

ANTIBODY THERAPIES FOR SARS-COV-2 INFECTION

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format
5 in lieu of a paper copy, and is hereby incorporated by reference into the
specification. The name of the text file containing the Sequence Listing is
930585_413WO_SEQUENCE_LISTING.txt. The text file is 327 KB, was created on
June 10, 2021, and is being submitted electronically via EFS-Web.

BACKGROUND

10 A novel betacoronavirus emerged in Wuhan, China, in late 2019. As of June 9,
2021, approximately 174 million cases of infection by this virus (termed, among other
names, SARS-CoV-2 and Wuhan coronavirus) were confirmed worldwide, and had
resulted in approximately 3.7 million deaths. Therapies for preventing or treating
SARS-CoV-2 infection and COVID-19 are needed.

15 SUMMARY

In one aspect, the present disclosure provides a use of an antibody or antigen-
binding fragment that is capable of binding to a surface glycoprotein of a SARS-CoV-2
expressed on a cell surface of a host cell and/or on a virion, in the manufacture of a
medicament for treating a SARS-CoV-2 infection in a subject, wherein the use
20 comprises that a single dose of the medicament is to be administered to the subject,
wherein the antibody comprises a heavy chain variable domain (VH) comprising a
CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising
a CDRL1, a CDRL2, and a CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1,
CDRL2, and CDRL3 comprise the amino acid sequences set forth in: (1) SEQ ID
25 NOS.:106, 121, 108, 169, 170, and 171, respectively; or (2) SEQ ID NOS.:106, 107,
108, 169, 170, and 171, respectively.

In another aspect, the present disclosure provides a use of an effective amount of (i) an antibody or antigen-binding fragment that is capable of binding to a surface glycoprotein of a SARS-CoV-2 expressed on a cell surface of a host cell and/or on a virion, or (ii) a composition comprising (ii)(a) the antibody or antigen-binding fragment and (ii)(b) a pharmaceutically acceptable excipient, carrier, or diluent, in the manufacture of a medicament for treating SARS-CoV-2 infection in a subject, wherein the antibody comprises a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in: (1) SEQ ID NOS.:106, 121, 108, 169, 170, and 171, respectively; or (2) SEQ ID NOS.:106, 107, 108, 169, 170, and 171, respectively.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the design of a clinical study of recombinant monoclonal IgG1 antibody sotrovimab (also called, *e.g.*, S309 N55Q LS herein) for treatment of mild to moderate COVID-19 disease.

Figures 2A-2D show a timeline of events for a clinical study of sotrovimab for treatment of mild to moderate COVID-19 disease.

Figure 3 shows the study design for a clinical study of sotrovimab for treatment of severe to critical COVID-19 disease.

Figure 4 shows the study design for a clinical study of sotrovimab for post-exposure prophylaxis of COVID-19 disease.

Figure 5 shows the binding site of sotrovimab on the spike protein of SARS-CoV-2. The SARS-CoV-2 receptor-binding domain is shown, with the ACE2 receptor-

CLAIMS

What is claimed is:

1. Use of an antibody or antigen-binding fragment that is capable of binding to a surface glycoprotein of a SARS-CoV-2 expressed on a cell surface of a host cell and/or on a virion, in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the use comprises that a single dose of the medicament is to be administered to the subject,

wherein the antibody comprises a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3,

wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in:

- (1) SEQ ID NOS.:106, 121, 108, 169, 170, and 171, respectively; or
- (2) SEQ ID NOS.:106, 107, 108, 169, 170, and 171, respectively.

2. Use of an effective amount of (i) an antibody or antigen-binding fragment that is capable of binding to a surface glycoprotein of a SARS-CoV-2 expressed on a cell surface of a host cell and/or on a virion, or (ii) a composition comprising (ii)(a) the antibody or antigen-binding fragment and (ii)(b) a pharmaceutically acceptable excipient, carrier, or diluent, in the manufacture of a medicament for treating SARS-CoV-2 infection in a subject,

wherein the antibody comprises a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3,

wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in:

- (1) SEQ ID NOS.:106, 121, 108, 169, 170, and 171, respectively; or
- (2) SEQ ID NOS.:106, 107, 108, 169, 170, and 171, respectively.

3. The use of claim 2, wherein the use comprises that a single dose of the antibody or antigen-binding fragment of (i) or the composition of (ii) is to be administered to the subject.

4. The use of any one of claims 1-3, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO.:113 and the VL comprises the amino acid sequence set forth in SEQ ID NO.:168; or wherein the VH comprises the amino acid sequence set forth in SEQ ID NO.:105 and the VL comprises the amino acid sequence set forth in SEQ ID NO.:168.

5. The use of any one of claims 1-4, wherein the antibody or antigen-binding fragment further comprises an Fc polypeptide or a fragment thereof.

6. The use of any one of claims 1-5, which is an IgG, IgA, IgM, IgE, or IgD isotype; or which is an IgG isotype selected from IgG1, IgG2, IgG3, and IgG4; or which is an IgG1 isotype.

7. The use of any one of claims 5-6, wherein the Fc polypeptide or fragment thereof comprises:

(i) a mutation that enhances binding to a FcRn as compared to a reference Fc polypeptide that does not comprise the mutation; and/or

(ii) a mutation that enhances binding to a FcγR as compared to a reference Fc polypeptide that does not comprise the mutation.

8. The use of claim 7, wherein the mutation that enhances binding to a FcRn comprises: M428L; N434S; N434H; N434A; N434S; M252Y; S254T; T256E; T250Q; P257I; Q311I; D376V; T307A; E380A; or any combination thereof; or:

(i) M428L/N434S;

(ii) M252Y/S254T/T256E;

(iii) T250Q/M428L;

- (iv) P257I/Q311I;
- (v) P257I/N434H;
- (vi) D376V/N434H;
- (vii) T307A/E380A/N434A; or
- (viii) any combination of (i)-(vii); or
M428L/N434S.

9. The use of any one of claims 7-8, wherein the mutation that enhances binding to a FcγR comprises S239D; I332E; A330L; G236A; or any combination thereof, and optionally does not comprise S239D; or:

- (i) S239D/I332E;
- (ii) S239D/A330L/I332E;
- (iii) G236A/S239D/I332E; or
- (iv) G236A/A330L/I332E.

10. The use of any one of claims 1-9, wherein the antibody or antigen-binding fragment comprises the CH1-CH3 amino acid sequence of SEQ ID NO.:173 or 265 and the CL amino acid sequence of SEQ ID NO.:174; or

wherein the antibody or antigen-binding fragment comprises the CH1-CH3 amino acid sequence of SEQ ID NO.:175 or 266 and the CL amino acid sequence of SEQ ID NO.:174.

11. The use of any one of claims 1-10, wherein the antibody or antigen-binding fragment comprises a heavy chain polypeptide and a light chain polypeptide, wherein:

- (i) the heavy chain polypeptide comprises the VH amino acid sequence set forth in SEQ ID NO.:113 and the CH1-CH3 amino acid sequence set forth in SEQ ID NO.:173 or 265; and
- (ii) the light chain comprises the VL amino acid sequence set forth in SEQ ID NO.:168 and the CL amino acid sequence set forth in SEQ ID NO.:174, and

wherein, optionally, the use comprises that a single dose of the antibody or antigen-binding fragment is to be administered the subject; or

wherein the antibody or antigen-binding fragment comprises a heavy chain polypeptide and a light chain polypeptide, wherein:

(i) the heavy chain polypeptide comprises the VH amino acid sequence set forth in SEQ ID NO.:113 and the CH1-CH3 amino acid sequence set forth in SEQ ID NO.:175 or 266; and

(ii) the light chain comprises the VL amino acid sequence set forth in SEQ ID NO.:168 and the CL amino acid sequence set forth in SEQ ID NO.:174, and

wherein, optionally, the use comprises that a single dose of the antibody or antigen-binding fragment is to be administered to the subject.

12. The use of any one of claims 1-11, wherein the subject:

(i) is aged 18 to 49 years;

(ii) is 18 years old or older, or 19 years old or older;

(iii) has mild to moderate COVID-19;

(iv) has severe COVID-19;

(v) has severe to critical COVID-19;

(vi) has had fewer than seven days or 5 or fewer days since onset of symptoms;

(vii) has had seven days or more since onset of symptoms;

(viii) has had a positive reverse-transcriptase–polymerase-chain-reaction or antigen SARS-CoV-2 test result;

(ix) is 55 years of age or older, or 65 years old or older;

(x) has one or more of: diabetes requiring medication, obesity (body-mass index $>30 \text{ kg/m}^2$), chronic kidney disease (estimated glomerular filtration rate $<60 \text{ mL/min/1.73 m}^2$), congestive heart failure (New York Heart Association class II or higher), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion), and

moderate to severe asthma (subject requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year); or

(xi) any combination of (i)-(x); or

the subject is 18 or more years of age with laboratory-confirmed (*e.g.*, by PCR test) SARS-CoV-2 infection; or

the subject has a clinical status of Grade 4 (hospitalized, oxygen by mask or nasal prongs), 5 (hospitalized, on non-invasive ventilation, or high flow oxygen), 6 (hospitalized, intubation and mechanical ventilation) or 7 (ventilation and additional organ support - pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)), as defined by the WHO clinical severity score, 9-point ordinal scale; or

the subject has mild-to-moderate COVID-19; or

the subject is at-risk of progression to severe COVID-19; optionally wherein following administration of the antibody, antigen-binding fragment, or composition to the subject, the subject is at a reduced risk of hospitalization for COVID-19; or

the subject has or is at risk for progressing to severe COVID-19, wherein, optionally, severe COVID-19 comprises (i) hypoxemia (O_2 saturation $\leq 93\%$ on room air or $\text{PaO}_2/\text{FiO}_2 < 300$) requiring oxygen supplementation for more than 1 day or (ii) the subject requiring $\geq 4\text{L}/\text{min}$ oxygen supplementation or equivalent; or

the subject has or is at risk for progressing to critical COVID-19, wherein, optionally, critical COVID-19 comprises respiratory failure requiring at least one of the following: invasive mechanical ventilation and ECMO; shock; and multi-organ dysfunction/failure; or

the subject is less than seven days since onset of symptoms; or wherein the subject is seven days or more since onset of symptoms; or the subject is any one or more of (i)-(iii):

(i) 18 or older and has a positive SARS-CoV-2 test result (by any validated test *e.g.* RT-PCR on any specimen type);

(ii) (1) hospitalized with severe COVID-19 disease defined as requirement for supplemental oxygen or non-invasive ventilation consistent with Grade 4 or Grade 5

disease or (2) hospitalized with critical COVID-19 disease defined as those on mechanical ventilation (Grade 6 or Grade 7 disease));

(iii) is male or female, wherein, optionally, (1) the woman is non-childbearing potential (WONCBP) or (2) is a woman of child-bearing potential (WOCBP) and uses a contraceptive method; or

the subject had or has close contacts to a person with a confirmed SARS-CoV-2 infection; or

is a resident of a nursing home or a long-term care facility; is a hospice care worker; is a healthcare provider or healthcare worker; is a first responder; is a family member or other close contact of a subject diagnosed with or suspected of having a SARS-CoV-2 infection, is overweight or clinically obese; is or has been a smoker; has or had chronic obstructive pulmonary disease (COPD); is asthmatic (e.g., having moderate to severe asthma); has an autoimmune disease or condition (e.g., diabetes); has a compromised or depleted immune system (e.g., due to AIDS/HIV infection, a cancer such as a blood cancer, a lymphodepleting therapy such as a chemotherapy, a bone marrow or organ transplantation, or a genetic immune condition); has chronic liver disease; has cardiovascular disease; and/or has a pulmonary or heart defect; and/or works or otherwise spends time in close proximity with others, such as in a factory, shipping center, hospital setting, or the like.

13. The use of any one of claims 1-12, comprising that the antibody, antigen-binding fragment, or composition is to be administered to the subject intravenously, optionally over the course of 30 minutes, 60 minutes, or 90 minutes.

14. The use of any one of claims 1-13, comprising that the antibody, antigen-binding fragment, or composition is to be administered to the subject intramuscularly.

15. The use of any one of claims 1-14, wherein the use comprises that the antibody or antigen-binding fragment is to be administered to the subject at a dose of up

to 100 mg, up to 150 mg, up to 200 mg, up to 250 mg, up to 300 mg, up to 350 mg, up to 400 mg, up to 450 mg, or up to 500 mg; or at a dose in a range from 50 mg to 500 mg, or in a range from 50 mg to 250 mg, or in a range from 50 mg to 100 mg, or in a range from 100 mg to 500 mg, or in a range from 250 mg to 500 mg; or that 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, or 500 mg of the antibody or antigen-binding fragment is to be administered to the subject; or that 50, 150, 250, or 500 mg of the antibody or antigen-binding fragment is to be administered to the subject; or that 500 mg of the antibody or antigen-binding fragment is to be administered to the subject.

16. The use of any one of claims 1-15, comprising that the antibody, antigen-binding fragment, or composition is to be administered to the subject 2, 3, 4, 5, 6, 7, 8, 9, or 10 times, or more.

17. The use of any one of claims 1-16, comprising that the antibody, antigen-binding fragment, or composition is to be administered to the subject a plurality of times, wherein a second or successive administration is performed at about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 24, about 48, about 74, about 96 hours, or more, following the first or preceding administration.

18. The use of any one of claims 1-35, wherein treating comprises preventing infection by SARS-CoV-2 and/or preventing COVID-19; or wherein treating comprises preventing progression of COVID-19 in the subject; or wherein treating comprises preventing contraction and/or transmission of symptomatic COVID-19; or wherein treating comprises preventing contraction and/or transmission of asymptomatic COVID-19.

19. The use of any one of claims 1-18, wherein treating comprises preventing or reducing:

- (1) one or more acute respiratory symptom selected from: cough; sputum production; sore throat; and shortness of breath; or
- (2) fever of greater than 38°C;
- (3) two or more of the following symptoms: fatigue; myalgias/arthralgias; chills; nausea/vomiting; diarrhea; and anosmia/dysgeusia; or one or more of the following symptoms: fever of greater than 38°C; chills; cough; sore throat; malaise; headache; myalgia; a change in smell or taste; nasal congestion/rhinorrhea; vomiting; diarrhea; shortness of breath on exertion.

20. The use of any one of claims 1-19, wherein the antibody or antigen-binding fragment was obtained from a non-clonal pool of cells stably transfected with a polynucleotide encoding the antibody or antigen-binding fragment, or the antibody or antigen-binding fragment was obtained from a clonal master cell bank.

21. The use of any one of claims 1-20, wherein the subject has received a vaccine for SARS-CoV-2 and the vaccine is determined to be ineffective, e.g., by post-vaccine infection or symptoms in the subject, by clinical diagnosis or scientific or regulatory criteria, or the subject has not received a vaccine for SARS-CoV-2.

22. The use of any one of claims 1-21, wherein the subject has received convalescent plasma therapy, remdesivir, or both, for SARS-CoV-2, or wherein the subject is further receiving or has received remdesivir, supplemental oxygen, ventilation therapy, respiration therapy, dexamethasone, tocilizumab, or any combination thereof.

23. The use of any one of claims 1-22, wherein treatment is to be administered to the subject having mild-to-moderate disease, optionally in an outpatient setting, or treatment is to be administered to a subject with moderate-to-severe disease, optionally, wherein the subject is to be hospitalized with COVID-19.