-11	2.08E-10	2.08	6.85E-12	8.63E-11	1.49	1.03E-11	5.18E-11	1.17
Y505F	4.34E-11	3.08E-10	1.07	2.06E-11	2.27E-10	1.14	1.84E-11	1.50E-10	1.32	1.62E-11	1.10E-10	0.82
Y505H	2.84E-11	1.64E-10	0.76	1.40E-11	8.52E-11	0.52	9.54E-12	5.75E-11	0.38	1.40E-11	5.52E-11	0.91

[a] Full sequences and/or key residues of the S protein from variants under surveillance; full S protein sequences: **B.1.1.7** (H69del, V70del, Y145del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), **B.1.351** (D80Y, D215G, L241del, L242del, A243del, K417N, E484K, N501Y, D614G, A701V), **P.1** (L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F), **B.1.617.2** (T19R, G142D, E156G, F157del, R158del, L452R, T478K, D614G, P681R, D950N), **B.1.617.1** (T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H), **BA.1** (A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F), **BA.1.1** (BA.1+R346K), **BA.2** (T19I, del24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K); key S protein residues: **AY.1** (K417N+L452R+T478K), **AY4.2** (Y145H+A222V+L452R+T478K), **B.1.427/B.1.429** (L452R), **B.1.526** (E484K), **B.1.621** (R346K+E484K+N501Y), **AV.1** (N439K+E484K), **B.1.619/B.1.619.1/B.1.625** (N440K+E484K), **C.1.2** (Y449H+E484K+N501Y).

[b] Where an IC_{50} value could not be accurately calculated, the change in mAb potency in the presence of each mutant was calculated by dividing the maximum antibody concentration tested (20nM) by the IC_{50} value calculated for casirivimab, imdevimab, or casirivimab+imdevimab in the presence of reference pVSV-SARS-CoV-2-S pseudoparticles.

[c] The IC_{50} and IC_{90} values for neutralization of this variant by mAb15160 and imdevimab were compared to different reference virus datasets than casirivimab and casirivimab+imdevimab.

del, deletion; ins, insertion; NA, not applicable; NC, not calculated due to poor or lack of neutralization; NT, not tested

Fold change calculated relative to D614G control

Table 19: Summary of IC_{50} and IC_{90} Values for REGN14284-Mediated Neutralization of Entry of pVSV-Luc-SARS-CoV-2-S Pseudotyped with S Protein Variants into Vero Cells

SARS-CoV-2 S Protein Variant		IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
Full Sequences or Key Residues of Variants under Surveillance [a] and Other Multi-Variant Lineages				
Alpha	B.1.1.7[a]	1.14E-11	7.58E-11	1.14
Beta	B.1.351[a]	9.73E-12	6.15E-11	0.98
Gamma	P.1[a]	8.34E-12	7.52E-11	0.84
Delta	B.1.617.2[a]	6.09E-12	6.07E-11	0.69
	K417N+L452R+T478K (AY.1) *	3.42E-12	3.53E-11	0.50

SARS-CoV-2 S Protein Variant		IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
	Y145H+A222V+ L452R+T478K (AY4.2)	2.53E-11	2.34E-10	0.75
Epsilon	W152C+L452R (B.1.427/B.1.429)	1.28E-11	9.23E-11	1.18
Iota	E484K (B.1.526)	5.40E-11	5.30E-10	1.61
Kappa	B.1.617.1[a]	4.24E-11	3.84E-10	1.26
Lambda	F490S+L452Q (C.37) *	1.20E-11	1.58E-10	1.17
Mu	R346K+E484K+N501Y (B.1.621)	9.89E-12	8.66E-11	0.99
Omicron	BA.1[a] *	8.86E-12	1.09E-10	1.63
	BA.1.1[a]	1.00E-11	1.03E-10	0.58
	BA.2[a] *	1.13E-11	1.54E-10	0.98
	BA.2.12.1[a] *	2.55E-11	2.12E-10	1.40
	BA.3[a]	2.22E-11	4.41E-10	2.52
	BA.4/BA.5[a] *	1.85E-11	1.89E-10	0.79
NA	C.1.2	3.16E-11	3.20E-10	0.94
All Single-Mutation Variants				
W152C		9.40E-12	6.46E-11	0.81
S247R		3.70E-12	3.53E-11	0.90
V308L		1.38E-11	1.30E-10	1.19
N334D		6.69E-12	1.75E-10	1.01
G339D		4.01E-11	2.86E-10	1.68
E340A		1.43E-11	1.28E-10	1.86
E340K		1.16E-11	8.07E-11	1.51
R346K		1.04E-11	9.43E-11	1.41
R346S		2.73E-11	1.05E-10	1.59
S371F		4.66E-11	2.80E-10	12.75
S371Y		4.00E-11	3.21E-10	7.78
A372T		1.16E-11	1.14E-10	1.56
T376A		2.64E-12	4.44E-11	0.72
T376S		1.54E-11	1.59E-10	0.65
D405N		8.15E-12	7.93E-11	0.47
E406W		1.67E-11	4.82E-10	1.91
R408S		9.12E-12	6.38E-11	2.49
K417T		6.45E-12	7.44E-11	1.76
Y421F		4.47E-12	8.04E-11	0.51
N439K		4.13E-11	8.23E-10	1.98
N439V		1.59E-11	1.97E-10	0.76

SARS-CoV-2 S Protein Variant	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
N440D	5.16E-11	5.34E-10	2.47
N440K	3.09E-11	7.31E-10	1.48
L441F	1.80E-11	1.36E-10	0.86
L441Q	2.78E-11	2.69E-10	1.33
K444L	NC	NC	>957.40[b]
K444M	5.23E-10	5.92E-09	25.03
K444N	NC	NC	>957.40[b]
K444Q	4.93E-09	5.90E-08	236.00
K444R	4.33E-12	4.92E-11	1.54
K444T	NC	NC	>5599.10[b]
V445A	1.88E-10	2.81E-09	57.18
V445T	9.18E-10	8.56E-09	53.44
G446D	2.34E-10	1.94E-09	20.28
G446R	3.37E-11	2.51E-10	10.23
G446S	8.96E-12	6.40E-11	2.72
G446V	3.38E-11	7.30E-10	9.46
G447V	2.35E-11	3.12E-10	8.34
N448S	2.62E-12	4.64E-11	0.30
Y449D	8.48E-12	1.01E-10	2.57
Y449F	7.32E-12	4.74E-11	0.85
Y449H	1.04E-11	8.45E-11	1.36
Y449N	7.92E-12	9.05E-11	0.46
Y449S	8.70E-12	8.60E-11	2.64
N450K	8.36E-12	1.19E-10	0.72
L452M	8.87E-12	6.13E-11	2.16
L452Q	2.61E-11	1.79E-10	1.10
L452R	5.49E-11	7.32E-10	1.63
F456L	5.87E-12	1.05E-10	0.67
Y473F	6.01E-12	8.57E-11	0.68
A475V	7.47E-12	8.37E-11	0.65
S477N	1.37E-11	2.02E-10	1.70
T478K	1.34E-11	1.69E-10	1.66
E484A	1.38E-11	1.74E-10	0.58
E484K	5.40E-11	5.30E-10	1.61
E484Q	3.04E-12	4.51E-11	0.35
G485S	8.52E-12	9.47E-11	0.50
G485V	9.62E-12	9.33E-11	1.10

SARS-CoV-2 S Protein Variant	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
F486S	1.79E-11	5.36E-10	2.03
F486V	6.23E-11	3.18E-10	7.72
Y489H	8.93E-13	4.43E-11	0.15
F490L	2.12E-11	1.41E-10	2.76
F490S	2.04E-11	1.19E-10	2.65
F490Y	1.20E-11	7.26E-11	0.70
Q498H	1.10E-11	1.41E-10	3.09
Q498R	2.24E-11	1.35E-10	0.94
T500A	1.46E-11	1.02E-10	4.07
T500F	8.56E-12	3.85E-11	2.40
T500N	2.28E-11	1.52E-10	3.45
N501T	5.57E-12	3.47E-11	1.69
N501Y	1.22E-11	1.42E-10	1.51
Y505H	2.46E-11	2.00E-10	1.03

* The values shown for the indicated variant/reference virus represent the geometric mean from at least 3 replicate assays.

[a] Full S protein sequences and/or key residues of variants under surveillance were assessed. Key residues assessed and the lineages they represent are shown in the table. Full sequences are indicated by footnote 'a' within the table and contain the following substitutions in the Wuhan-Hu-1 S protein reference sequence: **B.1.1.7** (H69del, V70del, Y145del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), **B.1.351** (D80Y, D215G, L241del, L242del, A243del, K417N, E484K, N501Y, D614G, A701V), **P.1** (L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F), **B.1.617.2** (T19R, G142D, E156G, F157del, R158del, L452R, T478K, D614G, P681R, D950N), **B.1.617.1** (T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H), **BA.1** (A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F), **BA.1.1** (BA.1+R346K), **BA.2** (T19I, del24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K), **BA.2.12.1** (BA.2+L452Q), **BA.3** (G142D, G339D, S371F, S373P, S375F, D405N, K417N D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K), **BA.4/BA.5** (both lineages have an identical S protein sequence [T19I, L24del, P25del, P26del, A27S, H69del, V70del, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K])

[b] Where an IC_{50} value could not be accurately calculated, the change in mAb potency in the presence of each mutant was calculated by dividing the maximum antibody concentration tested (20nM) by the IC_{50} value calculated for the antibody in the presence of reference pVSV-SARS-CoV-2-S pseudoparticles.

del, deletion; ins, insertion; NC, not calculated due to poor or lack of neutralization

mAb14284 was tested at concentrations ranging from approximately 300fM to 20nM. Fold change over reference (ref) virus was calculated by dividing the IC_{50} value determined for the antibody in the presence of a particular variant by the IC_{50} value determined for the antibody in the presence of reference pseudoparticles (pVSV-SARS-CoV-2 pseudotyped with the D614G mutation) from the same assay.

Example 5: Anti-SARS-CoV-2 Antibodies block RBD binding to hACE2 as determined by ELISA

[000212] An ELISA-based blocking assay was used to determine the ability of anti-SARS-CoV-2 antibodies to block the binding of the SARS-COV-2 Spike protein receptor binding domain (RBD) to its receptor, human angiotensin converting enzyme 2 (hACE2).

[000213] The SARS-CoV-2 protein used in this assay was comprised of the receptor binding domain (RBD) portion of the SARS-CoV-2 Spike protein (amino acids Arg319-Phe541) expressed with a C-terminal myc-myc-6-Histidine tag (SARS-CoV-2 RBD.mmh). The human ACE-2 protein used in the experiments was purchased from R&D Systems, comprising a portion of the human ACE-2 extracellular domain (amino acids Leu18-Ser740) and a C-terminal 10-Histidine tag (hACE-2-10His; ACE2 NCBI Accession No. Q9BYF1).

[000214] Experiments were carried out using the following procedure. The hACE-2-10His receptor was coated at 2 μg/ml in PBS on a 96-well microtiter plate overnight at 4 °C. Nonspecific binding sites were subsequently blocked using a 0.5% (w/v) solution of BSA in PBS. In other microtiter plates, a constant amount of 300pM of SARS-CoV-2 RBD.mmh protein was bound for one hour with anti-SARS-COV-2-S antibodies or an irrelevant human IgG1 antibody control at dilutions from 1.7pM to 100nM in PBS + 0.5% BSA. The fixed concentration of SARS-CoV-2 RBD was selected to be near the concentration which generated 50% of the maximal binding (EC50 value) to the plate-adhered hACE-2. The antibody-protein complexes were transferred to the microtiter plate coated hACE-2-10His. After 1 hour of incubation at room temperature, the wells were washed, and plate-bound SARS-COV-2 RBD.mmh was detected with a polyclonal goat anti-myc antibody conjugated with horseradish peroxidase (HRP) (NovusBio). The plates were then developed using TMB substrate solution (BD Biosciences, #51-2606KC and #51-2607KC) according to the manufacturer's recommended procedure and absorbance at 450nm was measured on a Victor X5 plate reader (PerkinElmer, Shelton CT).

[000215] Binding data were analyzed using a sigmoidal dose-response model within Prism™ software (GraphPad). The calculated IC50 value, defined as the concentration of antibody required to block 50% of SARS-CoV-2 RBD binding to plate-coated hACE2, was used as an indicator of blocking potency. Percent blocking of anti-SARS-CoV-2-S antibody at a given concentration was calculated based on the following formula:

$$\% \text{ Blocking} = 100 - \left(\frac{[\text{Experimental Signal}_{(\text{highest Ab conc})} - \text{Background Signal}_{(\text{buffer})}]}{[\text{Maximum Signal}_{(\text{hEGF.mFc alone})} - \text{Background Signal}_{(\text{buffer})}]} \text{ x100} \right)$$

[000216] Antibodies that blocked binding less than or equal to 50% at the highest concentration tested were classified as non-blockers and IC50 values were not reported for those antibodies.

[000217] The ability of anti-SARS-CoV-2 antibodies to block SARS-CoV-2 RBD binding to human ACE2 was assessed using a blocking ELISA. In this assay 300pM SARS-COV-2 RBD.mmh was titrated with a wide concentration range of the anti-SARS-COV-2-S antibody. The inhibition of the binding of the SARS-COV-2 RBD to hACE-2 in the presence of the SARS-COV-2 antibody was evaluated. The plate-bound SARS-COV-2 RBD.mmh was detected with a HRP-conjugated goat anti-myc antibody. The IC50 values and maximum blocking at the highest tested concentrations of the SARS-COV-2 antibodies are summarized in Table 20.

[000218] Of the fifty-six antibodies tested, forty-two displayed antibody concentration-dependent blocking of SARS-COV-2 RBD binding to hACE-2 with maximum blocking ranging from 61% to about 100% at the highest antibody concentration tested (100nM). The IC50 values for the identified blocking antibodies ranged from 102pM to 19.7nM. The remaining fourteen antibodies displayed less than 50% blocking activity at the highest concentration tested and were classified as non-blockers. An isotype control, mAb193281, was also used as a control.

Table 20: Blocking potency of Anti-SAR-COV-2-S Antibodies on Spike RBD-hFc Binding to Immobilized Human ACE-2

mAb#	Antibody blocking 300pM SARS-COV-2.mmh binding to hACE-2	
	IC_{50}, M	% Blocking at 100nM mAb concentration
mAb13457	1.97E-08	75

mAb13458	8.73E-10	81
mAb13459	4.43E-09	78
mAb14230	9.97E-09	85
mAb14231	Nbl	2
mAb14232	1.80E-08	87
mAb14233	Nbl	-7
mAb14234	4.62E-09	92
mAb14235	2.34E-10	96
mAb14247	4.46E-10	95
mAb14248	Nbl	-12
mAb14249	Nbl	-12
mAb14255	1.57E-10	92
mAb14256	4.80E-10	95
mAb14257	3.65E-10	95
mAb14258	1.21E-10	93
mAb14259	1.03E-08	89
mAb14260	1.27E-10	96
mAb14280	1.74E-09	98
mAb14281	3.97E-10	100
mAb14282	5.02E-10	96
mAb14283	3.73E-10	97
mAb14284	3.67E-10	98
mAb14285	1.70E-09	96
mAb14286	6.41E-10	94
mAb14287	Nbl	2

mAb14288	Nbl	5
mAb14290	Nbl	-1
mAb14289	3.78E-10	98
mAb14291	Nbl	-8
mAb14292	2.54E-10	95
mAb14293	Nbl	-1
mAb14294	2.44E-10	94
mAb14295	Nbl	5
mAb14296	Nbl	20
mAb14297	Nbl	16
mAb14312	1.34E-10	98
mAb14313	1.64E-08	63
mAb14314	Nbl	21
mAb14315	1.72E-08	61
mAb14316	Nbl	-9
mAb15156	2.69E-10	103
mAb15157	3.57E-10	103
mAb15158	3.09E-10	103
mAb15159	1.56E-10	102
mAb15160	2.04E-10	96
mAb15161	5.84E-10	94
mAb15162	7.56E-10	95
mAb15163	2.17E-10	95
mAb15164	2.45E-10	99
mAb15165	1.89E-10	99

mAb15166	4.75E-10	98
mAb15167	1.06E-09	96
mAb15170	1.02E-10	82
mAb15150	2.54E-10	98
mAb15151	6.41E-10	98
mAb193281	Nbl	15
mAb193281	Nbl	16

Nbl: Non-Blocking - % blocking is less than or equal to 50%.

Example 6: pH sensitivity of anti-SARS-CoV-2-S monoclonal antibodies binding to monomeric SARS-CoV-2-S RBD reagents measured at 37 ºC

[000219] The dissociation rate constants (k_d) for 56 purified anti-SARS-CoV-2-S monoclonal antibodies at neutral and acidic pH conditions were determined using a real-time surface plasmon resonance (SPR)-based Biacore T200 or Biacore 4000 biosensor. All binding studies were performed at 37 °C using running buffers of 0.05% v/v Surfactant Tween-20-containing PBS at pH7.4, pH6.0, and pH5.0 (PBS-T-pH7.4, -pH6.0, and -pH5.0, respectively). The Biacore CM5 sensor chip surface was first derivatized by amine coupling with a mouse anti-human Fc specific mAb (Regeneron, mAb2567) to capture anti-SARS-CoV-2 monoclonal antibodies. The ligand examined for binding to anti-SARS-CoV-2 monoclonal antibodies was a recombinant protein comprising the SARS-COV-2 RBD extracellular domain expressed with a C-terminal tag of myc-myc-hexahistidine (SARS-COV-2 RBD-MMH; SEQ ID NO: 1069). Solutions of 90nM SARS-COV-2 RBD-MMH were prepared in PBS-T-pH7.4 buffer and then injected over the antibody surfaces at a flow rate of 25µL/min for 3 minutes followed by a dissociation phase of bound SARS-COV-2 RBD-MMH with the running buffers at pH7.4, pH6.0, or pH5.0 flowing over for 8 minutes. An isotype control, mAb1932, was also used as a control.

[000220] The dissociation rate constants (k_d) in three pH running buffers were determined by fitting the real-time binding sensorgrams to a 1:1 binding model using Scrubber 2.0c curve-fitting software. The dissociative half-life (t½) was calculated from the k_d values as:

$$t½ \text{ (min)} = \frac{\ln(2)}{60 * kd}$$

[000221] The resultant k_d and t½ values for binding of monomeric SARS-COV-2 RBD-MMH to 56 anti-SARS-CoV-2 monoclonal antibodies captured on anti-hFc surfaces at pH6.0 and pH5.0 at 37°C are summarized in Table 21 and Table 22, respectively, and the results at pH7.4 are listed in both tables for comparison.

Table 21: Comparison of the Dissociation Rate Constant and Dissociative Half-life of the Interaction of Monomeric SARS-COV-2 RBD-MMH to Anti-SARS-CoV-2 Monoclonal Antibodies at pH7.4 and pH 6.0 at 37 °C.

									t½ Ratio of
mAb Captured	mAb Capture Level (RU)	RBD.mmh Bound at pH 7.4 (RU)	kd at pH7.4 (1/s)	t½ at pH7.4 (min)	mAb Capture Level (RU)	RBD.mmh Bound at pH7.4 (RU)	Kd at pH6.0 (1/s)	t½ at pH6.0 (min)	pH7.4 to pH6.0
mAb14284	386.5	146.9	6.24E-04	18.5	369.4	144.5	5.74E-04	20.1	0.9
mAb14312	276.1	95.2	8.59E-04	13.5	257.6	94.8	1.77E-03	6.5	2.1
mAb14294	222.4	83.2	9.20E-04	12.6	207	91.1	5.65E-04	20.5	0.6
mAb14315	238	83.3	9.80E-04	11.8	217.5	82.5	9.46E-04	12.2	1
mAb14292	241.2	73.4	1.41E-03	8.2	218.6	74	1.78E-03	6.5	1.3
mAb14235	202.9	71.2	1.48E-03	7.8	185.2	80.8	1.14E-03	10.1	0.8
mAb14247	137.5	40.8	1.58E-03	7.3	107.4	43.8	1.67E-03	6.9	1.1
mAb13458	290.7	96.5	1.61E-03	7.2	265.5	98.6	1.99E-03	5.8	1.2
mAb14283	246.6	87.7	1.69E-03	6.9	224.5	86.3	2.00E-03	5.8	1.2

mAb14289	**246.7**	**86.1**	**1.85E-03**	**6.2**	**224**	**84**	**2.72E-03**	**4.2**	**1.5**
mAb14260	**208**	**74.5**	**1.88E-03**	**6.2**	**192.7**	**83**	**1.66E-03**	**6.9**	**0.9**
mAb14258	**245.1**	**85.9**	**2.13E-03**	**5.4**	**221.1**	**85**	**5.48E-04**	**21.1**	**0.3**
mAb13457	**309**	**103.3**	**2.14E-03**	**5.4**	**279.3**	**100.8**	**3.09E-03**	**3.7**	**1.5**
mAb14234	**133.8**	**37.9**	**2.21E-03**	**5.2**	**103**	**44.5**	**1.43E-03**	**8.1**	**0.6**
mAb13459	**301.6**	**106.8**	**2.29E-03**	**5.1**	**290**	**114.8**	**2.39E-03**	**4.8**	**1.1**
mAb14313	**275.7**	**94.2**	**2.51E-03**	**4.6**	**255**	**97.1**	**4.10E-03**	**2.8**	**1.6**
mAb14255	**288.4**	**97.5**	**4.93E-03**	**2.3**	**262.3**	**96.4**	**5.13E-03**	**2.3**	**1**
mAb14281	**256.9**	**83.5**	**6.59E-03**	**1.8**	**233.5**	**85.2**	**7.34E-03**	**1.6**	**1.1**
mAb14230	**224.5**	**67.6**	**7.71E-03**	**1.5**	**193.5**	**70.7**	**7.97E-03**	**1.4**	**1.1**
mAb14257	**234.8**	**82.3**	**7.78E-03**	**1.5**	**220.2**	**91.3**	**8.42E-03**	**1.4**	**1.1**
mAb14286	**259**	**84.3**	**9.68E-03**	**1.2**	**234.5**	**87.2**	**9.99E-03**	**1.2**	**1**
mAb14256	**258.4**	**80.2**	**1.11E-02**	**1**	**234.3**	**84.4**	**9.55E-03**	**1.2**	**0.8**
mAb14282	**215.3**	**73.5**	**1.26E-02**	**0.9**	**199.9**	**83.5**	**9.85E-03**	**1.2**	**0.8**
mAb14280	**255**	**72.4**	**2.40E-02**	**0.5**	**230.3**	**78.4**	**1.90E-02**	**0.6**	**0.8**
mAb14285	**213**	**64.2**	**2.58E-02**	**0.4**	**200.2**	**77.1**	**1.44E-02**	**0.8**	**0.5**
mAb14232	**58.1**	**8.2**	**3.11E-02**	**0.4**	**34.4**	**23**	**1.24E-02**	**0.9**	**0.4**
mAb14259	**233.1**	**12**	**IC**	**IC**	**210.5**	**16.7**	**IC**	**IC**	**IC**
mAb14314	**255.1**	**5.8**	**IC**	**IC**	**244.4**	**12.5**	**IC**	**IC**	**IC**
mAb14231	**272**	**0.1**	**NB**	**NB**	**244.5**	**5**	**NB**	**NB**	**NB**

mAb14233	**197**	**1.7**	**NB**	**NB**	**164.3**	**3.3**	**NB**	**NB**	**NB**
mAb14248	**230.5**	**0.9**	**NB**	**NB**	**205.6**	**5.5**	**NB**	**NB**	**NB**
mAb14249	**215.1**	**0.2**	**NB**	**NB**	**198.1**	**8.7**	**NB**	**NB**	**NB**
mAb14287	**254.4**	**1.1**	**NB**	**NB**	**233**	**4.3**	**NB**	**NB**	**NB**
mAb14288	**216.2**	**0.9**	**NB**	**NB**	**201.3**	**8.8**	**NB**	**NB**	**NB**
mAb14290	**245**	**0.3**	**NB**	**NB**	**223.1**	**5.1**	**NB**	**NB**	**NB**
mAb14291	**200.5**	**0.9**	**NB**	**NB**	**185**	**9.5**	**NB**	**NB**	**NB**
mAb14293	**257.1**	**1.4**	**NB**	**NB**	**233.3**	**5.8**	**NB**	**NB**	**NB**
mAb14295	**259.7**	**2.1**	**NB**	**NB**	**239.1**	**1.6**	**NB**	**NB**	**NB**
mAb14296	**276.5**	**1.7**	**NB**	**NB**	**257.1**	**4.1**	**NB**	**NB**	**NB**
mAb14297	**229**	**2.2**	**NB**	**NB**	**214.7**	**9.3**	**NB**	**NB**	**NB**
mAb14316	**201.7**	**2.1**	**NB**	**NB**	**180.1**	**5.6**	**NB**	**NB**	**NB**
mAb15156	**268.5**	**92.6**	**6.73E-03**	**1.7**	**258.3**	**96.4**	**9.70E-03**	**1.2**	**1.4**
mAb15157	**311.9**	**106.3**	**4.05E-03**	**2.9**	**301.7**	**107.8**	**7.66E-03**	**1.5**	**1.9**
mAb15158	**306.9**	**111.4**	**3.10E-04**	**37**	**294.7**	**118.1**	**2.90E-04**	**40.1**	**0.9**
mAb15159	**92.9**	**31.9**	**2.31E-04**	**50**	**79.8**	**36.3**	**4.12E-04**	**28.1**	**1.8**
mAb15160	**178.8**	**58.2**	**2.18E-03**	**5.3**	**164.8**	**59.9**	**2.83E-03**	**4.1**	**1.3**
mAb15161	**121.5**	**39.8**	**1.13E-03**	**10.3**	**106.2**	**43.7**	**1.07E-03**	**10.8**	**0.9**
mAb15162	**330.8**	**116.4**	**3.00E-03**	**3.9**	**321.2**	**120.1**	**3.54E-03**	**3.3**	**1.2**

mAb15163	230.9	81.9	4.94E-04	23.4	211.7	82.4	1.04E-03	11.1	2.1
mAb15164	400.6	144.9	2.26E-03	5.1	398.3	154.4	2.10E-03	5.5	0.9
mAb15165	290.4	110	1.64E-03	7.1	279.8	115	1.28E-03	9.1	0.8
mAb15166	244.5	65.2	3.00E-02	0.4	234.8	66	3.01E-02	0.4	1
mAb15167	419.3	117.5	2.08E-02	0.6	415.8	124.2	1.62E-02	0.7	0.8
mAb15170	309.8	120.5	1.07E-04	108.4	304.6	128.6	8.00E-05	144.5	0.7
mAb15150	246.1	87.8	1.12E-04	103.4	233.4	89.7	3.81E-05	303.5	0.3
mAb15151	611.4	219.4	6.80E-03	1.7	612.7	227.1	4.54E-03	2.5	0.7
mAb1932	314	0.6	NB	NB	294.3	7.7	NB	NB	NB

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Table 22: Comparison of the Dissociation Rate Constant and Dissociative Half-life of the Interaction of Monomeric SARS-COV-2 RBD-MMH (SEQ ID NO: 1069) to Anti-SARS-CoV-2 Monoclonal Antibodies at pH7.4 and pH 5.0 at 37°C.

mAb Captured	mAb Capture Level (RU)	RBD.mmh Bound at pH 7.4 (RU)	kd at pH5.0 (1/s)	t½ at pH5.0 (min)	mAb Capture Level (RU)	RBD.mmh Bound at pH7.4 (RU)	Kd at pH5.0 (1/s)	t½ at pH5.0 (min)	t½ Ratio of pH7.4 to pH5.0
mAb14284	386.5	146.9	6.24E-04	18.5	387.2	158.8	7.36E-04	15.7	1.2
mAb14312	276.1	95.2	8.59E-04	13.5	274.5	96.7	5.58E-03	2.1	6.4
mAb14294	222.4	83.2	9.20E-04	12.6	210.4	97.6	4.52E-04	25.5	0.5

mAb14315	238	83.3	9.80E-04	11.8	228.3	101.2	7.00E-04	16.5	0.7
mAb14292	241.2	73.4	1.41E-03	8.2	229.2	85	2.19E-03	5.3	1.5
mAb14235	202.9	71.2	1.48E-03	7.8	184.9	80.8	1.19E-03	9.7	0.8
mAb14247	137.5	40.8	1.58E-03	7.3	107.1	51.9	1.91E-03	6.1	1.2
mAb13458	290.7	96.5	1.61E-03	7.2	270.3	90.9	4.01E-03	2.9	2.5
mAb14283	246.6	87.7	1.69E-03	6.9	237.7	91.7	5.12E-03	2.3	3
mAb14289	246.7	86.1	1.85E-03	6.2	235.5	89.3	4.60E-03	2.5	2.5
mAb14260	208	74.5	1.88E-03	6.2	193.8	82.4	2.02E-03	5.7	1.1
mAb14258	245.1	85.9	2.13E-03	5.4	230.8	103.4	5.08E-04	22.7	0.2
mAb13457	309	103.3	2.14E-03	5.4	293.7	104.7	4.52E-03	2.6	2.1
mAb14234	133.8	37.9	2.21E-03	5.2	98.5	40.4	1.66E-03	7	0.7
mAb13459	301.6	106.8	2.29E-03	5.1	293.9	105.8	3.70E-03	3.1	1.6
mAb14313	275.7	94.2	2.51E-03	4.6	265.2	80.8	5.73E-03	2	2.3
mAb14255	288.4	97.5	4.93E-03	2.3	274.8	94.1	6.35E-03	1.8	1.3
mAb14281	256.9	83.5	6.59E-03	1.8	241	51.7	1.17E-02	1	1.8
mAb14230	224.5	67.6	7.71E-03	1.5	201.1	60.3	9.24E-03	1.3	1.2
mAb14257	234.8	82.3	7.78E-03	1.5	224.7	45.2	1.72E-02	0.7	2.1
mAb14286	259	84.3	9.68E-03	1.2	246.3	82.4	6.64E-03	1.7	0.7
mAb14256	258.4	80.2	1.11E-02	1	239.7	54.1	9.27E-03	1.2	0.8
mAb14282	215.3	73.5	1.26E-02	0.9	201.9	62.4	6.71E-03	1.7	0.5

mAb14280	255	72.4	2.40E-02	0.5	241.4	61.7	1.03E-02	1.1	0.5
mAb14285	213	64.2	2.58E-02	0.4	202	51.5	2.50E-03	4.6	0
mAb14232	58.1	8.2	3.11E-02	0.4	22.3	10.1	6.56E-04	17.6	0
mAb14259	233.1	12	IC	IC	214.1	1.8	IC	IC	IC
mAb14314	255.1	5.8	IC	IC	252.9	3.4	IC	IC	IC
mAb14231	272	0.1	NB	NB	249.9	-1.3	NB	NB	NB
mAb14233	197	1.7	NB	NB	173.5	6.6	NB	NB	NB
mAb14248	230.5	0.9	NB	NB	210.3	-0.8	NB	NB	NB
mAb14249	215.1	0.2	NB	NB	198.6	1.9	NB	NB	NB
mAb14287	254.4	1.1	NB	NB	240.6	0.3	NB	NB	NB
mAb14288	216.2	0.9	NB	NB	203.7	4	NB	NB	NB
mAb14290	245	0.3	NB	NB	228.9	-0.6	NB	NB	NB
mAb14291	200.5	0.9	NB	NB	188.5	3.2	NB	NB	NB
mAb14293	257.1	1.4	NB	NB	243.1	-0.2	NB	NB	NB
mAb14295	259.7	2.1	NB	NB	250.3	8.7	NB	NB	NB
mAb14296	276.5	1.7	NB	NB	267.7	-1	NB	NB	NB
mAb14297	229	2.2	NB	NB	218.2	3.1	NB	NB	NB
mAb14316	201.7	2.1	NB	NB	181.3	0.9	NB	NB	NB
mAb15156	268.5	92.6	6.73E-03	1.7	259.6	103.6	1.58E-02	0.7	2.3

mAb15157	**311.9**	**106.3**	**4.05E-03**	**2.9**	**301.7**	**107.5**	**7.02E-03**	**1.6**	**1.7**
mAb15158	**306.9**	**111.4**	**3.10E-04**	**37**	**296.4**	**121.6**	**9.70E-05**	**118.9**	**0.3**
mAb15159	**92.9**	**31.9**	**2.31E-04**	**50**	**73.6**	**45.5**	**4.29E-04**	**27**	**1.9**
mAb15160	**178.8**	**58.2**	**2.18E-03**	**5.3**	**160.8**	**61.3**	**2.28E-03**	**5.1**	**1**
mAb15161	**121.5**	**39.8**	**1.13E-03**	**10.3**	**100.8**	**51.4**	**9.80E-04**	**11.8**	**0.9**
mAb15162	**330.8**	**116.4**	**3.00E-03**	**3.9**	**335.3**	**130.8**	**5.40E-03**	**2.1**	**1.8**
mAb15163	**230.9**	**81.9**	**4.94E-04**	**23.4**	**221.3**	**83.2**	**3.77E-03**	**3.1**	**7.6**
mAb15164	**400.6**	**144.9**	**2.26E-03**	**5.1**	**409.6**	**159**	**2.00E-03**	**5.8**	**0.9**
mAb15165	**290.4**	**110**	**1.64E-03**	**7.1**	**289.5**	**126.8**	**9.73E-04**	**11.9**	**0.6**
mAb15166	**244.5**	**65.2**	**3.00E-02**	**0.4**	**233.6**	**60**	**3.50E-02**	**0.3**	**1.2**
mAb15167	**419.3**	**117.5**	**2.08E-02**	**0.6**	**422.4**	**126**	**1.33E-02**	**0.9**	**0.6**
mAb15170	**309.8**	**120.5**	**1.07E-04**	**108.4**	**314.3**	**141.1**	**6.62E-05**	**174.4**	**0.6**
mAb15150	**246.1**	**87.8**	**1.12E-04**	**103.4**	**236.7**	**92.6**	**1.00E-05**	**1155**	**0.1**
mAb15151	**611.4**	**219.4**	**6.80E-03**	**1.7**	**632.9**	**230.7**	**4.39E-03**	**2.6**	**0.6**
mAb1932	**314**	**0.6**	**NB**	**NB**	**305.2**	**1.9**	**NB**	**NB**	**NB**

NB: No binding (NB) was observed under the current experimental conditions.

IC: Observed binding did not fit to the binding simulation model and no binding kinetic parameters were determined under the current experimental conditions.

Example 7: Cross-competition between anti-SARS-CoV-2-S antibodies

[000222] Binding competition between 41 anti-SARS-CoV-2-S monoclonal antibodies (mAbs) was determined using a real time, label-free bio-layer interferometry (BLI) assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). The entire experiment was performed at 25°C in a buffer containing 10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% v/v Surfactant Tween-20, and 1mg/mL BSA, pH7.4 (HBS-EBT) with the sample plate shaking at a speed of 1000rpm. To assess whether mAbs compete with one another for binding to their respective epitopes on SARS-COV-2 RBD extracellular domain expressed with a C-terminal myc-myc-hexahistidine (SARS-COV-2 RBD-MMH; SEQ ID NO: 1069) tag, ~ 0.52-0.63nm of SARS-COV-2 RBD-MMH was first captured onto anti-Penta-His antibody coated Octet biosensor tips (Fortebio Inc, # 18-5122) by submerging the biosensor tips for 90 seconds in wells containing 10 µg/mL solution of SARS-COV-2 RBD-MMH. The SARS-COV-2 RBD-MMH captured biosensor tips were then saturated with a first anti-SARS-CoV-2 monoclonal antibody (mAb-1) by dipping into wells containing 50µg/mL mAb-1 for 4 minutes. The tips were then submerged into wells containing 50µg/mL of a second anti-SARS-CoV-2 monoclonal antibody (mAb-2) for 4 minutes. Between steps the tips were rinsed with HBS-ETB. The real-time binding response was monitored during the entire course of the experiment and the binding response at the end of every step was recorded. The response of mAb-2 binding to SARS-COV-2 RBD-MMH pre-complexed with mAb-1 was compared to the mAb-2 binding signal where the mAb-1 was a nonbinding isotype control, and the percentage reduction of mAb-2 binding was calculated. If pre-binding of mAb-1 resulted in a > 50% reduction of mAb-2 binding, and reversing the order of binding for the mAb pair also exhibited > 50% reduction in binding, mAb-1 and mAb-2 were classified as competing mAbs. FIG. 1 displays the results from cross-competition studies for anti-SARS-CoV-2 mAbs in a matrix format. Table 23 lists the competing mAbs for each anti-SARS-CoV-2 mAb included in the experiment.

Table 23. Cross-competing anti-SARS-CoV-2-S monoclonal antibodies upon binding to immobilized SARS-COV-2 RBD-MMH (SEQ ID NO: 1069)

mAb-1	mAb-2 Competing with mAb-1
mAb14312	mAb14256
	mAb14255
	mAb14257
	mAb14285
	mAb14286
	mAb14280
	mAb14282
	mAb14281
mAb14256	mAb14312
	mAb14286
	mAb14280
	mAb14282
	mAb14284
	mAb10985
mAb14255	mAb14312
	mAb14258

	mAb14257
	mAb14285
	mAb14286
	mAb14280
	mAb14282
mAb10933	**mAb14258**
	mAb14257
	mAb14285
	mAb14286
	mAb14280
	mAb14282
mAb14258	**mAb14255**
	mAb10933
	mAb14258
	mAb14257
	mAb14285
	mAb14286
	mAb14280

	mAb14282
	mAb14283
mAb14257	**mAb14312**
	mAb14255
	mAb10933
	mAb14258
	mAb14286
	mAb14280
	mAb14282
	mAb14313
	mAb14283
mAb14285	**mAb14312**
	mAb14255
	mAb10933
	mAb14258
	mAb14286
	mAb14280
	mAb14282
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987

	mAb14289
mAb14286	**mAb14312**
	mAb14256
	mAb14255
	mAb10933
	mAb14258
	mAb14257
	mAb14285
	mAb14280
	mAb14282
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14260
mAb14280	**mAb14312**
	mAb14256
	mAb14255
	mAb10933
	mAb14258
	mAb14257

	mAb14285
	mAb14286
	mAb14282
	mAb14281
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
mAb14282	**mAb14312**
	mAb14256
	mAb14255
	mAb10933
	mAb14258
	mAb14257
	mAb14285
	mAb14286
	mAb14280
	mAb14281
	mAb10987
	mAb14289
mAb14281	**mAb14312**

	mAb14280
	mAb14282
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14315
mAb13457	**mAb14285**
	mAb14286
	mAb14280
	mAb14281
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14247

	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb13458	**mAb14285**
	mAb14286
	mAb14280
	mAb14281
	mAb13457
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb13459	**mAb14285**
	mAb14286

	mAb14280
	mAb14281
	mAb13457
	mAb13458
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb14313	**mAb14257**
	mAb14285
	mAb14286
	mAb14280
	mAb14281
	mAb13457
	mAb13458
	mAb13459

	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb14283	**mAb14258**
	mAb14257
	mAb14285
	mAb14286
	mAb14280
	mAb14281
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb10987
	mAb14289
	mAb14294

	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb10987	**mAb14285**
	mAb14286
	mAb14280
	mAb14282
	mAb14281
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb14289
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230

	mAb14284
mAb14289	**mAb14285**
	mAb14286
	mAb14280
	mAb14282
	mAb14281
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14230
	mAb14284
mAb14294	**mAb13457**
	mAb13458
	mAb13459
	mAb14313
	mAb14283

	mAb14289
	mAb14235
	mAb14234
	mAb14247
	mAb14230
	mAb14284
mAb14235	**mAb13457**
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb14234	**mAb13457**
	mAb13458
	mAb13459
	mAb14313

	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14247
	mAb14260
	mAb14315
	mAb14230
	mAb14284
mAb14247	**mAb13457**
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14260
	mAb14315
	mAb14230
	mAb14284

mAb14260	mAb14286
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14235
	mAb14234
	mAb14247
	mAb14315
	mAb14230
	mAb14284
mAb14315	mAb14281
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14235
	mAb14234
	mAb14247

	mAb14260
	mAb14230
mAb14230	**mAb13457**
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289
	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14315
	mAb14284
mAb14284	**mAb14256**
	mAb13457
	mAb13458
	mAb13459
	mAb14313
	mAb14283
	mAb10987
	mAb14289

	mAb14294
	mAb14235
	mAb14234
	mAb14247
	mAb14260
	mAb14230
mAb10985	**mAb14256**

[000223] Binding competition between 15 additional anti-SARS-Cov-2-S monoclonal antibodies was performed substantially as described above. Competition was determined using a real time, label-free bio-layer interferometry (BLI) assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). The entire experiment was performed at 25°C in a buffer containing 10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% v/v Surfactant Tween-20, and 1mg/mL BSA, pH7.4 (HBS-EBT) with the plate shaking at a speed of 1000rpm. To assess whether mAbs are able to compete with one another for binding to their respective epitopes on SARS-COV-2 RBD extracellular domain expressed with a C-terminal myc-myc-hexahistidine (SARS-COV-2 RBD-MMH; SEQ ID NO: 1069) tag, ~0.51nm of SARS-COV-2 RBD-MMH was first captured onto anti-Penta-His antibody coated Octet biosensor tips (Fortebio Inc, # 18-5122) by submerging the biosensor tips for 90 seconds in wells containing 10 µg/mL of SARS-COV-2 RBD-MMH. The SARS-COV-2 RBD-MMH captured biosensor tips were then saturated with a first anti-SARS-CoV-2 monoclonal antibody (mAb-1) by dipping into wells containing 50µg/mL mAb-1 for 4 minutes. The biosensor tips were then submerged into wells containing 50µg/mL of a second anti-SARS-CoV-2 monoclonal antibody (mAb-2) for 4 minutes. Between steps the biosensor tips were rinsed with HBS-ETB buffer. The real-time binding response was monitored during the entire course of the experiment and the binding response at the end of every step was recorded. The response of mAb-2 binding to SARS-COV-2 RBD-MMH pre-complexed with mAb-1 was compared to the mAb-2 binding signal where the mAb-1 was a nonbinding isotype control, and the percentage reduction of mAb-2 binding was calculated. If pre-binding of mAb-1 resulted in > 50% reduction of mAb-2 binding, and reversing the order of binding for the mAb pair also exhibited > 50% reduction of binding, mAb-1 and mAb-2 were classified as competing mAbs.

FIG. 2 displays the results from cross-competition studies for anti-SARS-Cov-2 mAbs in a matrix format. Table 24 lists the competing mAbs for each anti-SARS-CoV-2 mAb included in the experiment.

Table 24. Cross-competing anti-SARS-CoV-2-S monoclonal antibodies upon binding to immobilized SARS-COV-2 RBD-MMH (SEQ ID NO: 1069)

mAb-1	mAb-2 Competing with mAb-1
mAb10934	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15164
	mAb15165
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14312
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247

	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb10989	**mAb10934**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933

	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10987
	mAb14289
	mAb14283
mAb15158	**mAb10934**
	mAb10989
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255

	mAb14256
	mAb14312
	mAb10986
	mAb10985
	mAb14289
mAb15156	**mAb10934**
	mAb10989
	mAb15158
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986

	mAb14289
	mAb14283
mAb15157	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10985
	mAb14247
mAb15166	**mAb10934**

	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15167	**mAb10989mAb**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15150

	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15150	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb10954
	mAb15162
	mAb15170
	mAb15164
	mAb15165
	mAb15151

	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10985
mAb10954	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255

	mAb14256
	mAb14312
	mAb10986
	mAb10985
mAb15162	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10985
mAb15159	**mAb10989**

	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb10954
	mAb15162
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10985
mAb15170	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150

	mAb10954
	mAb15162
	mAb15159
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
	mAb10985
mAb15164	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170

	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15165	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163

	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15151	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15161	**mAb10934**

	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15160	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166

	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb10933	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159

	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb15163	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161

	mAb15160
	mAb10933
	mAb14255
	mAb14256
	mAb14312
	mAb10986
mAb14255	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14256
	mAb14312
	mAb10986

mAb14256	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14312
	mAb10986
	mAb10985
mAb14312	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb15157

	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb10986
mAb10986	**mAb10989**
	mAb15158
	mAb15156
	mAb15157
	mAb15166
	mAb15167
	mAb15150
	mAb10954
	mAb15162
	mAb15159

	mAb15170
	mAb15164
	mAb15165
	mAb15151
	mAb15161
	mAb15160
	mAb10933
	mAb15163
	mAb14255
	mAb14256
	mAb14312
	mAb10985
mAb10985	**mAb15158**
	mAb15157
	mAb15150
	mAb10954
	mAb15162
	mAb15159
	mAb15170
	mAb14256
	mAb10986
mAb14232	**mAb10934**
	mAb10987
	mAb14289
	mAb14283

	mAb14247
	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb10987	**mAb10934**
	mAb10989
	mAb14232
	mAb14289
	mAb14283
	mAb14247
	mAb14234
	mAb14230
	mAb14315
	mAb14284

	mAb14235
	mAb14294
mAb14289	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb14232
	mAb10987
	mAb14283
	mAb14247
	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb14283	**mAb10934**
	mAb10989
	mAb15158
	mAb15156
	mAb14312
	mAb14232
	mAb10987
	mAb14289
	mAb14247
	mAb14234
	mAb14230

	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb14247	**mAb10934**
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb14234	**mAb10934**
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247
	mAb14230
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb14230	**mAb10934**

	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247
	mAb14234
	mAb14315
	mAb14284
	mAb14235
	mAb14294
mAb14315	**mAb10934**
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247
	mAb14234
	mAb14230
	mAb14284
	mAb14235
	mAb14294
mAb14284	**mAb10934**
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247

	mAb14234
	mAb14230
	mAb14315
	mAb14235
	mAb14294
mAb14235	**mAb10934**
	mAb14232
	mAb10987
	mAb14289
	mAb14283
	mAb14247
	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14294
mAb14294	**mAb14232**
	mAb10987
	mAb14289
	mAb14283
	mAb14247
	mAb14234
	mAb14230
	mAb14315
	mAb14284
	mAb14235

Example 8: Characterization of anti-SARS-CoV-2-S mAbs in an ADCC surrogate assay (FcγR3a Val176 signaling assay)

[000224] The ability of antibodies targeting the spike protein of SARS-CoV-2 to interact with FcγR3a, an Fc-receptor prominently expressed on NK cells that induces antibody dependent cell-mediated cytotoxicity (ADCC), was measured in a surrogate bioassay using reporter cells and target cells bound to antibodies. In this assay, engineered Jurkat T cells expressed the reporter gene luciferase under the control of the transcription factor NFAT (NFAT-Luc) along with the high affinity human FcγR3a 176Val allotype receptor (Jurkat/NFAT-Luc/hFcγR3a 176Val). Target cells were engineered Jurkat T cells expressing human CD20 (used as a positive control with CD20 targeting human IgG1 antibody) alone or in combination with the full-length SARS-CoV-2 spike protein. Reporter cells were incubated with target cells, and engagement of FcγR3a via the Fc domain of human IgG1 antibodies bound to target cells led to the activation of the transcription factor NFAT in the reporter cells and drove the expression of luciferase which was then measured via a luminescence readout.

Target cells

[000225] Jurkat/hCD20: Jurkat T cells were engineered to constitutively express full length human CD20 (amino acids M1-P297 of NCBI accession number NP_690605.1). Jurkat/hCD20 cells were stained for CD20 expression and maintained in RPMI + 10% FBS + P/S/G + 250 g/ml hygromycin growth medium. These cells were used as a negative control.

[000226] Jurkat/hCD20/SARS-CoV-2 spike: Jurkat/hCD20 T cells were engineered to constitutively express full-length SARS-CoV-2 spike protein (amino acids M1-T1273 of NCBI accession number YP_009724390.1). Jurkat/hCD20/SARS-CoV-2 spike cells were sorted for high expression of the spike protein and maintained in RPMI + 10% FBS + P/S/G + 1 μg/ml puromycin + 250 g/ml hygromycin growth medium.

Reporter cells

[000227] Jurkat/NFAT-Luc/FcγR3a 176Val: Jurkat T cells were engineered to stably express a Nuclear Factor of Activated T-cells (NFAT) luciferase reporter construct along with the high affinity human FcγR3a 176Val allotype receptor (amino acids M1-K254 of accession number P08637 VAR_003960). Engineered reporter cells were maintained in RPMI1640 + 10% FBS + P/S/G + 0.5 μg/ml puromycin + 500 μg/ml G418 growth media.

Assay set-up

[000228] One day before the experiment, Jurkat reporter cells were split to 7.5 x 10^5 cells/ml in RPMI1640 + 10% FBS + P/S/G + 0.5 µg/ml puromycin + 500 µg/ml G418 growth media. Jurkat target cells were split to 5 x 10^5 cells/ml in RPMI1640 + 10% FBS + P/S/G + 0.5 µg/ml puromycin + 250 µg/ml hygromycin growth media.

[000229] On the day of the experiment, the target and reporter cells were transferred into assay media (RPMI + 10% FBS + P/S/G) and added at a 3:2 ratio (3 x 10^4/well target cells and 2 x 10^4/well reporter cells) to 384-well white microtiter plates.

[000230] Anti-SARS-CoV-2 spike protein antibodies, a negative isotype-matched control antibody, and a positive control antibody for ADCC (anti-CD20) were titrated in an 11-point, 1:3 serial dilution ranging from 1.7 pM to 100 nM final concentration, with the final 12th point containing no antibody. All samples were tested in duplicates. Plates were incubated at 37°C/5% CO_2 for 5 h followed by the addition of an equal volume of ONE-Glo™ (Promega) reagent to lyse cells and detect luciferase activity. The emitted light was captured in Relative Light Units (RLU) on a multi-label plate reader Envision (PerkinElmer). EC50 values of the antibodies were determined from a 4 parameter logistic equation over a 12-point dose response curve (including the background signal) using GraphPad Prism software. Maximum fold induction was calculated using the following equation:

[000231] Fold Induction = Max Average RLU within tested dose range of each antibody / Average RLU (background signal = no antibody)

[000232] The EC50 values and fold inductions are summarized in Table 25.

Results with Jurkat/hCD20/SARS-CoV-2 spike target cells

[000233] Each of the tested anti-SARS-CoV-2-S antibodies showed greater fold induction than the negative control antibody. The EC50 values ranged from 60.4 pM to 3.4 nM, and the fold induction values ranged from 3.9x to 13.5x. The positive CD20 control antibody showed a fold induction of 29.9x with an EC50 value of 18.1 pM.

Results with Jurkat/hCD20 target cells

[000234] Each of the 41 anti-SARS-CoV-2-S antibodies except one (mAb14312) behaved similarly to the negative control antibody showing minimal activity. mAb14312 had an EC50 value of 18.4 nM and a fold induction value of 2.0. The positive CD20 control antibody showed a fold induction value of 29.4x with an EC50 value of 33.7 pM.

Table 25: Surrogate ADCC assay results

mAb #	Jurkat CD20		Jurkat/CD20/spike	
	EC50 (M)	Fold induction	EC50 (M)	Fold induction
mAb13457	ND	1.2	1.50E-10	9.1
mAb13458	ND	1.2	1.43E-10	10.2
mAb13459	ND	1.2	1.42E-10	9.9
mAb14230	ND	1.1	1.79E-10	9.8
mAb14231	ND	1.2	3.25E-09	7.9
mAb14232	ND	1.2	1.31E-10	10.8
mAb14233	ND	1.1	2.80E-10	11.0
mAb14234	ND	1.1	2.69E-10	12.6
mAb14235	ND	1.0	1.43E-10	10.8
mAb14247	ND	1.0	1.79E-10	11.3
mAb14248	ND	1.0	1.79E-10	12.8
mAb14249	ND	1.2	2.51E-10	10.3
mAb14255	ND	1.0	1.67E-10	9.5
mAb14256	ND	1.0	4.48E-10	6.1
mAb14257	ND	1.0	2.39E-10	8.8
mAb14258	ND	1.0	2.82E-10	7.5
mAb14259	ND	1.0	3.94E-10	8.7
mAb14260	ND	1.1	3.63E-10	6.0
mAb14280	ND	1.1	2.67E-10	13.5
mAb14281	ND	1.1	1.65E-10	10.3
mAb14282	ND	1.1	2.57E-10	10.7
mAb14283	ND	1.1	1.39E-10	9.1

mAb14284	ND	1.1	1.56E-10	9.0
mAb14285	ND	1.1	2.43E-10	11.0
mAb14286	ND	1.0	2.04E-10	11.0
mAb14287	ND	1.0	1.23E-09	6.2
mAb14288	ND	1.0	5.10E-10	6.7
mAb14289	ND	1.0	1.30E-10	6.3
mAb14290	ND	1.0	3.42E-09	9.5
mAb14291	ND	1.1	3.02E-10	9.7
mAb14292	ND	1.0	3.86E-10	9.2
mAb14293	ND	1.1	7.88E-10	9.3
mAb14294	ND	1.0	6.04E-11	10.5
mAb14295	ND	1.0	1.93E-10	11.5
mAb14296	ND	1.0	4.11E-10	8.1
mAb14297	ND	1.0	1.24E-10	7.9
mAb14312	1.84E-08	2.0	1.68E-10	7.5
mAb14313	ND	1.1	1.55E-10	7.1
mAb14314	ND	1.1	NC	3.9
mAb14315	ND	1.1	6.24E-11	9.3
mAb14316	ND	1.0	1.89E-10*	9.1
mAb1932 – Negative Control	ND	1.3	ND	1.5
mAb2959 – Positive Control	3.37E-11	29.4	1.81E-11	29.9

* At high concentrations the signal decreased (hook effect); points on the hook were removed prior to EC50 determination

NC: Not calculated because the data did not fit a 4-parameter logistic equation

ND: Not determined because a concentration-dependent response was not observed

Fold Induction = Max Average RLU within tested dose range of each antibody / Average RLU (background signal = no antibody)

[000235] From the initial mAbs tested, a select few were chosen for further follow-up to run alongside antibodies described in U.S. Patent No. 10,787,501. The EC50 values and fold inductions are summarized in Table 26.

Results with Jurkat/hCD20/SARS-CoV-2 spike target cells

[000236] Each of the newly purified SARS-CoV-2 spike antibodies showed greater fold induction than the negative control antibody. The EC50 values of the newly purified SARS-CoV-2 spike antibodies ranged from 188 pM to 575 pM, and the fold induction values ranged from 2.0x to 3.2x. The positive CD20 control antibody showed a fold induction of 27.0x with an EC50 value of 51.8 pM.

Results with Jurkat/hCD20 target cells

[000237] Each of the newly purified SARS-CoV-2 spike antibodies behaved similarly to the negative control antibody showing minimal activity. By contrast, the positive CD20 control antibody showed a fold induction value of 23.5x with an EC50 value of 142 pM.

Table 26: Surrogate ADCC assay results

mAb # or Name	Jurkat CD20		Jurkat/CD20/spike	
	EC50 (M)	Fold induction	EC50 (M)	Fold induction
mAb14255	ND	1.1	1.88E-10	3.2
mAb14256	ND	1.1	5.75E-10	2.0
mAb14257	ND	1.2	2.63E-10	2.2
mAb14258	ND	1.2	2.06E-10	2.7
mAb10984†	ND	1.0	5.86E-10	1.3
mAb10986†	ND	1.0	NC	1.4

mAb10964†	ND	1.2	1.11E-10	1.8
mAb10977†	ND	1.3	NC	4.1
mAb10933†	ND	1.1	6.47E-10	2.9
mAb10987†	ND	1.0	4.71E-10	4.5
mAb10989†	ND	1.1	6.23E-10	6.5
mAb1932 – Negative Control	ND	1.2	ND	1.2
mAb2959 – Positive Control	1.42E-10	23.5	5.18E-11	27.0

†Antibody described in U.S. Patent No. 10,787,501

NC: Not calculated because the data did not fit a 4-parameter logistic equation.

ND: Not determined because a concentration-dependent response was not observed

Fold Induction = Max Average RLU within tested dose range of each antibody / Average RLU (background signal = no antibody)

[000238] A subsequent round of testing on newly-purified antibodies was also performed. The EC50 values and fold inductions are summarized in Table 27.

Results with Jurkat/hCD20/SARS-CoV-2 spike target cells

[000239] Each of the newly purified anti-SARS-CoV-2-S antibodies showed greater fold induction than the negative control antibody. The EC50 values of the SARS-CoV-2 spike antibodies ranged from 81.7 pM to 905 pM, and the fold induction values ranged from 4.2x to 13.0x. The positive CD20 control antibody showed a fold induction of 46.7x with an EC50 value of 74.4 pM.

Results with Jurkat/hCD20 target cells

[000240] All the newly purified SARS-CoV-2-S antibodies behaved similarly to the negative control antibody, showing minimal activity. By contrast, the positive CD20 control antibody showed a fold induction value of 62.1x with an EC50 value of 145 pM.

Table 27: Surrogate ADCC assay results

mAb # or Name	Jurkat CD20		Jurkat/CD20/spike	
	EC50 (M)	Fold induction	EC50 (M)	Fold induction
mAb15156	ND	1.1	3.47E-10	4.2
mAb15157	ND	1.3	3.98E-10	4.8
mAb15158	ND	1.2	3.81E-10	7.0
mAb15159	ND	1.0	4.17E-10	5.0
mAb15160	ND	1.2	2.98E-10	5.4
mAb15161	ND	1.2	4.94E-10	5.9
mAb15162	ND	1.1	9.05E-10	5.8
mAb15163	ND	1.1	3.42E-10*	8.2
mAb15164	ND	1.2	2.23E-10*	12.7
mAb15165	ND	1.1	2.01E-10	13.0
mAb15166	ND	1.1	8.17E-11	9.5
mAb15167	ND	1.0	1.11E-10	7.3
mAb15170	ND	1.0	6.26E-10	5.4
mAb15150	ND	1.1	4.59E-10	5.2
mAb15151	ND	1.4	3.51E-10	6.0
mAb14255§	ND	1.1	1.37E-10	8.6
mAb14256§	ND	1.0	2.63E-10	3.7
mAb14315§	ND	1.0	9.96E-11*	11.5
mAb10985†	ND	1.1	4.72E-10	3.7
mAb10933†	ND	1.0	8.76E-11	7.7
mAb10987†	ND	1.0	7.20E-11	10.2
mAb1932 – Negative Control	ND	1.2	ND	3.7

mAb2959 – Positive Control	1.45E-10	62.1	7.44E-11	46.7

†Antibody described in U.S. Patent No. 10,787,501

§Antibody described in Table 25 and/or Table 26

* At high concentrations the signal decreased (hook effect); points on the hook were removed prior to EC50 determination

ND: Not determined because a concentration-dependent response was not observed

Fold Induction = Max Average RLU within tested dose range of each antibody / Average RLU (background signal = no antibody)

Example 9: Characterization of anti-SARS-CoV-2-S mAbs in an ADCP assay

[000241] The ability of antibodies targeting the spike protein of SARS-CoV-2 to induce phagocytosis of Jurkat cells engineered to express the SARS-CoV-2 full length spike protein was evaluated. Macrophages differentiated from monocytes in the presence of macrophage colony-stimulating factor (M-CSF) were used as effector cells in an antibody dependent cellular phagocytosis (ADCP) assay. An IgG1 isotype as a negative control was evaluated in parallel. Phagocytosis was assessed by measuring the number of fluorescently labeled target cells colocalizing with fluorescently labeled macrophages using an Opera Phenix High-Content Screening System.

Target cells

[000242] Jurkat/hCD20/SARS-CoV-2 spike: Jurkat T cells were engineered to constitutively express full length human CD20 (amino acids M1-P297 of NCBI accession number NP_690605.1) as well as full-length SARS-CoV-2 spike protein (amino acids M1-T1273 of NCBI accession number YP_009724390.1). Jurkat/hCD20/SARS-CoV-2 spike cells were sorted for high expression of the spike protein and maintained in RPMI + 10% FBS + P/S/G + 1 μg/ml puromycin + 250 μg/ml hygromycin growth medium.

Effector cells

[000243] Macrophages differentiated from monocytes in the presence of M-CSF: Frozen CD14+ monocytes (Lonza) were thawed, resuspended in assay media (RPMI 1640 supplemented with 10% FBS, 100 U/ml penicillin, 100 μg/ml streptomycin, and 292 μg/ml L-glutamine,

NaPyr, HEPES, and NEAA), supplemented with 100 ng/ml M-CSF, and plated at 5.2 x 10^4 cells/well into clear-bottom, collagen-coated 96-well black plates for differentiation into macrophages over 9 days.

Assay set-up

[000244] One day before the experiment, Jurkat target cells were split to 5 x 10^5 cells/ml in their respective growth media.

[000245] On the day of the experiment, target cells and monocyte-derived macrophages were incubated in PBS supplemented with either CellTrace CFSE dye or CellTrace Violet dye, respectively, for 15 minutes at 37°C, 5% CO_2.

[000246] CFSE-labeled target cells were washed and resuspended in assay media (RPMI 1640 supplemented with 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin, and 292 µg/ml L-glutamine, NaPyr, HEPES, NEAA, and 10 µM BME) and added in duplicate to 96-well U-bottom plates at a density of 5 x 10^4 cells/well. Anti-SARS-CoV-2 spike and the IgG1 control antibodies were titrated in assay media in a 1:5 serial dilution ranging from 51 fM to 20 nM final concentration and added to the plates. The zero-antibody point was represented by 10 fM in GraphPad Prism.

[000247] After 15 minutes of incubation on ice the mixture of target cells, with or without titrated antibody, was then transferred to plates containing the violet-labelled macrophages and plates were incubated at 37°C, 5% CO2 for 30 minutes. Wells were washed with PBS 3 times, followed by addition of 4.21% formaldehyde in PBS supplemented with 2.5 µM DRAQ5.

[000248] After a 20 minute incubation, wells were washed with PBS and imaged in both the 488 nm (CFSE-labelled target cells) and 375 nm (violet-labelled macrophages) excitation channels using an Opera Phenix High-Content Screening System. Image analysis was performed in Harmony software. Image segmentation in the 375 nm excitation channel was used to identify the macrophage population. Image segmentation in the 488 nm excitation channel was used to identify the target cells. Phagocytosis was quantified by identifying the macrophage population which contained target cells within them.

[000249] Percent phagocytosis was calculated by comparing number of macrophages undergoing phagocytosis to total macrophage cell number.

$$\% \text{ ADCP} = \frac{\text{Violet labelled macrophages containing CFSE-labelled target cells}}{}$$

Total violet labelled macrophages

[000250] For EC_{50} determinations, % ADCP was analyzed with GraphPad Prism using a 4-parameter logistic equation over a 10-point dose response curve, including the no antibody control. Maximum (Max) % ADCP was determined as the highest mean % ADCP value measured within tested dose range. The experiment was performed using a single donor in duplicate except for the following antibodies which were performed with no replicates: mAb10933, mAb10987, mAb10989, mAb1932, mAb10985, mAb14234, mAb10986, and mAb14259.

[000251] The EC_{50} values and maximum (Max) % ADCP are summarized in Table 28.

[000252] Results with Jurkat/hCD20/SARS-CoV-2 spike cells: Each of the 21 anti-SARS-CoV-2 spike antibodies showed greater Max % ADCP compared to IgG1 control antibody. The EC_{50} values of the SARS-CoV-2 spike antibodies ranged from 5.22 pM to 1.12 nM, and Max % ADCP ranged from 16.72% to 39.89%.

Table 28: ADCP Activity

	ADCP	
Antibody treatment	**Max % ADCP**	**EC50 [M]**
mAb10933†	33.12	3.88E-11
mAb10987†	36.30	3.19E-11
mAb10989†	33.02	4.82E-11
mAb1932	7.69	ND
mAb10985†	31.80	2.17E-10
mAb14234	32.84	7.27E-11
mAb14249	32.60	1.69E-10
mAb14255	21.17	1.73E-11
mAb14256	19.50	NC

mAb14287	33.24	NC
mAb14288	25.86	6.14E-10
mAb14290	16.72	NC
mAb14291	32.85	4.12E-10
mAb14295	35.30	4.57E-10
mAb14296	31.60	5.07E-10
mAb14312	27.77	1.69E-11
mAb14314	16.72	1.12E-09
mAb14315	34.80	6.30E-11
mAb14316	37.72	2.54E-10
mAb10964†	34.03	5.22E-12
mAb10986†	39.89	7.13E-11
mAb14259	39.56	NC

†Antibody described in U.S. Patent No. 10,787,501

ND: Not determined because a concentration-dependent response was not observed.

NC: Not calculated because the data did not fit a 4-parameter logistic equation.

Max (%ADCP) is the highest mean % ADCP value within tested dose range.

Example 10: Structure determination of antibody-bound spike protein and interactions

[000253] To better understand the binding of mAb10987 and mAb14256 to the spike protein RBD, structural analysis was performed via cryo-electron microscopy (cryoEM). Fab fragments of mAb14256 and mAb10987 were isolated using FabALACTICA kit (Genovis). 25 µg of the mAb14256 Fab and 25 µg of mAb10987 Fab were mixed with 15 µg of SARS-CoV-2-S RBD and incubated on ice for 30 min. For cryoEM grid preparation, the protein sample was diluted to 0.94 mg/mL and 0.15% PMAL-C8 amphipol was added. 3 µL of protein was deposited onto a freshly plasma cleaned UltrAufoil grid (0.6/1.0, 300 mesh). Excess solution was blotted away using filter paper and plunge frozen into liquid ethane using a Vitrobot Mark IV. The cryoEM grid was transferred to a Titan Krios (Thermo Fisher) equipped with a K3 detector (Gatan).

Movies were collected using EPU (Thermo Fisher) at 105,000x magnification, corresponding to a pixel size of 0.86 Å. A dose rate of 15 electrons per pixel per second was used and each movie was 2 seconds, corresponding to a total dose of ~40 electrons per $Å^2$.

[000254] All cryoEM data processing was carried out using cryoSPARC v3.2.0. 6,106 aligned micrographs were collected and 5,735 aligned micrographs were selected for further processing on the basis of estimated defocus values and CTF fit resolutions. An initial set of particles picked using blob picker were subjected to 2D classification to generate templates for template picking.~1.4 million particles picked by template picking were subjected to multiple rounds of 2D classification to remove unbound Fabs and particles containing an incomplete complex. *Ab initio* reconstruction with three classes generated two classes containing 301,461 particles that corresponded to the full mAb10987 Fab - mAb14256 Fab - RBD complex. Heterogeneous refinement of those two classes was performed where one class showed a good quality map while the other showed high preferred orientation. Non-uniform refinement of the particles in the 'good' class containing 189,200 particles was followed by local refinement, resulting in a 3.86 Å resolution (FSC=0.143) map that was used for model building. Into this map, models of the RBD (taken from PDB code 6M0J) were manually placed and the two Fabs (taken from prior antibody structures, mAb10987 from PDB 6XDG and mAb14256 from another mAb14256 model) . These models were then manually rebuilt using Coot and real-space refined against the map using Phenix.

[000255] Confirming the above-described data, single-particle cryoEM of the complex of SARS-CoV-2 spike RBD bound to Fab fragments of mAb14256 and mAb10987 shows that the two antibodies in this cocktail can simultaneously bind to distinct regions of the RBD (FIG. 3, FIG. 4). A 3D reconstructed map of the complex with nominal resolution of 3.9Å showed that both Fab fragments bound to non-overlapping regions on the surface of the RBD, confirming that they are non-competing antibodies. mAb14256 bound at the top of the RBD, extensively overlapping the binding site for ACE2. On the other hand, the epitope for mAb10987 was located on the side of the RBD, well away from the mAb14256 epitope, and had little to no overlap with the ACE2 binding site. The structure also revealed that mAb14256 competed with mAb10933 and mAb10985, although combinations of these antibodies still may be desirable because of different microepitope binding and the need to bind and neutralize different SARS-CoV-2 spike protein variants.

[000256] Using similar techniques, the structural basis for mAb15160 binding to SARS-CoV-2 RBD was investigated. Cryo-EM was used to determine the structure of the SARS-CoV-2 RBD in complex with the antigen-binding (Fab) fragments of mAb15160 and mAb14315. The resulting 3.18 Å-resolution structure revealed that mAb15160 binds to a small epitope on the top (*i.e.*, closest to the target cell membrane) surface of the SARS-CoV-2 RBD (FIG. 5). Analysis of the binding interface between the SARS-CoV-2 RBD and the antibody Fab fragment indicate that the mAb15160 Fab contacts the RBD with both its heavy chain (13 residue-residue interactions) and light chain (13 residue-residue interactions). A total of 13 SARS-CoV-2 RBD residues are involved in mAb15160 binding. The functional impact of K417N, E484A, and Q493R, all of which are present in the Omicron variant, as well as other substitutions within the binding epitope, was assessed in neutralization studies discussed above. mAb15160 retained neutralization potency against the K417N and E484A individual mutations. There was an impact on the neutralization potency against the Q493R individual mutation (5-fold reduction compared with reference pseudoparticles); however, the neutralization potency of mAb15160 was within 1.5-fold against pseudoparticles pseudotyped with the full S protein sequence from the BA.1, BA.1.1, and BA.2 (Omicron) lineages compared with reference pseudoparticles.

[000257] Using similar techniques, the structural basis for mAb14284 binding to SARS-CoV-2 Wuhan-Hu-1 and BA.1 (omicron lineage) RBDs was investigated. Cryo-EM was used to determine the structure of the antigen-binding (Fab) fragments of mAb14284 and mAb15160 with the RBD from the Wuhan-Hu-1 strain and BA.1 lineage. The resulting 3.3 and 3.4 Å-resolution structures, respectively, revealed that mAb14284 binds to an upper patch on both the Wu-1 and BA.1 RBD in a manner that is competitive with ACE2 binding (FIG. 6). Analysis of the binding interface between the mAb14284 Fab fragment and the SARS-CoV-2 RBDs from Wu-1 and BA.1 indicate that mAb14284 binds to the same location on the Wu-1 and BA.1 RBDs, with the same epitope residues except for 4 changes located at the periphery (Table 29, below). Epitope residues mutated in the BA.1 variant (N440K, G446S, Q498R, N501Y) relative to the ancestral Wu-1 strain are accommodated in the structure without major changes at the antibody-antigen interface.

Table 29: Summary of Interactions between mAb14284 Fab Residues and SARS-CoV-2 RBD Residues

Type of Interaction	Wuhan-Hu-1 RBD Residue	mAb14284 Residue(s) Interacting with Indicated RBD Residue		BA.1 RBD Residue	mAb14284 Residue(s) Interacting with Indicated RBD Residue	
		Heavy Chain	Light Chain		Heavy Chain	Light Chain
Hydrogen bond/salt bridge (<4 Å)	**Asn439**	-	Tyr34	**-**	-	-
	Lys444	Trp55, Asp56	-	**Lys444**	Trp55	-
	Val445	Arg60	-	**-**	-	-
	Gly447	Arg60	-	**Gly447**	Arg60	-
	Gln498*	-	Thr95	**Arg498***	-	Thr95
	-	-	-	**Thr500**	-	Val31
Hydrophobic (<5 Å)	**Asn440***	Ile102, Pro103	-	**Lys440***	Ile102, Pro103	-
	Leu441	Ser32, Gly33	-	**Leu441**	Ser32	-
	Ser443	Ile102	-	**Ser443**	Ile102	-
	Lys444	Tyr54, Trp55, Asp56, Asp58, Arg60, Ile102	-	**Lys444**	Tyr54, Trp55, Asp58, Ile102	-
	Val445	Trp49, Leu52, Tyr54, Arg60, His100	Tyr93, Ser97, Thr98	**Val445**	Trp49, Leu52, Tyr54, Arg60, His100	Tyr93, Ser97, Thr98
	Gly446*	Arg60	Ser96	**Ser446***	Arg60	Ser96
	Gly447	Arg60	-	**Gly447**	Arg60	-
	-	-	-	**Tyr449**	Arg60	-
	Gln498*	-	Thr95	**Arg498***	-	Thr95
	Pro499	Ile102	Tyr34,Tyr93	**Pro499**	Ile102	Tyr34,Tyr93
	Thr500	-	Leu29, Gly30, Tyr93, Thr94	**Thr500**	-	Leu29, Thr94, Thr95
	Asn501*	-	Val31	**Tyr501***	-	Val31
	Gly502	-	Val31	**Gly502**	-	Val31

SARS-CoV-2 Wuhan-Hu-1 and BA.1 S protein RBD residues that interact with residues of the mAb14284 Fab heavy chain and light chain are indicated. A hyphen "-" indicates that no interaction was observed between the indicated RBD residue and the indicated antibody chain. Residues were selected based on the presence of hydrogen bonds/salt bridges with interatomic distances <4 Å (not including hydrogen atoms) or hydrophobic surfaces with interatomic distances <5 Å. An asterisk "*" indicates an RBD residue mutated in the BA (Omicron) lineages.

[000258] To assess the degree of variability of the mAb14284 epitope across currently circulating SARS-CoV-2 viruses, the sequences of 3,825,870 publicly available SARS-CoV-2 genomes identified between 01 Jan 2022 and 16 June 2022 (*i.e.*, during the Omicron wave) were utilized. The sequences collected during this period likely consist mostly of Omicron sequences, however, other circulating variants, such as Delta, may also be included in this analysis.

[000259] Between 01 Jan 2022 and 16 June 2022, the RBD residues bound by mAb14284 were ≥99.96% conserved relative to the Wuhan-Hu-1 strain at each position, with the exception of 4 residues, N440, G446, Q498, and N501, which are mutated in the Omicron variant (*i.e.*, BA lineages) (Table 30). The frequencies of N440, G446, Q498, and N501 across this monitoring period were 22, 59, 13, and 12%, respectively; instead, N440K, Q498R, and N501Y, all of which are present in the Omicron variant, had become predominant. While G446 remains the predominant residue during this period, 39% of sequences contain the G446S mutation, which is present in the BA.1 lineage of the Omicron variant

[000260] The functional impact of N440K, G446S, Q498R, and N501Y, as well as other substitutions within the binding epitope identified during the conservation analysis (specified below in Table 30) was assessed in neutralization studies as discussed in Example 4. mAb14284 retained neutralization potency against all epitope residue variants tested except mutations of K444. The K444L, K444M, K444N, K444Q, and K444T individual substitutions resulted in a >5-fold change compared with reference pseudoparticles; however, the neutralization potency of mAb14284 was within 1.5-fold against pseudoparticles pseudotyped with the most predominant (ie, 0.0141%) K444 variant, K444R (Table 19).

Table 30: Summary of Frequencies of REGN14284 Epitope Variants Across Publicly Available SARS-CoV-2 Genomes from 01 Jan 2022 through 16 June 2022

AA Position in RBD	Reference Sequence (Wuhan-Hu-1)		Observed Order of Frequency for Epitope Variants (High to Low)			
			1st		2nd	
	Residue	Freq (%)	Residue	Freq (%)	Residue	Freq (%)
440	N	22.3472	K	78.1540	del	0.0026
441	L	99.9942	del	0.0025	F	0.0016
443	S	99.9964	del	0.0024	N	0.0002
444	K	99.9699	R	0.0141	N	0.0095
445	V	99.9834	A	0.0082	I	0.0033
446	G	58.9933	S	38.6232	V	0.0133

AA Position in RBD	Reference Sequence (Wuhan-Hu-1)		Observed Order of Frequency for Epitope Variants (High to Low)			
			1st		2nd	
	Residue	Freq (%)	Residue	Freq (%)	Residue	Freq (%)
447	G	99.9948	del	0.0033	S	0.0005
449	Y	99.9643	H	0.0199	N	0.0137
498	Q	12.7255	R	87.5676	L	0.0115
499	P	99.9840	del	0.0095	R	0.0025
500	T	99.9832	del	0.0097	S	0.0031
501	N	12.3329	Y	87.9706	del	0.0101
502	G	99.9853	del	0.0104	L	0.0007

A total of 3,825,870 publicly available SARS-CoV-2 genome sequences identified January 1 2022 through June 16, 2022 were analyzed against the reference (Wuhan-Hu-1) SARS-CoV-2 genome. The data collected during this period likely reflects mostly Omicron sequences, however, other circulating variants, such as Delta, may also be included in this analysis. The frequency (freq) of variants within the mAb14284 epitope (as determined by structural studies described herein) was calculated. The amino acid (AA) position indicates the residue in the SARS-CoV-2 S protein RBD (as displayed in Table 29). For each AA position within the epitope, the frequencies of reference residues and the 2 most frequent variant residues are shown. "Del" indicates a deletion at that AA position. The functional impact of the most predominant circulating epitope residue variants assessed through June 16, 2022 (N439K, N439V, N440D, N440K, L441F, L441Q, K444L, K444M, K444N, K444Q, K444R, K444T, V445A, V445T, G446D, G446R, G446S, G446V, G447V, N448S, Y449D, Y449F, Y449H, Y449N, Y449S, Q498H, Q498R, T500A, T500F, T500N, N501T, N501Y) is summarized in Table 19.

Example 11: In Vitro VSV-SARS-CoV-2-S Virus Escape Mutant Selection in the Presence of mAb15160

[000261] To assess SARS-CoV-2 escape mutant selection, Vero cells were infected with replicating VSV-SARS-CoV-2-S (Wuhan-Hu-1 strain), and incubated with a range of concentrations of mAb15160 or IgG1 isotype control for 4 days. Infected cells were monitored for virus-induced cytopathic effect (CPE) as a read-out for virus replication. Loss of neutralization efficacy, as assessed by observable CPE in the presence of increasing concentration of antibodies, indicated potential selection of escape mutants. Supernatants containing virus were collected from wells with the highest mAb concentration and observable CPE, and further passaged in the presence of the same mAb. After passaging, supernatants containing virus were subjected to RNA sequence analysis and all amino acid changes in the S protein were designated as "putative escape mutations" if the amino acid change was present in

anti-SARS-CoV-2 S protein mAb-treated samples, but neither in input virus (inoculum) nor control samples (IgG1 control or no-mAb control).

[000262] CPE at ≥90% was observed in the presence of 0.016 to 50 μg/mL mAb15160 within the first passage. Deep sequencing of viral genomes after the first passage under selection with mAb15160 identified 2 putative escape mutations in the SARS-CoV-2 RBD binding epitope for mAb15160—F486V and Y489H. Of note, neither of these individual mutations are found in the prominent Omicron and Delta variants or in any other prior variant of concern, indicating that there is no current clinical concern with respect to these mutations.

[000263] The functional impact of each putative escape mutant on mAb15160 activity was assessed in neutralization assays, as discussed above. F486V and Y489H reduced the neutralization activity of mAb15160 by >531-fold and 122-fold, respectively, compared with reference pseudoparticles, confirming that F486V and Y489H are escape mutants of mAb15160.

Example 12: In Vitro Effector Function Activities of mAb15160

[000264] The ability of mAb15160 to mediate antibody dependent cellular phagocytosis (ADCP) of fluorescently labeled target cells engineered to express full length (FL) SARS-CoV-2 S protein (Jurkat/hCD20/SARS-CoV-2 S FL) was assessed in the presence of fluorescently-labeled primary MDM effector cells from two independent donors that were differentiated with macrophage colony-stimulating factor (MCSF). Results demonstrated that mAb15160 mediated concentration-dependent ADCP of Jurkat/hCD20/SARS-CoV-2 S FL cells with EC_{50} values in the picomolar range (Table 31), while no ADCP was observed with parental cells that did not express SARS-CoV-2 S protein. An IgG1 isotype control did not mediate ADCP of either Jurkat/hCD20/SARS-CoV-2 S FL or Jurkat/hCD20 cell lines, whereas an anti-CD20 IgG1 control mediated ADCP of both Jurkat/hCD20/SARS-CoV-2 S FL and Jurkat/hCD20 cell lines, demonstrating the capacity of effector cells used in the assay to phagocytose each of the tested cell lines.

Table 31: Summary of EC_{50} and Maximum Phagocytosis Values for ADCP of Target Cells Mediated by mAb15160

mAb(s)	MDM Donor #1				MDM Donor #2			
	Jurkat/hCD20/ SARS-CoV-2 S FL		Jurkat/hCD20		Jurkat/hCD20/ SARS-CoV-2 S FL		Jurkat/hCD20	
	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)
mAb15160	7.81E-11	27.5	ND	14.7	4.76E-11	31.1	ND	11.1
mAb10933 (casirivimab)	9.70E-12	28.3	ND	14.0	2.23E-11	28.6	ND	11.5
mAb10987 (imdevimab)	2.91E-11	32.3	ND	14.8	1.98E-11	30.4	ND	10.7
casirivimab+imdevimab	1.20E-10	49.5	ND	15.5	5.78E-11	48.2	ND	15.1
IgG1 isotype control	ND	13.1	ND	16.9	ND	9.6	ND	14.6
Anti-CD20 IgG1	1.01E-09	31.1	7.75E-10	45.4	1.49E-10	30.3	4.67E-10	45.2

[a] Maximum (max) ADCP is defined as the highest mean percentage ADCP value observed within the concentration range tested (0nM to 20nM, where 0nM is the no-antibody control).

ND, not determined because a concentration-dependent increase was not observed

[000265] mAb15160 was evaluated for the ability to mediate antibody dependent cell-mediated cytotoxicity (ADCC) against Jurkat/hCD20/SARS-CoV-2 S FL and Jurkat/hCD20 target cells using human primary natural killer (NK) cells from three independent donors as effector cells. Results demonstrate that mAb15160 mediates ADCC against Jurkat/hCD20/SARS-CoV-2 S FL target cells, but not SARS-CoV-2-negative parental cells, with varying activity demonstrated with each NK donor (donor #3 > donor #2; donor #1 showed no activity (Table 32). An IgG1 control did not mediate ADCC of either Jurkat/hCD20/SARS-CoV-2 S FL or Jurkat/hCD20 cell lines, whereas a positive control, anti-CD20 IgG1, mediated ADCC of both Jurkat/hCD20/SARS-CoV-2 S FL and Jurkat/hCD20 cell lines, demonstrating cytotoxic potential of all NK cells used in the assay against each tested cell line.

Table 32: Summary of EC_{50} and Maximum Cytotoxicity Values for ADCC Against Target Cells Mediated by mAb15160

mAb(s)	NK Donor #1				NK Donor #2				NK Donor #3			
	Jurkat/hCD20/ SARS-CoV-2 S FL		Jurkat/hCD20		Jurkat/hCD20/ SARS-CoV-2 S FL		Jurkat/hCD20		Jurkat/hCD20/ SARS-CoV-2 S FL		Jurkat/hCD20	
	EC_{50} (M)	Max Cyto-toxicity[a] (%)	EC_{50} (M)	Max Cyto-toxicity[a] (%)	EC_{50} (M)	Max Cyto-toxicity[a] (%)	EC_{50} (M)	Max Cyto-toxicity[a] (%)	EC_{50} (M)	Max Cyto-toxicity[a] (%)	EC_{50} (M)	Max Cyto-toxicity[a] (%)
mAb15160	ND	1.8	NC	4.6	NC	6.3	ND	3.1	6.32E-11	12.9	ND	0.0
mAb10933 (casirivimab)	ND	1.4	NC	4.7	NC	5.0	NC	3.6	4.89E-11	11.1	ND	1.2
mAb10987 (imdevimab)	7.42E-10	8.1	NC	3.9	5.05E-09	10.5	ND	1.9	6.44E-11	26.6	ND	1.3
casirivimab + imdevimab	ND	1.6	ND	0.8	NC	4.1	ND	4.8	3.60E-11	15.4	ND	0.0
IgG1 isotype control	ND	1.8	ND	0.7	ND	0.0	NC	6.4	ND	0.0	ND	0.5
Anti-CD20 IgG1	2.63E-12	20.0	3.03E-12	21.0	8.19E-12	15.1	8.08E-13	26.8	3.53E-14	14.5	NC	37.7

[a] Maximum (max) cytotoxicity is defined as the highest mean percentage cytotoxicity value observed within the concentration range tested

NC, Not calculated because the data did not fit a 4-parameter logistic equation; ND, Not determined because a concentration-dependent increase was not observed.

[000266] mAb15160 was evaluated for the ability to mediate the activation of FCGR3A signaling in a surrogate ADCC reporter bioassay using Jurkat T cells engineered to express a nuclear factor of activated T cells-luciferase (NFAT-Luc) reporter gene and human FCGR3A (Jurkat/NFAT-Luc/FCGR3A) in the presence of Jurkat/hCD20/SARS-CoV-2 S FL target cells. Engagement of FCGR3A via the Fc domain of human IgG1 antibodies bound to target cells leads to the activation of NFAT and drives the expression of luciferase, which is then measured via a luminescence readout. In agreement with results from ADCC assays using primary NK cells, results from the ADCC-surrogate reporter assay demonstrate that mAb15160 mediates a concentration-dependent increase in luciferase activity from reporter cells expressing FCGR3A in the presence of Jurkat/hCD20/SARS-CoV-2 S FL target cells with an EC_{50} of $2.97x10^{-10}$ M. The IgG1 negative control did not activate FCGR3A in the presence of Jurkat/hCD20/SARS-CoV-2 S FL or Jurkat/hCD20 cell lines.

[000267] mAb15160 was evaluated for the ability to mediate CDC against Jurkat/hCD20/SARS-CoV-2 S FL and Jurkat/hCD20 target cells in the presence of 5% pooled (ie, from several donors) NHS. Results demonstrate that mAb15160 does not mediate CDC

against Jurkat/hCD20/SARS-CoV-2 S FL or Jurkat/hCD20 cells in the presence of 5% NHS at antibody concentrations ranging from 0.95pM to 1μM. NHS used in the assay was evaluated in the same target cell lines for the ability to mediate CDC using the positive control, anti-CD20 IgG1. In the presence of NHS, the anti-CD20 IgG1 mediated CDC against target cell lines in a concentration-dependent manner. In the absence of NHS, the anti-CD20 IgG1 did not mediate lysis against any of the tested target cell lines.

Example 13: In Vitro VSV-SARS-CoV-2-S Virus Escape Mutant Selection in the Presence of mAb14284

[000268] To assess SARS-CoV-2 escape mutant selection, Vero cells were infected with replicating pseudotyped VSV-SARS-CoV-2-S (Wuhan-Hu-1 strain) and incubated with a range of concentrations of mAb14284 or IgG1 isotype control for 4 days. Infected cells were monitored for virus-induced cytopathic effect (CPE) as a read-out for virus replication. Loss of neutralization efficacy, as assessed by observable CPE in the presence of increasing concentration of antibodies, indicated potential selection of escape mutants. Supernatants containing virus were collected from wells with the highest mAb concentration and observable CPE, and further passaged in the presence of the same mAb. After passaging, supernatants containing virus were subjected to RNA sequence analysis and all amino acid changes in the S protein were designated as "putative escape mutations" if the amino acid change was present in the mAb14284-treated sample, but not in the IgG1 control sample.

[000269] CPE at ≥90% was observed in the presence of 0.016 to 50 μg/mL mAb14284 within the first passage (Table 33). Deep sequencing of viral genomes after the first passage under selection with mAb14284 identified 3 putative escape mutations in the SARS-CoV-2 RBD binding epitope for REGN14284—K444E, K444N, and V445D (Table 34).

[000270] The functional impact of putative escape mutant, K444N, on mAb14284 activity was assessed in neutralization assays discussed in Example 4. The K444N variant resulted in a complete loss of mAb14284 neutralization activity compared with reference pseudoparticles (Table 19), confirming that K444N is an escape mutant of mAb14284.

[000271] Functional assays of K444E and V445D are ongoing. However, the K444L, K444M, K444N, K444Q, K444T, V445A, and V445T mutations all resulted in a reduction or complete

loss of mAb14284 neutralization activity; mAb14284 neutralization activity was retained against the K444R mutation (Table 19).

Table 33: Selection of Putative VSV-SARS-CoV-2-S Virus Escape Mutants

Antibody	CPE (%)						
	50 µg/mL	10 µg/mL	2 µg/mL	0.4 µg/mL	0.08 µg/mL	0.016 µg/mL	No mAb
	Passage 1						
mAb14284	**≥90**	≥90	≥90	≥90	≥90	≥90	≥90
IgG1 Control	**≥90**	≥90	≥90	≥90	≥90	≥90	**≥90**

Vero cells were infected with VSV-SARS-CoV-2-S virus in the presence of mAb14284 or IgG1 isotype control mAb at a range of concentrations (0.016 to 50 µg/mL total) for 4 days. Cells were screened for virus replication by monitoring for virus-induced CPE. Supernatants containing virus were collected from wells with the highest antibody concentrations and detectable viral replication (≥20% CPE). Deep sequencing of viral RNA from was performed to determine the identity of putative escape mutations. A no antibody control (0 µg/mL) was sequenced to monitor for tissue culture adaptation. Bold, underlined text indicates samples that were sequenced.

Table 34: Deep Sequencing of Passaged Virus Identifies Putative Escape Mutations in the Receptor Binding Domain

Genomic position	4407	4409	4411
Reference nucleotide	A	G	T
Variant nucleotide	G	T	A
Gene position	1330	1332	1334
Mutation nature	nSNP	nSNP	nSNP
AA position	444	444	445
Reference AA	K	K	V
Variant AA	E	N	D
Inoculum	0%	0%	0%
mAb14284	7%	19%	67%
IgG1 Isotype Control	0%	0%	0%
No Ab	0%	0%	0%

Viral RNA from wells with the highest mAb concentration that showed detectable CPE was isolated 4 days post-infection. Deep sequencing was performed to identify changes in S protein sequence relative to the Wuhan-Hu-1 reference sequence. Only RBD variants are summarized in this table.

Example 14: In Vitro Effector Function Activities of mAb14284

[000272] IgG antibodies that are bound to target cells can mediate effector functions via their constant (Fc) region by interacting with specific FCGRs expressed on macrophages and natural killer (NK) cells, leading to antibody-dependent cellular phagocytosis (ADCP) and antibody-

dependent cellular cytotoxicity (ADCC), respectively, or by binding to complement proteins, leading to complement-dependent cytotoxicity (CDC), resulting in the destruction of target cells.

[000273] A series of in vitro studies was conducted to assess the ability of mAb14284 to mediate ADCP, ADCC, and CDC against target cells expressing full-length (FL) SARS-CoV-2 S protein from the Wuhan-Hu-1 strain (AA 1-1273), and BA.1 and BA.2 omicron lineages (AA 1-1270). To allow for simultaneous testing of an anti-CD20 IgG1 positive control antibody, target cell lines were also engineered to stably express human CD20 (hCD20).

[000274] Specifically, mAb14284 was assessed for the ability to: 1) mediate ADCP of target cells using monocyte-derived macrophages (MDM) as effector cells; 2) mediate ADCC of target cells using primary natural killer (NK) cells as effector cells; 3) activate FCGR3A signaling in an ADCC-surrogate reporter assay; and 4) mediate CDC of target cells in the presence of normal human serum (NHS).

[000275] The ability of mAb14284 to mediate ADCP of fluorescently labeled Jurkat/hCD20 target cells expressing FL Wu-1, BA.1, or BA.2 S protein was assessed in the presence of fluorescently labeled primary MDM effector cells from two independent donors that were differentiated with macrophage colony-stimulating factor (MCSF). mAb14284 mediates concentration-dependent ADCP of Jurkat/hCD20 cells expressing SARS-CoV-2 Wu-1, BA.1, or BA.2 S protein with EC_{50} values in the picomolar range (Table 35), while no ADCP was observed with parental cells that do not express SARS-CoV-2 S protein. An IgG1 isotype control did not mediate ADCP of any of the tested cell lines, whereas an anti-CD20 IgG1 control mediated ADCP of all tested cell lines, demonstrating the capacity of effector cells used in the assay to phagocytose each cell line evaluated.

Table 35: Summary of EC_{50} and Maximum Phagocytosis Values for ADCP of Target Cells Mediated by mAb14284

mAb(s)	Jurkat/hCD20/SARS-CoV-2 Wu-1 S		Jurkat/hCD20/SARS-CoV-2 BA.1 S		Jurkat/hCD20/SARS-CoV-2 BA.2 S		Jurkat/hCD20	
	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)
MDM Donor #1								
mAb14284	NC	38.6	3.11E-11	44	4.37E-11	46.5	ND	0
IgG1 isotype control	8.78E-11	45.5	7.97E-11	61.5	2.30E-10	37.4	1.77E-10	54.9
Anti-CD20 IgG1	ND	2	ND	4.4	ND	4.1	ND	4.5

mAb(s)	Jurkat/hCD20/SARS-CoV-2 Wu-1 S		Jurkat/hCD20/SARS-CoV-2 BA.1 S		Jurkat/hCD20/SARS-CoV-2 BA.2 S		Jurkat/hCD20	
	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)	EC_{50} (M)	Max ADCP[a] (%)
MDM Donor #1								
MDM Donor #2								
mAb14284	1.64E-11	49.7	3.73E-11	60.9	8.74E-11	43.8	ND	0
IgG1 isotype control	8.10E-11	87.3	8.21E-11	80.4	2.23E-10	22.5	3.18E-10	37.9
Anti-CD20 IgG1	ND	7.4	ND	1.5	ND	0	ND	0

[a] Maximum (max) ADCP is defined as the highest mean percentage ADCP value observed within the concentration range tested (0nM to 20nM, where 0nM is the no-antibody control).

NC, Not calculated because the data did not fit a 4-parameter logistic equation; ND, not determined because a concentration-dependent increase was not observed

[000276] mAb14284 was evaluated for the ability to mediate ADCC against Jurkat/hCD20 target cells expressing FL Wu-1, BA.1, or BA.2 S protein using human primary NK cells pooled from 3 donors as effector cells. Results demonstrate that mAb14284 mediates concentration-dependent ADCC against Jurkat/hCD20 expressing SARS-CoV-2 Wu-1, BA.1, or BA.2 S protein with EC_{50} values in the picomolar range (Table 36), but not against parental cells that do not express SARS-CoV-2 S protein. An IgG1 control did not mediate ADCC against any of the tested cell lines, whereas a positive control, anti-CD20 IgG1, mediated ADCC against all tested cell lines, demonstrating cytotoxic potential of the NK cells used in the assay against each cell line evaluated.

Table 36: Summary of EC_{50} and Maximum Cytotoxicity Values for ADCC Against Target Cells Mediated by REGN14284

mAb(s)	Jurkat/hCD20/ SARS-CoV-2 Wu-1 S		Jurkat/hCD20/ SARS-CoV-2 BA.1 S		Jurkat/hCD20/ SARS-CoV-2 BA.2 S		Jurkat/hCD20	
	EC_{50} (M)	Max Cytotoxicity[a] (%)	EC_{50} (M)	Max Cytotoxicity[a] (%)	EC_{50} (M)	Max Cytotoxicity[a] (%)	EC_{50} (M)	Max Cytotoxicity[a] (%)
mAb14284	6.41E-12	7.9	2.64E-11	8.3	5.37E-12	8.3	ND	0.4
IgG1 isotype control	ND	0.6	ND	0.2	ND	0.6	ND	0.6
Anti-CD20 IgG1	5.83E-12	16.9	3.03E-12	18.8	1.49E-11	18.7	1.17E-11	15.1

[a] Maximum (max) cytotoxicity is defined as the highest mean percentage cytotoxicity value observed within the concentration range tested

NC, Not calculated because the data did not fit a 4-parameter logistic equation; ND, Not determined because a concentration-dependent increase was not observed.

[000277] mAb14284 was evaluated for the ability to mediate the activation of FCGR3A signaling in a surrogate ADCC reporter bioassay using Jurkat T cells engineered to express a nuclear factor of activated T cells-luciferase (NFAT-Luc) reporter gene and human FCGR3A (Jurkat/NFAT-Luc/FCGR3A) in the presence of Jurkat/hCD20 target cells expressing FL SARS-CoV-2 Wu-1, BA.1, or BA.2 S protein. Engagement of FCGR3A via the Fc domain of human IgG1 antibodies bound to target cells leads to the activation of NFAT and drives the expression of luciferase, which is then measured via a luminescence readout.

[000278] In agreement with results from ADCC assays using primary NK cells, results from the ADCC-surrogate reporter assay demonstrate that mAb14284 mediates a concentration-dependent increase in luciferase activity from reporter cells expressing FCGR3A in the presence of SARS-CoV-2 Wu-1, BA.1, or BA.2 S protein-expressing target cells with picomolar EC_{50} values, but not against parental cells that do not express SARS-CoV-2 S protein. The IgG1 negative control did not activate FCGR3A in the presence of any cell line evaluated.

[000279] mAb14284 was evaluated for the ability to mediate CDC against Jurkat/hCD20/SARS-CoV-2 Wu-1 S, Jurkat/hCD20/SARS-CoV-2 BA.1 S, Jurkat/hCD20/SARS-CoV-2 BA.2 S, and Jurkat/hCD20 target cells in the presence of 5% pooled (*i.e.*,, from several donors) NHS. Results demonstrate that mAb14284 did not mediate CDC against parental Jurkat/hCD20 cells, nor Jurkat/hCD20 cells expressing full-length SARS-CoV-2 Wu.1, BA.1, or BA.2 S protein in the presence of 5% NHS at antibody concentrations ranging from 0.95pM to 1μM.

[000280] NHS used in the assay was evaluated in the same target cell lines for the ability to mediate CDC using the positive control, anti-CD20 IgG1. In the presence of NHS, the anti-CD20 IgG1 mediated CDC against target cell lines in a concentration-dependent manner. In the absence of NHS, the anti-CD20 IgG1 did not mediate lysis against any of the tested target cell lines.

Example 15: Phase 3 clinical trial assessing the safety and efficacy of mAb15160

[000281] After obtaining safety and tolerability data from healthy volunteers treated with mAb15160, a phase 3, randomized, double-blind, placebo-controlled study is initiated to assess the safety and efficacy of mAb15160 to prevent symptomatic COVID-19 (Table 37) . This is an

event-driven study that is anticipated to enroll approximately 5000 participants of age ≥ 18 years with and without risk factors for severe SARS-CoV-2 infection, who are PCR negative for SARS-CoV-2 at the time of randomization. Study participants are randomized in a 1:1 ratio into one of 2 treatment groups (300 mg mAb15160 administered once every 12 weeks (Q12W) or placebo) administered as subcutaneous (SC) injections over 6 months.

[000282] The primary endpoint of this study is symptomatic RT-qPCR confirmed SARS-CoV-2 infection. The secondary endpoints include the safety and tolerability of repeated SC injections of mAb15160. Safety assessments include, but are not limited to, collection of treatment emergent adverse events, vital signs, and safety laboratory tests. Blood is also drawn for drug concentration, immunogenicity, and serum neutralizing titer measurements. Administration of mAb15160 results in a reduction in the percentage of symptomatic SARS-CoV-2 infection as compared to the placebo group.

Table 37: Phase 3 study design

Hypothesis:	**Prophylaxis with mAb15160 prevents symptomatic SARS-CoV-2 infection.**
Treatment Arms and Dose:	mAb15160 (300 mg SC Q12W x2 doses) Placebo SC
Key Design Elements	This is an event-driven, phase 3, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of mAb15160 to prevent symptomatic COVID-19 This study enrolls approximately 5000 participants of age ≥ 18 years with and without risk factors for severe SARS-CoV-2 infection. Study participants will be randomized in a 1:1 ratio into one of 2 treatment groups (mAb15160, or placebo) administered as subcutaneous injections over 6 months.
Duration:	253 days
Population:	≥18 years-old with a SARS-CoV-2 negative RT-qPCR with and without risk factors for severe COVID-19
Number of subjects planned:	Approximately 5000 participants
Primary Endpoint:	Symptomatic RT-qPCR-confirmed SARS-CoV-2 infection cases during the 6-month efficacy assessment period
Secondary Endpoint:	Safety and tolerability of repeated SC injections of mAb15160 Serum concentration and Immunogenicity of mAb15160

Q12W = dosed once every 12 weeks

Example 16: Phase 3 clinical trial assessing the safety and efficacy of mAb15160 in pre-exposure prophylaxis

[000283] This is a phase 3, randomized, double-blind, placebo-controlled study in adults and adolescents to assess the safety and efficacy of mAb15160 as pre-exposure prophylaxis to prevent COVID-19. This event-driven study enrolls approximately 5000 participants of age ≥ 12 years. Study participants is randomized in a 1:1 ratio into one of 2 treatment groups (mAb15160 or placebo) administered as subcutaneous injections over 6 months. The study consists of three periods: a 1 to 14-day screening period, a 6-month prophylaxis and efficacy assessment period (EAP), and a 3-month follow-up period (see Table 38). Administration of mAb15160 results in a reduction in the percentage of symptomatic SARS-CoV-2 infection as compared to the placebo group.

Screening/Baseline

[000284] After participants provide informed consent, they are assessed for study eligibility. The screening visit occurs up to 14 days prior to the randomization and baseline visit, and in some subjects the screening, randomization and baseline visit may occur on the same day. To be included in the study, participants have a negative SARS-CoV-2 test result, preferably from a reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay from a sample collected within 72 hours of the baseline visit. Randomization will be stratified for assignment of treatment group by age group category (≥12 years to <18 years, ≥18 years to ≤65 years, >65 years), immunocompromised status (yes/no), and by prior vaccination (yes/no). Approximately 20% or more of participants enrolled will have a status of immunocompromised.

Treatment and Efficacy Assessment Period (EAP)

[000285] On day 1, after assessing available lab results, completing baseline assessments, sample collection, and randomization, all participants receive their first dose of study drug. Study drug is administered as a 2.5 ml subcutaneous (SC) injection in a blinded manner. Participants are randomized in a 1:1 ratio to one of the two treatment groups: mAb15160 (300 mg administered subcutaneously once every 8 weeks (SC Q8W) or placebo administered subcutaneously once every 8 weeks.

Table 38: Phase 3 study design

HYPOTHESIS	Prophylaxis with subcutaneous mAb15160 will prevent symptomatic SARS-CoV-2 infection.

	Note: Symptomatic SARS-CoV-2 infection is determined by a positive SARS-CoV-2 RT-qPCR result during the Efficacy Assessment Period (EAP) with at least one symptom occurring within ±10 days of a positive RT-qPCR. The EAP is from baseline to 6 months.	
STUDY OBJECTIVES AND ENDPOINTS	**Primary Objective:** • To evaluate the efficacy of mAb15160, compared with placebo, in preventing symptomatic SARS-CoV-2 infection.	**Primary Endpoint:** • Cumulative incidence of symptomatic, RT-PCR-confirmed SARS-CoV-2 infection cases during the efficacy assessment period (EAP)
	Secondary Objectives: • To evaluate the safety and tolerability of repeated SC injections of mAb15160 in the study population • To assess concentrations of mAb15160 in serum over time • To assess the immunogenicity of mAb15160	**Secondary Endpoints:** • Proportion of participants with treatment-emergent adverse events (TEAEs), during the EAP and follow-up period • Proportion of participants with TEAEs leading to study drug discontinuation during the EAP and follow-up period • Proportion of participants with treatment-emergent serious adverse events (SAEs) during the EAP and follow-up period • Proportion of participants with adverse events of special interest (AESIs) during the EAP • Concentrations of mAb15160 in serum over time • Incidence and titer of anti-drug antibodies (ADA), and incidence of neutralizing antibodies (NAb) to mAb15160 over time
	Exploratory Objectives: • To evaluate additional indicators of mAb15160 clinical efficacy and disease prevention, compared to placebo • To assess humoral immune response to SARS-CoV-2 at baseline and after administration of mAb15160 • To assess serum neutralization potential of mAb15160	**Exploratory Endpoints:** • Cumulative incidence of symptomatic, RT-PCR-confirmed SARS-CoV-2 infection cases during the follow-up period • Cumulative incidence of RT-PCR-confirmed SARS-CoV-2 infection cases (regardless of symptoms) during the EAP • Cumulative incidence of symptomatic, RT-PCR-confirmed SARS-CoV-2 infection cases during

	• To characterize viral variants by sequencing SARS-CoV-2 in participants who become infected post-baseline • To explore biomarkers predictive or indicative of safety and/or efficacy of mAb15160, COVID-19 vaccine response, SARS-CoV-2 infection and immune response, COVID-19 disease progression and clinical outcomes of mAb15160 • To explore relationships between mAb15160 exposure and selected efficacy and safety endpoints and/or biomarkers	the efficacy assessment period (EAP), in subgroups of those with one or more risk factors for severe COVID • Proportion of participants with ≥1 moderate COVID-19 symptom during the EAP and follow-up period • Proportion of participants with COVID-19-related hospitalization, emergency room visit, urgent care center visit or death during the EAP and follow-up period • Proportion of participants with COVID-19-related hospitalization or death during the EAP and follow-up period • Proportion of participants requiring supplemental oxygen due to COVID-19 during the EAP and follow-up period • Proportion of participants admitted to an intensive care unit (ICU) due to COVID-19 until the end of the follow-up period • Proportion of participants requiring mechanical ventilation due to COVID-19 until the end of the follow-up period • Absolute levels, change from baseline and percentage change from baseline in serum anti-SARS-CoV-2 antibodies such as anti-nucleocapsid protein IgG measured at baseline and after administration of mAb15160 over time • Absolute values of serum neutralizing inhibitory dilution 50% (ID50) titers at baseline and post-mAb15160 treatment against D614G and omicron variants • Change from baseline in ID50 after mAb15160 treatment against D614G and omicron variants
PATIENT POPULATION		
Number of Subjects	Approximately 5000 participants are enrolled in the study.	

Study Population	This study enrolls participants with or without risk factors for progression to severe COVID-19, and who are RT-PCR negative at study entry.
Inclusion Criteria	1. Age ≥12 years of age at screening. *Note: participants ≥12 and <18 years of age must be immunocompromised and will only be enrolled where permitted by local requirements.* 2.Has a SARS-CoV-2-negative RT-PCR result from a sample collected ≤72 hours prior to randomization or using a local RT-PCR test and sample collection following assay standards. *Notes: The result should be reviewed and confirmed negative prior to dosing.* *Nasopharyngeal swab sample is highly preferred but other sample types (such as nasal, oropharyngeal [OP], or saliva) adhering to local standards are acceptable.* 3.Is willing and able to: a.Provide informed consent signed by study participant or legally acceptable representative b.Comply with clinic visits and study-related procedures, including providing nasopharyngeal swab samples 4.Is judged by the investigator to be in stable health (including those who have a chronic stable medical condition) based on medical history, physical examination, vital sign measurements, and laboratory measurements performed at screening and/or prior to administration of study drug
Exclusion Criteria	1. Has a life expectancy of less than 2 years 2. Has symptoms consistent with COVID-19 (as determined by the investigator) 3. Has a history of COVID-19 infection or has received a SARS-CoV-2 investigational, authorized, or approved vaccine within 90 days prior to randomization 4. Planned use of any investigational, authorized, or approved vaccine for COVID-19 during the EAP 5. Prior, current, or planned use of any of the following treatments: COVID-19 convalescent plasma, other monoclonal antibodies against SARS-CoV-2 (eg, bamlanivimab and etesevimab, tixagevimab and cilgavimab, sotrovimab), or any other COVID-19 treatment (authorized, approved, or investigational) *Note: prior use is defined as the past 30 days or within 5 half-lives of the treatment (whichever is longer) from screening* 6. Is planned to initiate intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) therapy 7. Has known active symptomatic infection with influenza or other respiratory pathogen, confirmed by a diagnostic test 8. Current hospitalization or was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit

	9. Has known allergy or hypersensitivity to components of the study drugs 10. Is pregnant or is breastfeeding. 11. Is a woman of childbearing potential (WOCBP)[1] who is unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include: a. Abstinence[2,3] b. Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening c. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) d. Bilateral tubal ligation [1]WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation. [2]Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. [3]Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods 12. Is in, or is planned to enter a quarantine center 13. Is a member of the clinical site study team or their immediate family member

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Table 39: Sequences Excluded from ST.26-Formatted Sequence Listing

SEQ ID NO:	Sequence
13	gaggtcagt
14	EVS
33	gagggcaat
34	EGN
67	gagggcact
68	EGT
85	gaggacagt
86	EDS
105	gctgcatcc
106	AAS
125	ggtgcatcc
126	GAS
163	ggtaacagc
164	GNS
183	agtaatgat
184	SND
203	gacaatgat
204	DND
241	gatgcatcc
242	DAS
261	ggtgcaaca
262	GAT
299	agtgataat
300	SDN
319	gtcaataat
320	VNN
391	aaggcatct

392	KAS
445	gataaaaac
446	DKN
464	gaactcact
465	ELT
484	gatgtcact
485	DVT
504	gaggtcact
505	EVT
524	gagggcagt
525	EGS
541	gatgtcagt
542	DVS
577	gaaaataat
578	ENN
633	ttgggttct
634	LGS
653	ttgggatct
705	tctgcatcc
706	SAS
775	aaagacagt
776	KDS
795	ggtaacacc
796	GNT
846	aagatttct
847	KIS
915	ggtcacacc
916	GHT
932	aggaataat
933	RNN

968	tgggcatct
969	WAS
1000	ggtgcatcc
1001	GAS
1021	gctgcatcc
1022	AAS
1041	gatgtcagt
1042	DVS
1061	ggtaacagc
1062	GNS

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CLAIMS

1. An isolated recombinant antibody or antigen-binding fragment thereof that specifically binds to a coronavirus spike protein (CoV-S), wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2, and HCDR3, comprising the amino acid sequences of SEQ ID NOs: 552, 554, and 556, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions, LCDR1, LCDR2, and LCDR3, comprising the amino acid sequences of SEQ ID NOs: 84, 14, and 560, respectively.

2. The antibody or antigen-binding fragment of claim 1, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 550.

3. The antibody or antigen-binding fragment of claim 1, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 558.

4. The antibody or antigen-binding fragment of claim 1, wherein the HCVR comprises the amino acid sequence of SEQ ID NO: 550, and the LCVR comprises the amino acid sequence of SEQ ID NO: 558.

5. The antibody or antigen-binding fragment of any one of claims 1-4 that is an antibody comprising a human IgG heavy chain constant region selected from isotype IgG1 or IgG4.

6. The antibody or antigen-binding fragment of any one of claims 1-4 that is an antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 562.

7. The antibody or antigen-binding fragment of any one of claims 1-4 that is an antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO: 564.

8. The antibody or antigen-binding fragment of any one of claims 1-4 that is an antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 562, and a light chain comprising the amino acid sequence of SEQ ID NO: 564.

9. The antibody or antigen-binding fragment of any one of claims 1-8, comprising a heavy chain constant region with 252Y, 254T and 256E modifications.

10. The antibody or antigen-binding fragment of any one of claims 1-9, which:

(i) is multispecific; or

(ii) is an antibody or antigen-binding fragment wherein said CoV-S is SARS-CoV-2-S.

11. A complex comprising an antibody or antigen-binding fragment of any one of claims 1-10 bound to a CoV-S polypeptide, or a complex comprising an antibody or antigen-binding fragment of any one of claims 1-10 bound to SARS-CoV-2-S.

12. A polynucleotide molecule encoding an antibody or antigen-binding fragment thereof of any one of claims 1-10.

13. A vector comprising the polynucleotide molecule of claim 12.

14. A set of polynucleotide molecules, wherein:

(a) the first polynucleotide molecule encodes a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2, and HCDR3, comprising the amino acid sequences of SEQ ID NOs: 552, 554, and 556, respectively, or the first polynucleotide molecule encodes a heavy chain comprising the amino acid sequence of SEQ ID NO: 562; and

(b) the second polynucleotide molecule encodes a LCVR comprising three light chain complementarity determining regions, LCDR1, LCDR2, and LCDR3, comprising the amino acid sequences of SEQ ID NOs: 84, 14, and 560, respectively, or the second polynucleotide molecule encodes a light chain comprising the amino acid sequence of SEQ ID NO: 564.

15. A set of vectors comprising the first polynucleotide molecule and the second polynucleotide molecule, respectively, of claim 14.

16. An isolated host cell comprising the set of vectors of claim 15.

17. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-10, and pharmaceutically acceptable carrier or diluent.

18. A kit comprising the antibody or antigen-binding fragment of any one of claims 1-10, and a further therapeutic agent.

19. The kit of claim 18, wherein the further therapeutic agent is a second antibody or an antigen-binding fragment thereof that binds a SARS-CoV-2 spike protein.

20. A vessel or injection device comprising the antibody or antigen-binding fragment of any one of claims 1-10.

21. Use of an antibody or antigen binding fragment thereof of any one of claims 1-10 in the manufacture of a medicament for treating or preventing infection with a coronavirus in a subject in need thereof.

22. Use of an antibody or antigen binding fragment thereof of any one of claims 1-10 in the manufacture of a medicament for preventing one or more COVID-19 symptoms resulting from infection with a coronavirus in a subject in need thereof.

23. The use of claim 21 or 22, wherein said coronavirus is selected from the group consisting of SARS-CoV-2, SARS-CoV, and MERS-CoV.

24. The use of claim 23, wherein said coronavirus is SARS-CoV-2.

25. The use of claim 24, wherein the SARS-CoV-2 is an omicron variant of SARS-CoV-2.

26. The use of claim 25, wherein the omicron variant of SARS-CoV-2 is selected from BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3, or BA.4/BA.5.

27. The use of any one of claims 21-26, wherein the medicament is to be administered to the subject in combination with a further therapeutic agent.

28. The use of claim 27, wherein the further therapeutic agent is a second antibody or an antigen-binding fragment thereof that binds a SARS-CoV-2 spike protein.

29. The use of claim 27, wherein the further therapeutic agent is an anti-viral drug or a vaccine.

30. A method for making the antibody or antigen-binding fragment of any one of claims 1-10, comprising:

(a) introducing into a host cell one or more polynucleotides encoding said antibody or antigen-binding fragment;

(b) culturing the host cell under conditions favorable to expression of the one or more polynucleotides; and

(c) isolating the antibody or antigen-binding fragment from the host cell and/or a medium in which the host cell is grown.