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(54) Title: ANTIBODIES FOR PROPHYLAXIS OR TREATMENT OF SARS- COV-2 INFECTIONS

(57) Abstract: The present disclosure relates to antibodies and antigen-binding fragments thereof binding to SARS-CoV-2 which may neutralize a SARS-CoV-2 infection. Also provided are polynucleotides that encode the antibodies and antigen-binding fragments thereof, vectors, host cells, and related compositions, as well as methods of using the antibodies, nucleic acids, vectors, host cells, and related compositions to prevent or treat a SARS-CoV-2 infection in a subject.

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ANTIBODIES FOR PROPHYLAXIS OR TREATMENT OF SARS- COV-2 INFECTIONS

Technical field

The present disclosure relates to antibodies and antigen-binding fragments thereof
5 binding to SARS-CoV-2 which may neutralize a SARS-CoV-2 infection in an *in vitro*
model of infection and/or in an animal model of infection and/or in a human subject.
Also provided are polynucleotides that encode the antibodies and antigen-binding
fragments thereof, vectors, host cells, and related compositions, as well as methods of
10 using the antibodies, nucleic acids, vectors, host cells, and related compositions to
prevent or treat a SARS-CoV-2 infection in a subject.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) outbreak in late
2019 quickly spread globally and has caused unseen societal disruptions and many
15 millions have died from COVID-19. The SARS-CoV-2 viral particle is decorated with a
trimeric spike protein (S), which comprises an S1 subunit that binds host cells and an
S2 subunit that mediates membrane fusion. The S1 subunit comprises two important
antigenic domains; The N-terminal domain (NTD) and the receptor binding domain
(RBD). The RBD is the region that binds the host angiotensin-converting enzyme 2
20 (ACE2) receptor and hence critically important for viral cell entry (Rogers et al Science
2020). The prime determinants for antibodies ability to neutralize SARS-CoV-2
infection have been extensively studied and 7 distinct motifs have been mapped on
RBD with varying degree of overlap with the ACE2 footprint (Hastie et al Science
2021). NTD-directed antibodies are conformationally sensitive and affected by
25 mutations outside of the discrete footprint. This finding is consistent with that for
antibodies elicited by vaccines and antibodies targeting the NTD-domain are highly
sensitive to deletions and insertions that have been described in many circulating
strains.

The development of monoclonal antibody therapies has moved at an incredible pace
30 and many highly potent antibodies were rapidly cloned from convalescent individuals
and went through pre-clinical and clinical studies in a matter of months (Cao et al 2020
Cell, Baum et al 2020 Science, Lundgren et al 2020 NEJM). Passive infusion of
monoclonal antibodies has proven highly effective in limiting COVID-19 disease when
35 given early after infection (Chen et al 2020 NEJM) and furthermore monoclonal

antibodies have also clearly been shown to provide prophylactic protection (O'Brien et al 2021 NEJM).

5 However, over the past 2 years intense viral genomic surveillance has discovered multiple emergences of Variants of Concern (VoC). Most prominent are SARS-CoV-2 variants such as B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta) and most recently B.1.1.529 (Omicron) that all contain mutations, many in Spike, that mediate resistance to therapeutic monoclonal antibodies. Importantly, some of these VoC have increased transmissibility, and limit effectiveness of vaccine-induced immunity (Viana et al 2022 Nature, Carreno et al 2021 Nature). Of particular concern is the rapidly spreading VoC Omicron that has been shown to escape monoclonal antibody therapy; among the currently approved antibodies only Sotrovimab retain anti-viral efficacy (Cao et al 2021 Nature). Therefore, antibodies binding epitopes of higher vulnerability for viral replication (i.e. fitness cost of mutations) are of prime importance. Interestingly, the parent antibody of Sotrovimab was isolated from a survivor of SARS-CoV-1 infection and thus commonalities in antigenic sites across sarbecoviruses may be preferable targets for monoclonal therapies with broad efficacy against VoC.

Summary

20 There is a need for therapeutic antibodies and antigen-binding fragments thereof capable of binding to SARS-CoV-2, for instance by binding to the SARS-CoV-2-Spike protein. These antibodies may be neutralizing antibodies and can be used for treating and/or preventing viral infection with SARS-CoV-2 and COVID-19 diseases. The present disclosure addresses this need, by providing anti-SARS-CoV-2 spike protein antibodies and antigen-binding fragments thereof. The present disclosure provides neutralizing antibodies and antigen-binding fragments thereof that specifically bind to SARS-CoV-2 spike protein.

30 Some embodiments of the disclosure relate to an isolated antibody or antigen-binding fragment thereof capable of binding a SARS-CoV-2 spike protein, wherein said isolated antibody or antigen-binding fragment thereof comprises:

- i) Three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence set forth in any of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41,

43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 129, 131, 133, 135 and 137, and

- ii) Three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence set forth in any of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 130, 132, 134, 136 and 138.

- 10 Furthermore, the disclosure relates to a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as described herein.

In some embodiments, the disclosure relates to a method of treating, alleviating or preventing corona virus infections by administering the isolated antibody or antigen-binding fragment thereof or the pharmaceutical composition as described herein.

Other embodiments of the disclosure relate to an isolated antibody or antigen-binding fragment thereof or the pharmaceutical composition as described herein for use in the treatment, alleviation or prevention of corona virus infections.

20

In a further embodiment, the disclosure relates to a kit of parts comprising the isolated antibody or antigen-binding fragment thereof as described herein and instructions for use.

- 25 Other embodiments of the disclosure relate to a polynucleotide encoding an isolated antibody or antigen-binding fragment thereof as described herein.

A further embodiment of the disclosure relates to a vector comprising the polynucleotide as described here above.

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Other embodiments of the disclosure relate to use of the vector described herein for gene delivery of said anti-SARS-CoV-2 antibody to a subject in need thereof. In a further embodiment the disclosure relates to use of the vector described herein for gene therapy.

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Other embodiments of the disclosure relate to a method of treating, alleviating or preventing coronavirus diseases, such as COVID-19 infections, by administering the vector described herein to a subject in need thereof.

- 5 Further, an embodiment of the disclosure relates to the vector described herein for use in the treatment, alleviation or prevention of coronavirus disease, such as COVID-19 infections.

- 10 Other embodiments of the disclosure relate to a pharmaceutical composition comprising the vector described herein.

In a further embodiment the disclosure relates to a kit of parts comprising the vector described herein and instructions for use.

15 Description of Drawings

Figure 1: Example of mesoscale binding data from antibodies of the disclosure.

- The quantity of each monoclonal antibody (mAb) binding to a specific coronavirus protein is displayed in arbitrary units (AU)/mL. mAbs were analyzed at a concentration of 2 µg/ml. **A.** The tested antibodies display specific binding to SARS-CoV-2 spike protein. **B.** mAb 31259 displays specific binding to SARS-CoV-1 spike protein, indicative of specificity to a conserved epitope. **C.** mAb 31963 displays specific binding to SARS-CoV-2 nucleocapsid.
- 20

Figure 2: Example of mesoscale ACE2 competition data from antibodies of the disclosure.

25

- A.** The quantity of each mAb binding to SARS-CoV-2 spike RBD, is displayed in arbitrary units (AU)/mL. mAbs were analyzed at a concentration of 2 µg/ml. The tested antibodies display specific binding to SARS-CoV-2 spike RBD. **B.** Antibody ability to outcompete ACE2-Spike interaction displayed as ACE2 competition % of SARS-Cov-2 Spike and Omicron Spike with mAbs final total dilutions tested ranged from 20 µg/ml – 0.256ng/ml in 5 fold steps is shown. All tested mAbs show potent ACE2 competition of SARS-CoV-2, as well as clear ACE2 competition (29044 + 31259) or loss of ACE2 competition towards Omicron Spike (31283).
- 30

Figure 3: Full neutralization curves of antibodies of the disclosure towards viral variants of interest.

Full neutralization of the virus with mAbs final total dilutions tested ranged from 20 µg/ml – 0.256ng/ml in 5 fold steps is shown. **A.** mAb 31259 and mAb 31283. **B.** mAb 31307 and mAb 31330. **C.** mAb 31331 and mAb 29044). All tested antibodies show potent neutralization of SARS-CoV-2, as well as clear neutralization or loss of neutralization towards several viral variants. Additionally mAb 31259 shows neutralization of SARS-CoV-1, comparable to that of other viral SARS-CoV-2 variants.

Figure 4: Full neutralization curves of antibodies of the disclosure towards viral variants of interest.

Full neutralization of the virus with mAbs final total dilutions tested ranged from 20 µg/ml – 0.256 ng/ml in 5 fold steps is shown. All tested antibodies retain their neutralization capability seen in the pseudovirus assay, when tested against the full-length real virus. This confirms the effect seen in the pseudovirus assay.

Figure 5: mAb 31283 prophylactic treatment effect on disease course in mice.

8 mice were treated with 400 µg mAb 31283 I.P. 24 hours prior to SARS-CoV-2 exposure, while the control group was treated with 400 µg human anti-tetanus mAb. **A.** The weight of the animals was monitored daily, as well as visible signs of behavior indicating lung infections. **B.** A statistical significant probability of surviving was seen in the mAb 31283 treated mice compared to controls.

Figure 6: mAb 31259 and mAb 31283 prophylactic treatment effect on mice viral copies in lungs.

3 mice in each group were treated with 4 µg, 40 µg or 400 µg mAb 31259 or mAb 31283, and 5 mice were treated with a human IgG anti-tetanus antibody (control). A dose dependent reduction is observed for mAb 31283 treated mice, while the mAb 31259 dose given partly reduce RNA viral copies detected, likely due to lower potency (higher IC50 value).

Figure 7: mAb 31259 and mAb 31283 prophylactic treatment effect on mice infectious viral copies.

3 mice in each group were treated with 4 µg, 40 µg, 400 µg or 700 µg mAb 31283 or mAb 31259, and 5 mice were treated with a human IgG anti-tetanus antibody. A dose

dependent reduction is observed for both mAb 31259 and mAb 31283 treated mice. The mAb 31283 shows a significant reduction in viral copies at 40 µg and 400 µg. The mAb 31259 doses given partly reduce infectious copies, a higher dose of this less potent mAb may have the same effect as observed for mAb 31283.

5

Figure 8: Western Blot of SARS-CoV-2 mAbs H4 and A23-58.1.

Western Blot (WB) shows expression of H4 and A23-58.1 in cell culture supernatant after 1, 4 or 7 days. Mock is used as negative control to identify unspecific protein bands. No unspecific bands are detected in lanes 1, 4 and 7. mAb specific bands are detected in lanes 2, 3, 5, 6, 8, and 9 for H4 and A23-58.1 respectively. Bands are detected at 25 kDa, 50kDa and 75 kDa. Since this is a denatured blot, the 25kDa band represents mAb Light chain, the 50kDa band represents the heavy chain, and 75 kDa band represents antibodies that have not been denatured in the process. WB shows that mAb expression of accumulates over time with a relative minor higher expression of A23-58.1 compared to H4.

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Figure 9: mAb supernatant pseudovirus neutralization.

Plots show frequency of infection after pseudovirus variants, SARS-CoV-2S wt, Alpha, Beta, and Delta neutralization using 8 five-fold dilutions of day 7 supernatants expressing mAbs (A) H4 or (B) A23-58.1 from AAV plasmid transfection. mAb A23-58.1 shows greater neutralization effect than H4 because infection is completely neutralized at the first supernatant dilution for all 4 SARS-CoV-2 variants.

20

Figure 10: Mesoscale ACE2 competition data from mAbs concentration gradients against Omicron variants of concern (VoC).

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A-B. ACE2 competition % of SARS-Cov-2 Omicron VoC Spike with mAbs final total dilutions tested ranged from 20ug/ml – 0.256ng/ml in 5 fold steps is shown. mAb 29044 show potent ACE2 competition of SARS-CoV-2 Omicron variant of concern BA.2.75 and BA.5 and mAb 31259 show potent ACE2 competition of all SARS-CoV-2 Omicron variants of concern, whereas sotrovimab do not have the ability to compete with ACE2 against either of the four variants of concern.

30

Figure 11: Mesoscale binding data from mAbs.

A-B. The quantity of each mAb binding to a specific coronavirus protein is displayed in arbitrary units (AU)/mL. MAbs were analyzed in a five-fold dilution series from 20ug/ml

35

– 0.256ng/ml antibody. Binding to SARS-CoV-2 Omicron Spike from VoC XBB.1, BQ.1, BA.2.75, and BA.5 were assessed. Both mAb 29044 and mAb 31259 bind SARS-CoV2 Omicron Spike variants XBB.1, BQ.1, BA.2.75, BA,5 in a dose-dependent manner.

5 **Figure 12: Expression of mAb 29044, mAb 31259 and mAb A23-58.1 from AAV vector.**

Western Blot (WB) shows expression of mAb 29044, mAb 31259 and mAb A23-58.1 in cell culture supernatant after 3 or 6 days. eGFP is used as negative control to identify unspecific protein bands. No unspecific bands are detected in lanes 1 and 5. mAb
10 specific bands are detected in lanes 2, 3, 4 and 6, 7, 8 for mAb 29044, mAb 31259 and mAb A23-58.1, respectively. Bands are detected at 25 kDa, 50kDa and 75 kDa. Since this is a denatured blot, the 25kDa band represents mAb Light chain, the 50kDa band represents the heavy chain, and 75 kDa band represents antibodies that have not been denatured in the process. WB shows that mAb expression of accumulates over time.

15

Figure 13: AAV mice data

A. Schematic representation of experiment: 8-12 weeks old heterozygote B6.Cg-Tg(K18-ACE2)2Primn/J mice were subjected to intramuscular (i.m.) or intravenous (i.v.) administration of AAV8-A23. 4 weeks after AAV treatment, mice were exposed to
20 11.8 TCID₅₀ SARS-CoV-2 intranasally. Four days after SARS-CoV-2 exposure the mice were anesthetized, and lungs were harvested and homogenized. Infectious viral units were estimated by a TCID₅₀ assay using lung homogenate. B. Displays the estimate of viral units in lung tissue from intramuscular (i.m.) or intravenous (i.v.) administered mice.

25

Figure 14: Recombinant antibodies in mice

A. 21 mice were treated with either 2 mg mAb 31259 (n=6), 400 µg mAb 31283 (n=8) or 400 µg mAb 29044 (n=7) I.P. 24 hours prior to SARS-CoV-2 exposure, while the control group (n=14) was treated with 400 µg human anti-tetanus mAb. B. The weight
30 of the animals was monitored daily, as well as visible signs of behavior indicating lung infections. C. A statistical significant probability of surviving was seen in the mAb 31259, mAb 31283 or mAb 29044 treated mice compared to controls.

Detailed description

Some embodiments of the disclosure relates to an isolated antibody or antigen-binding fragment thereof capable of binding a SARS- CoV-2 spike protein, wherein said isolated antibody or antigen-binding fragment thereof comprises:

- 5 i) Three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence set forth in any of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 129, 131, 133, 135 and 137, and
- 10 ii) Three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence set forth in in any of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 130, 132, 134, 136 and 138.
- 15

In some embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 1 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 2.

20

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 3 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 4.

25

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 5 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 6.

30

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 7 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 8.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 9 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 10.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 11 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 12.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 13 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 14.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 15 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 16.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 17 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 18.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 19 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 20.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 21 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 22.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 23 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 24.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 25 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 26.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 27 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 28.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 29 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 30.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 31 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 32.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 33 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 34.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 35 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 36.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 37 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 38.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 39 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 40.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 41 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 42.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 43 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 44.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 45 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 46.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 47 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 48.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 49 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 50.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 51 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 52.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 53 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 54.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 55 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 56.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 57 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 58.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 59 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 60.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 61 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 62.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 63 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 64.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 65 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 66.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 67 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 68.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 69 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 70.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 71 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 72.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 73 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 74.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 75 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 76.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 77 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 78.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 79 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 80.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 81 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 82.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 83 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 84.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 85 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 86.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 129 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 130.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 131 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 132.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid

sequence set forth in SEQ ID NO: 133 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 134.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 135 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 136.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 137 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 138.

15 In some embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 87, HCDR2 set forth in SEQ ID NO: 88, HCDR3 set forth in SEQ ID NO: 89, LCDR1 set forth in SEQ ID NO: 90, LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set forth in SEQ ID NO: 92.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 93, HCDR2 set forth in SEQ ID NO: 94, HCDR3 set forth in SEQ ID NO: 95, LCDR1 set forth in SEQ ID NO: 96, LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set forth in SEQ ID NO: 98.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 99, HCDR2 set forth in SEQ ID NO: 100, HCDR3 set forth in SEQ ID NO: 101, LCDR1 set forth in SEQ ID NO: 102, LCDR2 set forth in SEQ ID NO: 103, and LCDR3 set forth in SEQ ID NO: 104.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 105, HCDR2 set forth in SEQ ID NO: 106, HCDR3 set forth in SEQ ID NO: 107, LCDR1 set forth in SEQ ID NO: 108, LCDR2 set forth in SEQ ID NO: 109, and LCDR3 set forth in SEQ ID NO: 110.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 111, HCDR2 set forth in SEQ ID NO: 112,

HCDR3 set forth in SEQ ID NO: 113, LCDR1 set forth in SEQ ID NO: 114, LCDR2 set forth in SEQ ID NO: 115, and LCDR3 set forth in SEQ ID NO: 116.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 117, HCDR2 set forth in SEQ ID NO: 118, HCDR3 set forth in SEQ ID NO: 119, LCDR1 set forth in SEQ ID NO: 120, LCDR2 set forth in SEQ ID NO: 121, and LCDR3 set forth in SEQ ID NO: 122.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 123, HCDR2 set forth in SEQ ID NO: 124, HCDR3 set forth in SEQ ID NO: 125, LCDR1 set forth in SEQ ID NO: 126, LCDR2 set forth in SEQ ID NO: 127, and LCDR3 set forth in SEQ ID NO: 128.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 157, HCDR2 set forth in SEQ ID NO: 158, HCDR3 set forth in SEQ ID NO: 159, LCDR1 set forth in SEQ ID NO: 160, LCDR2 set forth in SEQ ID NO: 161, and LCDR3 set forth in SEQ ID NO: 162.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 163, HCDR2 set forth in SEQ ID NO: 164, HCDR3 set forth in SEQ ID NO: 165, LCDR1 set forth in SEQ ID NO: 166, LCDR2 set forth in SEQ ID NO: 167, and LCDR3 set forth in SEQ ID NO: 168.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 169, HCDR2 set forth in SEQ ID NO: 170, HCDR3 set forth in SEQ ID NO: 171, LCDR1 set forth in SEQ ID NO: 172, LCDR2 set forth in SEQ ID NO: 173, and LCDR3 set forth in SEQ ID NO: 174.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 175, HCDR2 set forth in SEQ ID NO: 176, HCDR3 set forth in SEQ ID NO: 177, LCDR1 set forth in SEQ ID NO: 178, LCDR2 set forth in SEQ ID NO: 179, and LCDR3 set forth in SEQ ID NO: 180.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 181, HCDR2 set forth in SEQ ID NO: 182,

HCDR3 set forth in SEQ ID NO: 183, LCDR1 set forth in SEQ ID NO: 184, LCDR2 set forth in SEQ ID NO: 185, and LCDR3 set forth in SEQ ID NO: 186.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 187, HCDR2 set forth in SEQ ID NO: 188, HCDR3 set forth in SEQ ID NO: 189, LCDR1 set forth in SEQ ID NO: 190, LCDR2 set forth in SEQ ID NO: 191, and LCDR3 set forth in SEQ ID NO: 192.

10 In some embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 1 and the LCVR amino acid sequence set forth in SEQ ID NO: 2.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 3 and a LCVR amino acid sequence set forth in SEQ ID NO: 4.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 5 and the LCVR amino acid sequence set forth in SEQ ID NO: 6.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 7 and a LCVR amino acid sequence set forth in SEQ ID NO: 8.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 9 and a LCVR amino acid sequence set forth in SEQ ID NO: 10.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 11 and the LCVR amino acid sequence set forth in SEQ ID NO: 12.

35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 13 and a LCVR amino acid sequence set forth in SEQ ID NO: 14.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 15 and the LCVR amino acid sequence set forth in SEQ ID NO: 16.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 17 and a LCVR amino acid sequence set forth in SEQ ID NO: 18.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 19 and a LCVR amino acid sequence set forth in SEQ ID NO: 20.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 21 and the LCVR amino acid sequence set forth in SEQ ID NO: 22.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 23 and a LCVR amino acid sequence set forth in SEQ ID NO: 24.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 25 and the LCVR amino acid sequence set forth in SEQ ID NO: 26.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 27 and a LCVR amino acid sequence set forth in SEQ ID NO: 28.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 29 and a LCVR amino acid sequence set forth in SEQ ID NO: 30.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 31 and the LCVR amino acid sequence set forth in SEQ ID NO: 32.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 33 and a LCVR amino acid sequence set forth in SEQ ID NO: 34.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 35 and the LCVR amino acid sequence set forth in SEQ ID NO: 36.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 37 and a LCVR amino acid sequence set forth in SEQ ID NO: 38.

15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 39 and a LCVR amino acid sequence set forth in SEQ ID NO: 40.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 41 and the LCVR amino acid sequence set forth in SEQ ID NO: 42.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 43 and a LCVR amino acid sequence set forth in SEQ ID NO: 44.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 45 and the LCVR amino acid sequence set forth in SEQ ID NO: 46.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 47 and a LCVR amino acid sequence set forth in SEQ ID NO: 48.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 49 and a LCVR amino acid sequence set forth in SEQ ID NO: 50.

- 5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 51 and the LCVR amino acid sequence set forth in SEQ ID NO: 52.

- 10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 53 and a LCVR amino acid sequence set forth in SEQ ID NO: 54.

- 15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 55 and the LCVR amino acid sequence set forth in SEQ ID NO: 56.

- 20 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 57 and a LCVR amino acid sequence set forth in SEQ ID NO: 58.

- In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 59 and a LCVR amino acid sequence set forth in SEQ ID NO: 60.

- 25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 61 and the LCVR amino acid sequence set forth in SEQ ID NO: 62.

- 30 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 63 and a LCVR amino acid sequence set forth in SEQ ID NO: 64.

- 35 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 65 and the LCVR amino acid sequence set forth in SEQ ID NO: 66.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 67 and a LCVR amino acid sequence set forth in SEQ ID NO: 68.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 69 and a LCVR amino acid sequence set forth in SEQ ID NO: 70.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 71 and the LCVR amino acid sequence set forth in SEQ ID NO: 72.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 73 and a LCVR amino acid sequence set forth in SEQ ID NO: 74.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 75 and the LCVR amino acid sequence set forth in SEQ ID NO: 76.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 77 and a LCVR amino acid sequence set forth in SEQ ID NO: 78.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 79 and a LCVR amino acid sequence set forth in SEQ ID NO: 80.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 81 and the LCVR amino acid sequence set forth in SEQ ID NO: 82.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 83 and a LCVR amino acid sequence set forth in SEQ ID NO: 84.

- 5 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 85 and the LCVR amino acid sequence set forth in SEQ ID NO: 86.

- 10 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 129 and the LCVR amino acid sequence forth in SEQ ID NO: 130.

- 15 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 131 and the LCVR amino acid sequence forth in SEQ ID NO: 132.

- In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 133 and the LCVR amino acid sequence forth in SEQ ID NO: 134.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 135 and the LCVR amino acid sequence forth in SEQ ID NO: 136.

- 25 In other embodiments the isolated antibody or antigen-binding fragment thereof comprises the HCVR amino acid sequence set forth in SEQ ID NO: 137 and the LCVR amino acid sequence forth in SEQ ID NO: 138.

- 30 In some embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 87, HCDR2 set forth in SEQ ID NO: 88, HCDR3 set forth in SEQ ID NO: 89, LCDR1 set forth in SEQ ID NO: 90, LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set forth in SEQ ID NO: 92, the HCVR amino acid sequence set forth in SEQ ID NO: 29 and the LCVR amino acid sequence set forth in SEQ ID NO: 30.

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In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 93, HCDR2 set forth in SEQ ID NO: 94, HCDR3 set forth in SEQ ID NO: 95, LCDR1 set forth in SEQ ID NO: 96, LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set forth in SEQ ID NO: 98, the HCVR amino acid sequence set forth in SEQ ID NO: 37 and the LCVR amino acid sequence set forth in SEQ ID NO: 38.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 99, HCDR2 set forth in SEQ ID NO: 100, HCDR3 set forth in SEQ ID NO: 101, LCDR1 set forth in SEQ ID NO: 102, LCDR2 set forth in SEQ ID NO: 103, and LCDR3 set forth in SEQ ID NO: 104, the HCVR amino acid sequence set forth in SEQ ID NO: 43 and the LCVR amino acid sequence set forth in SEQ ID NO: 44.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 105, HCDR2 set forth in SEQ ID NO: 106, HCDR3 set forth in SEQ ID NO: 107, LCDR1 set forth in SEQ ID NO: 108, LCDR2 set forth in SEQ ID NO: 109, and LCDR3 set forth in SEQ ID NO: 110, the HCVR amino acid sequence set forth in SEQ ID NO: 53 and the LCVR amino acid sequence set forth in SEQ ID NO: 54.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 111, HCDR2 set forth in SEQ ID NO: 112, HCDR3 set forth in SEQ ID NO: 113, LCDR1 set forth in SEQ ID NO: 114, LCDR2 set forth in SEQ ID NO: 115, and LCDR3 set forth in SEQ ID NO: 116, the HCVR amino acid sequence set forth in SEQ ID NO: 55 and the LCVR amino acid sequence set forth in SEQ ID NO: 56.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 117, HCDR2 set forth in SEQ ID NO: 118, HCDR3 set forth in SEQ ID NO: 119, LCDR1 set forth in SEQ ID NO: 120, LCDR2 set forth in SEQ ID NO: 121, and LCDR3 set forth in SEQ ID NO: 122, the HCVR amino acid sequence set forth in SEQ ID NO: 65 and the LCVR amino acid sequence set forth in SEQ ID NO: 66.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 123, HCDR2 set forth in SEQ ID NO: 124, HCDR3 set forth in SEQ ID NO: 125, LCDR1 set forth in SEQ ID NO: 126, LCDR2 set forth in SEQ ID NO: 127, and LCDR3 set forth in SEQ ID NO: 128, the HCVR amino acid sequence set forth in SEQ ID NO: 67 and the LCVR amino acid sequence set forth in SEQ ID NO: 68.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 157, HCDR2 set forth in SEQ ID NO: 158, HCDR3 set forth in SEQ ID NO: 159, LCDR1 set forth in SEQ ID NO: 160, LCDR2 set forth in SEQ ID NO: 161, and LCDR3 set forth in SEQ ID NO: 162, the HCVR amino acid sequence set forth in SEQ ID NO: 129 and the LCVR amino acid sequence set forth in SEQ ID NO: 130.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 163, HCDR2 set forth in SEQ ID NO: 164, HCDR3 set forth in SEQ ID NO: 165, LCDR1 set forth in SEQ ID NO: 166, LCDR2 set forth in SEQ ID NO: 167, and LCDR3 set forth in SEQ ID NO: 168, the HCVR amino acid sequence set forth in SEQ ID NO: 131 and the LCVR amino acid sequence set forth in SEQ ID NO: 132.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 169, HCDR2 set forth in SEQ ID NO: 170, HCDR3 set forth in SEQ ID NO: 171, LCDR1 set forth in SEQ ID NO: 172, LCDR2 set forth in SEQ ID NO: 173, and LCDR3 set forth in SEQ ID NO: 174, the HCVR amino acid sequence set forth in SEQ ID NO: 133 and the LCVR amino acid sequence set forth in SEQ ID NO: 134.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 175, HCDR2 set forth in SEQ ID NO: 176, HCDR3 set forth in SEQ ID NO: 177, LCDR1 set forth in SEQ ID NO: 178, LCDR2 set forth in SEQ ID NO: 179, and LCDR3 set forth in SEQ ID NO: 180, the HCVR amino acid sequence set forth in SEQ ID NO: 135 and the LCVR amino acid sequence set forth in SEQ ID NO: 136.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 181, HCDR2 set forth in SEQ ID NO: 182, HCDR3 set forth in SEQ ID NO: 183, LCDR1 set forth in SEQ ID NO: 184, LCDR2 set forth in SEQ ID NO: 185, and LCDR3 set forth in SEQ ID NO: 186, the HCVR amino acid sequence set forth in SEQ ID NO: 33 and the LCVR amino acid sequence set forth in SEQ ID NO: 34.

In other embodiments the isolated antibody or antigen-binding fragment thereof comprises a HCDR1 set forth in SEQ ID NO: 187, HCDR2 set forth in SEQ ID NO: 188, HCDR3 set forth in SEQ ID NO: 189, LCDR1 set forth in SEQ ID NO: 190, LCDR2 set forth in SEQ ID NO: 191, and LCDR3 set forth in SEQ ID NO: 192, the HCVR amino acid sequence set forth in SEQ ID NO: 137 and the LCVR amino acid sequence set forth in SEQ ID NO: 138.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises a heavy chain constant sequence as set forth in SEQ ID NO: 140 and/or a light chain constant sequences as set forth in SEQ ID NO: 144.

In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises one or more amino acid substitutions, amino acid deletions or amino acid insertions. One amino acid substitution means that the amino acid differs between the original sequence and the variant sequence at one position.

In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises one amino acid substitution, amino acid deletion or amino acid insertion.

In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino

acid sequence comprises two amino acid substitutions, amino acid deletions or amino acid insertions.

5 In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises three amino acid substitutions, amino acid deletions or amino acid insertions.

10 In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises four amino acid substitutions, amino acid deletions or amino acid insertions.

15 In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises five amino acid substitutions, amino acid deletions or amino acid insertions.

20 In some embodiments of the present disclosure the isolated antibody or antigen-binding fragment thereof comprises a HCVR amino acid sequence and/or a LCVR amino acid sequence, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises one or more amino acid substitutions, amino acid deletions or amino acid insertions, wherein the one or more amino acid substitutions, amino acid deletions or amino acid insertions is not comprised in the CDR sequences.

25 In some embodiments the isolated antibody or antigen-binding fragment thereof is an antibody.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof is an antigen-binding fragment thereof.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof comprises an immunoglobulin constant region. The immunoglobulin constant region can be selected from IgG, IgM, IgA, IgD and IgE, such as IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2.

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In other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2. For example the antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 10 µg/mL, alternatively between 0.001 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 5 µg/mL, alternatively between 0.01 µg/mL and 4 µg/mL, alternatively between 0.01 µg/mL and 3 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 1 µg/mL. In other embodiments the antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 1 µg/mL, alternatively 0.001 µg/mL and 1 µg/mL, alternatively 0.01 µg/mL and 1 µg/mL, alternatively between 0.02 µg/mL and 1 µg/mL, alternatively between 0.03 µg/mL and 1 µg/mL, alternatively between 0.04 µg/mL and 1 µg/mL, alternatively between 0.05 µg/mL and 1 µg/mL, alternatively between 0.06 µg/mL and 1 µg/mL, alternatively between 0.07 µg/mL and 1 µg/mL, alternatively between 0.09 µg/mL and 1 µg/mL, alternatively between 0.1 µg/mL and 1 µg/mL.

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In other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ below 1 µg/mL, alternatively below 0.9 µg/mL, alternatively below 0.8 µg/mL, alternatively below 0.7 µg/mL, alternatively below 0.6 µg/mL, alternatively below 0.5 µg/mL, alternatively below 0.4 µg/mL, alternatively below 0.3 µg/mL, alternatively below 0.2 µg/mL, alternatively below 0.1 µg/mL, alternatively below 0.01 µg/mL, alternatively below 0.001 µg/mL, alternatively below 0.0001 µg/mL.

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In other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ below 0.1 µg/mL.

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In yet other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 0.1 µg/mL, alternatively 0.001 µg/mL and 0.1 µg/mL, alternatively 0.01 µg/mL and 0.1 µg/mL, alternatively between 0.02 µg/mL and 0.1 µg/mL, alternatively between 0.03 µg/mL and

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0.1 µg/mL, alternatively between 0.04 µg/mL and 0.1 µg/mL, alternatively between 0.05 µg/mL and 0.1 µg/mL, alternatively between 0.06 µg/mL and 0.1 µg/mL, alternatively between 0.07 µg/mL and 0.1 µg/mL, alternatively between 0.09 µg/mL and 0.1 µg/mL.

5 In other embodiments the isolated antibody or antigen-binding fragment thereof blocks interaction between Angiotensin-converting enzyme 2 (ACE2) and SARS- CoV-2 Spike protein.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof blocks interaction between ACE2 and SARS- CoV-2 Spike protein receptor binding domain (RBD).

15 In yet other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant. In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least two SARS-CoV-2 variants, such as at least three SARS-CoV-2 variants, such as at least four SARS-CoV-2 variants, such as at least five SARS-CoV-2 variants. The SARS-CoV-2 variant is selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.

20 In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from an Alpha strain. In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Beta strain. In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Gamma strain. In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Delta strain. In other embodiments the isolated antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from an Omicron strain.

30 In other embodiments the isolated antibody or antigen-binding fragment thereof binds to a plurality of SARS-CoV-2 variants such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Gamma strain, such as at least one SARS-CoV-2 variant from an Alpha

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strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain, such as at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain, such as at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain and at least one SARS-CoV-2 variant from an Omicron strain, such as at least one SARS-CoV-2 variant from a Delta strain and at least one SARS-CoV-2 variant from an Omicron strain.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof further binds to SARS-CoV-1. For example the isolated antibody or antigen-binding fragment thereof further neutralizes SARS-CoV-1.

In other embodiments the isolated antibody or antigen-binding fragment thereof has dual SARS-CoV-1 and SARS-CoV-2 neutralization. For example the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between
5 0.01 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 5 µg/mL, alternatively between 0.01 µg/mL and 4 µg/mL, alternatively between 0.01 µg/mL and 3 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 1 µg/mL.

10 In other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between 0.0001 µg/mL and 1 µg/mL, alternatively 0.001 µg/mL and 1 µg/mL, alternatively 0.01 µg/mL and 1 µg/mL, alternatively between 0.02 µg/mL and 1 µg/mL, alternatively between 0.03 µg/mL and 1 µg/mL, alternatively between 0.04 µg/mL and 1 µg/mL, alternatively between 0.05
15 µg/mL and 1 µg/mL, alternatively between 0.06 µg/mL and 1 µg/mL, alternatively between 0.07 µg/mL and 1 µg/mL, alternatively between 0.09 µg/mL and 1 µg/mL, alternatively between 0.1 µg/mL and 1 µg/mL.

In yet other embodiments the isolated antibody or antigen-binding fragment thereof
20 neutralizes SARS-CoV-1 with an IC₅₀ below 1 µg/mL, alternatively below 0.9 µg/mL, alternatively below 0.8 µg/mL, alternatively below 0.7 µg/mL, alternatively below 0.6 µg/mL, alternatively below 0.5 µg/mL, alternatively below 0.4 µg/mL, alternatively below 0.3 µg/mL, alternatively below 0.2 µg/mL, alternatively below 0.1 µg/mL.

25 In other embodiments the isolated antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between 0.0001 µg/mL and 0.1 µg/mL, alternatively 0.001 µg/mL and 0.1 µg/mL, alternatively 0.01 µg/mL and 0.1 µg/mL, alternatively between 0.02 µg/mL and 0.1 µg/mL, alternatively between 0.03 µg/mL and 0.1 µg/mL, alternatively between 0.04 µg/mL and 0.1 µg/mL, alternatively between 0.05
30 µg/mL and 0.1 µg/mL, alternatively between 0.06 µg/mL and 0.1 µg/mL, alternatively between 0.07 µg/mL and 0.1 µg/mL, alternatively between 0.09 µg/mL and 0.1 µg/mL.

Furthermore, the disclosure relates to a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof as described herein. In some

embodiments the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent.

5 In some embodiments, the disclosure relates to a method of treating, alleviating or preventing a corona virus infection by administering the isolated antibody or antigen-binding fragment thereof or the pharmaceutical composition as described herein to a subject.

10 Other embodiments of the disclosure relate to an isolated antibody or antigen-binding fragment thereof or the pharmaceutical composition as described herein for use in the treatment, alleviation or prevention of a corona virus infection.

15 In some embodiments, the disclosure relates to a method of diagnosing a corona virus infection by detecting and/or measuring the presence of SARS-CoV-2 and/or SARS-CoV-1 in a sample using the isolated antibody or antigen-binding fragment thereof as described herein.

20 In some embodiments, the sample is obtained from a subject, such as a human, having a corona virus infection.

Other embodiments of the disclosure relate to an isolated antibody or antigen-binding fragment thereof as described herein for use in a method of diagnosis of a corona virus infection.

25 In some embodiments, the corona virus infection is caused by SARS-CoV-2 and/or SARS-CoV-1.

30 Other embodiments of the disclosure relate to a diagnostic kit comprising the isolated antibody or antigen-binding fragment thereof as described herein.

In some embodiments, the isolated antibody or antigen-binding fragment thereof is labeled with a detectable label or reporter molecule. In some embodiments, the diagnostic kit further comprises a secondary antibody which which is labeled with a
35 detectable label or reporter molecule. In some embodiments, the detectable label or reporter molecule can be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I ; a fluorescent

moiety or chemiluminescent moiety, such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β -galactosidase, horseradish peroxidase, or luciferase.

5 In further embodiments, the present disclosure relates to a method for detecting the presence of spike protein in a sample comprising contacting the sample with an isolated antibody or antigen-binding fragment thereof of the disclosure and detecting the presence of a complex between SARS-CoV-2 and/or SARS-CoV-1 and the antibody or antigen-binding fragment thereof, wherein the presence of the complex
10 indicates the presence of SARS-CoV-2 and/or SARS-CoV-1.

In other embodiments the isolated antibody or antigen-binding fragment thereof may be used to detect and/or measure SARS-CoV-2 and/or SARS-CoV-1 in a sample. Exemplary assays for SARS-CoV-2 and/or SARS-CoV-1 may include, e.g., contacting
15 a sample with the isolated antibody or antigen-binding fragment thereof of the disclosure, wherein the isolated antibody or antigen-binding fragment thereof is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate SARS-CoV-2 and/or SARS-CoV-1 from samples. The presence of an antibody or antigen-binding fragment thereof complexed with SARS-CoV-2 and/or SARS-CoV-1
20 indicates the presence of SARS-CoV-2 and/or SARS-CoV-1 in the sample.

Alternatively, an unlabeled antibody or antigen-binding fragment thereof of the disclosure 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 ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I ; a fluorescent or chemiluminescent moiety such as
25 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 SARS-CoV-2 and/or SARS-CoV-1 in a sample include neutralization assays, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

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In further embodiments, the disclosure relates to a kit of parts comprising the isolated antibody or antigen-binding fragment thereof as described herein and instructions for use.

Other embodiments of the disclosure relate to a polynucleotide encoding an isolated antibody or antigen-binding fragment thereof as described herein. In some embodiments the polynucleotide encodes the following elements:

- 5 i) A leader signal,
 - ii) A heavy chain variable region (HCVR) sequence,
 - iii) A constant heavy chain sequence,
 - iv) A furin cleavage site,
 - v) A 2A peptide sequence,
 - vi) A leader signal,
 - 10 vii) A light chain variable region (LCVR) sequence, and
 - viii) A constant light chain sequence,
- optionally wherein said elements are arranged in the order from i) to viii).

A further embodiment of the disclosure relates to a vector comprising the
15 polynucleotide as described here above. In some embodiments the vector is an adeno-
associated virus (AAV) vector. In other embodiments the vector is a recombinant
vector. In yet other embodiments the vector comprises inverted terminal repeats
(ITRs). In other embodiments the vector comprises a promoter selected from the group
consisting of a CAG promoter, an UBC promoter and a MH promoter. In other
20 embodiments the vector comprises an EF-1 α promoter. In other embodiments the
vector comprises:

- i) A left ITR,
- ii) An EF-1 α promoter,
- iii) A polynucleotide according to the disclosure, and
- 25 iv) A right ITR.

In other embodiments the vector comprises an origin of replication (ori) and/or a
multicloning site, and/or a selectable marker. In yet other embodiments the vector
comprises:

- 30 i) A left ITR,
- ii) An EF-1 α promoter,
- iii) A T7 promoter,
- iv) The polynucleotide according to the disclosure,
- v) A poly(A) signal,
- 35 vi) A right ITR,

- vii) A F1 ori,
- viii) An AmpR promoter,
- ix) An AmpR, and
- x) An ori,

5 optionally wherein said elements are arranged in the order from i) to viii).

Other embodiments of the disclosure relate to use of the vector described herein for gene delivery of said anti-SARS-CoV-2 antibody to a subject in need thereof. In a further embodiment the disclosure relates to use of the vector described herein for
10 gene therapy.

Other embodiments of the disclosure relate to a method of treating, alleviating or preventing coronavirus diseases, such as COVID-19 infections, by administering the vector described herein to a subject in need thereof.

15 Further, an embodiment of the disclosure relates to the vector described herein for use in the treatment, alleviation or prevention of coronavirus disease, such as COVID-19 infections.

20 In some embodiments, the vector is delivered or administered to a subject having a coronavirus disease, such as a COVID-19 infection.

In some embodiments, the subject is an immunocompromised subject. In some embodiments, the subject is a moderately or severely immunocompromised subject.

25 In some embodiments, the subject is an immunocompromised subject, such as a moderately or severely immunocompromised subject, selected from the group consisting of:

- i) Subjects receiving active cancer treatment for tumors or cancers of the blood,
- 30 ii) Subjects having received an organ transplant and taking medicine to suppress the immune system,
- iii) Subjects having received a stem cell transplant within the last 2 years and/or subjects having received a stem cell transplant and taking medicine to suppress the immune system,

- iv) Subjects having a severe autoimmune disease, such as lupus, rheumatoid arthritis, Crohn's disease and ulcerative colitis, and/or subjects receiving B cell depletion therapy,
- 5 v) Subjects with moderate or severe primary immunodeficiency, such as DiGeorge syndrome or Wiskott-Aldrich syndrome, and
- vi) Subjects receiving active treatment with high-dose corticosteroids or other immunosuppressive drugs.

10 In some embodiments, the subject is receiving active cancer treatment for tumors or cancers of the blood. In some embodiments, the subject has received an organ transplant and are taking medicine to suppress the immune system. In some embodiments, the subject has received a stem cell transplant within the last 2 years and/or the subject has received a stem cell transplant and is taking medicine to suppress the immune system. In some embodiments, the subject has a severe

15 autoimmune disease, such as lupus, rheumatoid arthritis, Crohn's disease and ulcerative colitis, and/or receives B cell depletion therapy. In some embodiments, the subject has a moderate or severe primary immunodeficiency, such as DiGeorge syndrome or Wiskott-Aldrich syndrome. In some embodiments, the subject is receiving active treatment with high-dose corticosteroids or other immunosuppressive drugs.

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In some embodiment, the subjects receiving B cell depletion therapy is selected from the group consisting of:

- i) Patients receiving B cell antigen-targeting monoclonal antibodies to treat an underlying condition, such as for instance Rituximab targeting CD20, and/or
- 25 ii) Patients receiving immunosuppressive treatment in relation to solid organ transplantation, and/or
- iii) Patients with primary antibody deficiencies such as agammaglobulemia and Common Variable Immunodeficiency (CVID).

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In some embodiments, the underlying condition is selected from malignancies, such as follicular lymphoma, diffuse large B cell lymphoma or chronic lymphocytic leukemia, and/or autoimmune diseases, such as rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris

Other embodiments of the disclosure relate to a pharmaceutical composition comprising the vector described herein.

5 In a further embodiment the disclosure relates to a kit of parts comprising the vector described herein and instructions for use.

In some embodiments said one or more amino acid substitutions are conservative amino acid substitutions. In some embodiments said one or more amino acid substitutions are non-conservative amino acid substitutions.

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The genetic code specifies 20 standard amino acids naturally incorporated into polypeptides (proteinogenic): Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Tyr, Thr, Trp, Val, and 2 which are incorporated into proteins by unique synthetic mechanisms: Sec (selenocysteine, or U) and Pyl (pyrrolysine, O).

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These are all L-stereoisomers.

Aside from the 22 standard or natural amino acids, there are many other non-naturally occurring amino acids (non-proteinogenic or non-standard). They are either not found in proteins, or are not produced directly and in isolation by standard cellular machinery.

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Non-standard amino acids are usually formed through modifications to standard amino acids, such as post-translational modifications. Examples of unnatural amino acid residues are Abu, Aib, Nle (Norleucine), DOrn (D-ornithine, deguanylated arginine), Nal (beta-2-naphthyl-alanine), D-Nal (beta-2-naphthyl-D-alanine), DArg, DTrp, DPhe and DVal.

25

Any amino acids according to the present disclosure may be in the L- or D-configuration. If nothing is specified, reference to the L-isomeric form is preferably meant.

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Examples

The following abbreviations will be used throughout the examples:

BCR: B-cell receptor

COVID-19: Coronavirus disease 2019

PBMC: Peripheral blood mononuclear cells

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FB: Feature-barcode

GEX: Gene-expression BCR: B-cell receptor

VH: variable heavy chain

VL: variable light chain

PBMC: Peripheral blood mononuclear cells

5 SARS-CoV: Severe Acute Respiratory Syndrome CoronaVirus

SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus 2

VH: variable heavy chain

VL: variable light chain

mAb: Monoclonal antibody

10 I.P. Intraperitoneal

vg: vector genomes

Example 1: Antibody production

Background: Antibody production was achieved with 2 different methods.

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Method 1

PBMC from convalescent Covid 19 patients were pre-enriched for B-cells using EasySep human Pan-B-cell enrichment kit (Stemcell Technologies, Cambridge, UK). Antigen specific memory B-cells were sorted by FACS based on expression of CD19, IgG and IgA and binding to biotinylated SARS-CoV-2 spike protein S1 cat. # SPD-C82E9 or RBD cat. # S1N-C82E8 (Acrobiosystems, Newark, Delaware USA). Cells were sorted into bulk culture for differentiation into plasma cells by in vitro stimulation with human IL-21 and human CD40 ligand for seven days. Differentiated plasma cells were harvested and live cells FACS sorted as 1c/well into 384 well PCR plates (Thermo AB1384, Waltham, MA, USA). Cells were subjected to a two-step RT-PCR employed to sequentially amplify and link the VH and VL coding sequences from each ASC in single wells. The principle for linkage of cognate VH and VL sequences is described in detail in WO 2005/042774 and as described in Meijer P J, et al. Methods in Molecular Biology 525: 261-277, xiv. (2009). VH & VL from the linked PCR DNA band were subsequently separately cloned into VH and VL expression vectors using Asc/Xho & Nhe/Bsi restriction sites. Paired unique cognate VH and VL chains were co-expressed in CHO-S cells, and supernatants were harvested after 11 days and purified by protein A chromatography to yield full length human IgG1 antibodies.

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Method 2

PBMC from convalescent Covid 19 patients were pre-enriched for B-cells using EasySep human Pan-B-cell enrichment kit (Stemcell Technologies, Cambridge, UK). B-cells were sorted by FACS for 10X Genomics workflow by sorting of antigen specific memory B cells using a pool of 4 antigens. The biotinylated antigens were produced in-house and consisted of SARS-CoV-2 spike RBD and trimer (Wuhan strain), SARS-CoV-2 spike trimer with D614G mutation in S2 domain and SARS-CoV spike RBD. The antigens were bound to dextramers (dCODE Klickmer, Immudex, Virum, Denmark) barcoded with a DNA oligo and coupled to both PE fluorochrome and Streptavidin. Cells expressing CD19, IgG and IgA and binding to dextramer encoded antigens were sorted into bulk, and used for single cell sequencing with Chromium Next GEM Single Cell 5' Kit v2 (10X Genomics, CA, USA). The initial cDNA synthesis, which labels single cell transcripts with unique cell- and transcript barcodes, was followed by three parallel library preparations aimed at obtaining gene-expression profiles (GEX), V(D)J sequences (VDJ) and feature barcode (FB) read-outs for the four antigens on a single-cell level. The raw sequence data were processed using cellranger 6.0 multi and custom python- and R-scripts. The amino acid sequences coding the variable region of BCRs expressed by individual B cells were obtained for the cognate pairing of heavy (VH) and light chain (VL) from the VDJ data. Amino acid sequences for VH and VL were then reverse translated and codon optimized with regards to expression in CHO cells. The resulting DNA sequences were synthesized and, for VH, cloned into IgG1 wild-type pcDNA vectors at TWIST Bioscience (CA, USA), whereas VL DNA sequences were cloned into kappa- or lambda vectors depending on the light chain locus expressed by the B cell. Full-length IgG1 antibodies were expressed by transfection of the cognate heavy and light chain plasmids into ExpiCho-S cells as described in Meijer P J, et al. Methods in Molecular Biology 525: 261-277, xiv. (2009). Supernatants containing full length IgG1 antibodies were harvested after 11 days and used to screen for antigen binding.

Results:

Antibodies were produced in 4 different rounds.

Batch 1: Method 1 = 20 antibodies

Batch 2: Failed

Batch 3: Method 2 = 382 antibodies

Batch 4: Method 2 = 73 antibodies

Conclusion: 475 monoclonal antibodies have been produced for analysis of SARS-CoV-2 neutralization ability.

5 **Example 2: Mesoscale Serology**

Background: All expressed mAbs were screened for binding to various coronavirus proteins to eliminate unspecific mAbs. This was measured using the MSD Coronavirus Plate 1 (Meso Scale Discovery, Rockville, Maryland), following the manufacturers guidelines. Unspecific antibody binding was blocked using MSD Blocker A. All mAbs
10 were diluted to 2 µg/ml in Diluent100, before application to the plates. After sample incubation, bound IgG was detected by incubation with MSD SULFO-TAG Anti-Human IgG Antibody and subsequently measured on a MESO QuickPlex SQ 120 Reader after addition of GOLD Read Buffer B. Using the calibrator supplied with the mesoscale kits, the signals measured were converted to arbitrary units/mL (AU/mL) to allow inter-assay
15 comparison, with high AU/mL indicating potent binding of the mAb and low AU/mL indicating poor binding of the mAb.

Results: Data from selected antibodies of disclosure are displayed in Figure 1 and summarized in Table 1 below. In Figure 1A, tested antibodies clearly show binding of
20 SARS-CoV-2 spike, compared to negative controls. Additionally, several mAbs including mAb 31259 bind SARS-CoV-1 spike, and mAb 31963 binds SARS-CoV-2 Nucleocapsid, as shown in Figure 1B and 1C.

Basic mAb info	Mesoscale analysis AU/mL at 2 µg				
Ab ID	CoV-2 Spike	CoV-1 Spike	CoV-2 RBD	CoV-2 NTD	CoV-2 N
31259	89.856	159.492	170.239	0.008	0.166
31283	88.153	0.282	121.552	0.007	0.156
31307	87.546	0.308	122.473	0.007	0.323
31330	104.992	0.384	166.358	0.016	0.454
31331	103.113	0.472	163.167	0.017	0.385
Positive ctrl	99.103	0.211	96.548	0.005	0.170
Negative Ctrl	0.403	0.086	0.627	0.000	0.004

Ab ID	MERS	HKU1 Spike	OC43	H3 HongKong	BSA
31259	0.156	0.211	0.153	0.127	8.965
31283	0.161	0.134	0.085	0.155	1.681

31307	0.155	0.152	0.160	0.155	1.713
31330	0.293	0.326	0.222	0.451	1.426
31331	0.272	0.284	0.198	0.669	1.426
Positive ctrl	0.097	0.100	0.092	0.126	3.900
Negative Ctrl	0.004	0.007	0.009	0.004	3.900

Basic mAb info	Mesoscale analysis AU/mL at 2 µg				
Ab ID	CoV-2 Spike	CoV-1 Spike	CoV-2 RBD	CoV-2 NTD	Cov-2 N
31893	105.435	0.263	122.674	0.013	0.280
31894	109.235	0.302	121.632	0.012	0.199
31897	100.295	0.131	110.515	0.005	0.116
31922	4.877	1.122	0.012	0.001	0.008
31932	103.843	0.181	111.538	0.007	0.130
31963	0.035	0.013	0.070	0.001	90.802

Table 1: Summary of mesoscale binding of selected mAbs.

- 5 Conclusion: Several of the 400+ screened antibodies displayed a specific binding to SARS-CoV-2 proteins. mAb 31259 binds SARS-CoV-1 spike as well, indicative of specificity to a well-conserved epitope on coronavirus spike proteins.

Example 3: ACE2 Competition Assay

- 10 Background: All expressed mAbs were screened for their ability to compete with ACE2 interaction to various coronavirus proteins, to eliminate mAbs binding spike epitopes unlikely to result in virus neutralization. Spike and RBD targeting antibodies with the ability to compete with ACE2 binding were measured using the MSD Coronavirus Plate 1 or 9 as above. COVID-19 blocking antibody calibrator and 2 µg/ml antibody samples
- 15 were incubated after plate blocking. SULFO-Tag conjugated ACE2 was added before washing, allowing ACE2 to compete with antibody binding to spike and RBD antigens immobilized on the plate. Bound ACE2 was detected as described for the serology assay above, and antibody concentrations were subsequently calculated using calibrator dilution row signals and the MSD Discovery Workbench software. 1 AU/mL
- 20 corresponds to neutralizing activity of 1 µg/mL monoclonal antibody to SARS CoV-2 Spike Protein. For lead mAbs, binding and ACE2 competition sensitivity to SARS-CoV-2 spike receptor binding domains (RBD) containing point mutations from variants of concern was also analyzed using the MSD Coronavirus Plate 9. Further, MSD

Coronavirus Plate 23 containing spike from the omicron variant was used to assess mAb dilutions 20 µg/ml – 0.256ng/ml, and IC50 values were calculated.

Results: Data from selected antibodies of the disclosure are displayed in Figure 2. In Figure 2A, antibodies show capability to compete with ACE2 binding to SARS-CoV-2 spike receptor binding domain (RBD), compared to negative controls. Figure 2B displays curves from ACE2 inhibition % of SARS-CoV-2 spike and Omicron spike.

Collective mesoscale ACE2 competition sensitivity analysis to variant of concerns on lead mAbs may be viewed in Table 2 below.

Ab ID	31119	31137	31172	31184	31195	31206	31212
CoV-2 wt	0.045	0.100	0.045	0.045	5.116	0.745	0.085
E484K	0.033	0.117	0.033	0.033	0.033	0.033	0.033
E484K, N501Y RBD	0.052	0.125	0.042	0.037	0.037	0.022	0.037
K417N ,E484K, N501Y	0.033	0.126	0.057	0.057	0.057	0.057	0.057
K417T, E484K, N501Y	0.025	0.082	0.057	0.025	0.025	0.025	0.025
L452R	0.059	0.090	0.059	0.059	1.148	0.996	0.036
L452R, E484Q	0.016	0.085	0.016	0.016	0.016	0.675	0.016
N501Y, A570D	0.017	0.116	0.017	0.017	5.751	0.388	0.017
Q414K, N450K	0.013	0.132	0.013	0.013	23.467	0.755	0.013
S477N	0.036	0.096	0.036	0.036	4.935	0.712	0.087

Ab ID	31219	31224	31231	31243	31259	31270	31271
CoV-2 wt	0.045	0.092	0.045	0.045	0.610	0.076	0.168
E484K	0.033	0.033	0.033	0.033	0.577	0.033	0.159
E484K, N501Y RBD	0.037	0.037	0.037	0.037	0.500	0.011	0.147
K417N ,E484K, N501Y	0.057	0.057	0.057	0.057	0.533	0.057	0.149
K417T, E484K, N501Y	0.025	0.025	0.025	0.025	0.490	0.025	0.133
L452R	0.059	0.059	0.059	0.077	0.536	0.043	0.152
L452R, E484Q	0.016	0.016	0.016	0.016	0.544	0.016	0.150
N501Y, A570D	0.017	0.017	0.017	0.017	0.555	0.058	0.157
Q414K, N450K	0.013	0.013	0.013	0.092	0.414	0.120	0.181
S477N	0.036	0.086	0.036	0.059	0.614	0.075	0.155

Ab ID	31282	31283	31295	31306	31307	31317	31318
CoV-2 wt	0.187	5.116	0.120	0.045	5.116	0.090	0.045
E484K	0.033	2.101	0.115	0.089	4.046	0.046	0.033
E484K, N501Y RBD	0.054	1.219	0.123	0.081	0.073	0.037	0.013
K417N ,E484K, N501Y	0.057	0.800	0.113	0.078	0.057	0.049	0.057
K417T, E484K, N501Y	0.025	1.651	0.081	0.074	0.025	0.057	0.040
L452R	0.149	2.293	0.117	0.083	4.612	0.098	0.059

L452R, E484Q	0.016	2.601	0.107	0.067	4.778	0.060	0.016
N501Y, A570D	0.164	2.942	0.115	0.068	0.057	0.074	0.017
Q414K, N450K	0.263	4.958	0.156	0.087	23.467	0.147	0.013
S477N	0.186	4.935	0.115	0.075	4.935	0.091	0.036

Ab ID	31319	31329	31330	31331	31343	31344	31366
CoV-2 wt	0.729	0.070	5.116	1.609	5.116	0.072	0.100
E484K	0.737	0.063	0.033	0.284	0.033	0.067	0.112
E484K, N501Y RBD	0.182	0.058	0.072	0.200	0.054	0.079	0.083
K417N ,E484K, N501Y	0.218	0.056	0.057	0.146	0.057	0.080	0.110
K417T, E484K, N501Y	0.233	0.062	0.025	0.160	0.025	0.066	0.085
L452R	0.636	0.075	25.818	0.616	25.818	0.082	0.106
L452R, E484Q	0.670	0.016	0.036	0.293	0.089	0.077	0.091
N501Y, A570D	0.270	0.075	5.751	1.012	5.751	0.093	0.107
Q414K, N450K	0.819	0.114	23.467	1.737	23.467	0.120	0.132
S477N	0.728	0.077	4.935	1.432	4.935	0.080	0.105

Ab ID	31367	31378	31379	31391	31403	31409	31413
CoV-2 wt	0.443	0.173	0.561	0.045	0.118	0.051	0.096
E484K	0.450	0.168	0.566	0.076	0.093	0.063	0.119
E484K, N501Y RBD	0.433	0.136	0.623	0.097	0.078	0.063	0.095
K417N ,E484K, N501Y	0.472	0.169	0.645	0.091	0.089	0.052	0.118
K417T, E484K, N501Y	0.443	0.150	0.567	0.061	0.073	0.025	0.071
L452R	0.387	0.169	0.486	0.061	0.102	0.094	0.101
L452R, E484Q	0.397	0.152	0.504	0.042	0.080	0.016	0.081
N501Y, A570D	0.447	0.168	0.554	0.064	0.100	0.063	0.102
Q414K, N450K	0.394	0.158	0.494	0.087	0.138	0.112	0.117
S477N	0.435	0.169	0.566	0.056	0.113	0.036	0.094

Ab ID	31414	31415	31425	31426	31429
CoV-2 wt	0.514	0.097	0.109	0.416	0.095
E484K	0.510	0.093	0.100	0.411	0.085
E484K, N501Y RBD	0.588	0.087	0.098	0.419	0.065
K417N ,E484K, N501Y	0.576	0.096	0.114	0.436	0.084
K417T, E484K, N501Y	0.506	0.071	0.103	0.404	0.054
L452R	0.451	0.109	0.111	0.387	0.094
L452R, E484Q	0.454	0.082	0.101	0.372	0.085
N501Y, A570D	0.521	0.094	0.107	0.428	0.088
Q414K, N450K	0.455	0.129	0.139	0.369	0.130
S477N	0.505	0.104	0.102	0.421	0.087

Table 2: Collective mesoscale ACE2 competition sensitivity analysis to variant of concerns. The left column displays the Spike RBD mutation(s) that are characteristic for several SARS-CoV-2 variants of concern. Antibody concentrations displayed were

calculated using kit calibrator signals and the MSD Discovery Workbench software. 1 unit/mL corresponds to neutralizing activity of 1 µg/mL monoclonal antibody to SARS CoV-2 Spike Protein.

5 Conclusion: Several of the SARS-CoV-2 spike binding antibodies screened, display an ability to compete for ACE2 receptor binding to SARS-CoV-2 proteins, with affinity high enough to compete for ACE2 interaction. Sensitivity to specific spike point mutations from variants of concern was observed for several mAbs, however, several lead mAbs retain full ACE2 competition capability as well, especially SARS-CoV-1
10 binders/competitors. mAbs 29044 and 31259 clearly retain the ability to neutralize the omicron variant.

Example 4: Pseudovirus neutralization assay

Background: To assess the functionality of the antibodies' binding to coronavirus proteins and competing for ACE2 interaction, we performed a SARS-CoV-2 viral neutralization
15 assays. Here, sensitivities to spike mutations from variants of concern, discovered during mesoscale screening, were confirmed functionally as well, alongside SARS-CoV-1 neutralization of SARS-CoV-1 binders. Either pseudovirus expressing coronavirus spike proteins variants of interest, or full-length SARS-CoV-2 engineered to express eGFP,
20 were applied for analysis. mAbs were initially screened at single dilutions, followed by full neutralization curves of antibodies of interest; Eight 5-fold dilutions in DMEM with 10% FBS and 50U/mL P/S (cDMEM) of mAbs were mixed with virus and incubated at 37°C for 1 hour before addition of Vero TRMPSS2 SARS-CoV-2 permissive cells and further incubated for 24 hours at 37°C. The final total dilutions tested ranged from 20
25 µg/ml – 0.256ng/ml, and were all samples were analyzed in duplicates.

Due to pseudovirus expression of GFP, mAb neutralization capacity of both pseudovirus and full-length eGFP SARS-CoV-2 can be analyzed using flow cytometry after which frequency of infection can be determined and IC50 values calculated.

30 Cells were prepared for flow cytometry by first gently removing the culture media, and washing once with PBS. Second, cell suspensions were made by incubating each well with 75 µL Trypsin with EDTA (Biowest product code: X0930-100) for 15 min at 37 °C, followed by centrifugation at 500 g for 5 min at room temperature, and re-suspension in DMEM containing 10% FBS and 50 U/mL P/S. Cells were fixed in 1% PFA for at least
35 15 min at 4 °C, before eGFP expression was analyzed using a Miltenyi Biotec

MACSquant16 flow cytometer. A mock background signal was subtracted from all samples.

Results: The collective point-dilution neutralization performance for all screened mAbs towards wt SARS-CoV-2 was performed as described.

Preferred antibodies were identified based on these functional verifications of spike binding and ACE2 competition. Figure 3 displays curves from neutralization of pseudovirus SARS-CoV-2 WT, Alpha, Beta, Delta variants, as well as SARS-CoV-1, for selected antibodies. Figure 4 displays curves from neutralization of full-length eGFP SARS-CoV-2. Table 3 below displays a summary of the IC₅₀ values from Figure 3 and 4.

mAb ID	Pseudovirus					Full Length eGFP
	2S WT	1S WT	Alpha	Beta	Delta	2S WT
31259	1.01100	0.33210	1.60700	5.37100	3.89700	N.A
31283	0.01188	N.A	0.00747	0.08295	0.01801	0.00425
31307	0.00735	N.A	N.N	N.N	0.00689	0.00161
31330	0.00409	N.A	0.00187	N.N	0.00817	0.00032
31301	0.06070	N.A	0.04760	0.96040	0.02988	0.00450
29044	0.03226	N.A	0.00820	0.09314	0.02923	0.00506

Table 3: Summary of IC₅₀ values from selected antibodies of the disclosure.

N.N = No neutralization. The mutations in the spike protein of this viral variant has caused a loss of neutralization ability of this mAb. N.A = Not analyzed. Neutralization ability of this mAb towards this viral variant has not been analyzed – as mesoscale analysis has not indicated mAb-spike variant binding and/or ACE-2 competition.

Conclusion: Potent neutralization of SARS-CoV-2 and variants hereof is seen for all of the selected antibodies. Potency may be less for mAb 31259, however, this mAb neutralizes SARS-CoV-1 with equal potency to SARS-CoV-2, indicating that a conserved epitope may be targeted by mAb 31259, which could make it more resistant to mutation

escape from future SARS-CoV-2 variants. The pseudovirus neutralization ability of all lead mAbs are confirmed by neutralization of the full-length eGFP SARS-CoV-2.

5 **Example 5: In Vivo studies**

Background: To investigate the clinical potential of selected neutralizing antibodies discovered, *in vivo* prophylactic studies were performed. Heterozygous B6.Cg-Tg(K18-ACE2)²Primn/J mice, at least 8 weeks old were used for *in vivo* studies. Both males and females were included, the genders balanced between treatment groups. mAbs 31283 and 31259 were administered I.P. to the animals 18-24 hours prior to exposure to coronavirus. Saline water or a human IgG anti-tetanus antibody was administered to the control groups. 4 µg, 40 µg, 400 µg and 700 µg mAb (700 µg only for mAb 31259) total mAb was dosed for initial dose finding studies, with 400 µg total 31283 mAb dosed to each animal for the survival study.

15 The day after antibody treatment, animals were exposed to coronavirus assedated with 75 µg/g Ketamin, and 1 µg/g Medetomidin I.P. The mice were kept on a heating pad, and their eyes were covered with ophthalmological salve during the anesthesia period. The starting weight of all mice was noted. 15 ul containing 82 PFU SARS-CoV-2 was placed gently in the nostril of each mouse. Post exposure 1 µg/g Atipamezol was administered prior to the mice being returned to their come cages to wake up. The animal's weight was monitored daily after viral exposure, with a maximum of 20% weight loss allowed, as rapid weight-loss if a characteristic symptom of coronavirus infection in mice.

25 For survival studies, all mice were monitored daily until 20% weight loss occurred, or signs of inactivity and/or labored breathing was observed, after which they were euthanized. All remaining mice were euthanized 12 days post viral exposure. Euthanization was carried out by initiating anastesia with 5% isoflurane, followed by 30 cervical dislocation.

For dose treatment studies, the mice were euthanized on day 4 post viral exposure, and the lungs were harvested for viral quantification and outgrowth. Immediately after removal, both lungs were weighted, sliced into smaller pieces, and placed in an 35 Eppendorf tube containing 600ul RNase free PBS and a small metal bead. The lungs

were homogenized using a TissueLyser LT (Qiagen) for 5 min at max speed. The tubes were briefly spun down, and 400ul supernatant was removed to another Eppendorf tube, and frozen directly on dry ice. 500ul Buffer RLT containing 40ul 1M DTT/mL (From Qiagens RNeasy Mini Kit) was subsequently added to the remainder of the lung tissue and supernatant. The sample was homogenized again for 3min as max speed on the TissueLyser, and frozen immediately on dry ice.

Results: Mice weights were monitored daily in both the treatment and the control group during survival studies, to determine the impact of treatment on the disease course. As shown in Figure 5, mice treated with mAb 31283 largely maintained their weight throughout the observation period (Figure 5A), as well as remaining free of symptoms of coronavirus infections. In comparison, all control treated mice reaches the pre-define humane endpoints after 8 days (Figure 5B).

Conclusion: The disease courses in the two groups clearly display a prophylactic effect of mAb 31283. The animals maintain their weight well, compared to mice receiving control treatment. Furthermore, signs of lung infections such as heavy breathing and inactivity, described in the humane endpoints, were not observed for the majority of mAb 31283 treated mice. The result is significant probability of survival in the mAb 31283 treatment group compared to the control group, clearly demonstrating the prophylactic treatment efficacy of the mAb 31283.

Example 6: ddPCR RNA quantification

Background: To further analyze the prophylactic potential of mAb 31259 and mAb 31259, viral genome copies in the lungs were quantified. RNA was purified from 200ul of the lung samples homogenized with lysis buffer, using the RNeasy mini kit (Qiagen) following the manufacturer's instructions. 22 µL PCR reaction mixes were prepared in duplicates according to the manufacturers protocol, containing 5.5 µL One-Step RT-ddPCR Advanced Kit for Probes (Cat #:1864022), 2.2 ul Reverse Transcriptase, 1.1 ul 300 mM DTT, 250 nM nCOV_N1 Probe (IDT Cat #10006823), 1000 nM of each forward and reverse nCOV_N1 primers (IDT Cat#: 10006821/10006822) , and 10 µL RNA sample diluted 1 million times. Droplets were generated using the QX200 Droplet generator (Bio-Rad) and amplified in a C1000 Touch Thermal Cycler (Bio-Rad) under the following conditions; 25°C for 3 min, 50°C for 1 h, 40 cycles of 95°C for 30 s and 55°C for 1 min, lastly 98°C for 10 min and infinite hold on 12°C. Subsequently droplets

were read in a QX200 droplet reader (Bio-Rad) and analysis was performed in QuantaSoft™ analysis software (Bio-Rad). Total concentration per sample was calculated based on total N1 concentration per reaction, and normalized to lung volumes for the mice individually.

5

Results: The dose-response of mAb 31259 and mAb 31283 were investigated.

Treatment were given at doses; 4 µg, 40 µg, and 400 µg to 3 mice in each group. The viral loads are displayed as mio copies/mg lung in Figure 6, for both mAbs 31259 and mAb 31283.

10

Conclusion: A dose-dependent reduction in viral loads is seen for mAb 31283. mAb 31283 shows a significant reduction in viral copies at 40 µg and 400 µg, though with a break-through infection in both groups. This may be due to the injection route I.P.

where intestines may be hit, influencing the uptake of the antibody. mAb 31259 treated mice display a partly reduction, however, with a less potent IC50 than mAb 31283, this is to be expected, and higher doses may be needed to see the same effect as for mAb 31283.

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Example 7: TCID50 determination

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Background: To further analyze the prophylactic potential of mAb 31259 and mAb 31259, infectious viral copies in the lungs were quantified. An estimation of infectious viral units in lung homogenates was carried out for each mouse. TCID50 analysis was set up as follows: Five-fold serial dilutions, of each mouse lung homogenate was made in DMEM containing 10% FBS and 50 U/mL P/S. 50 µL of each dilution was incubated with 2,000 Vero76 cmcy hTMPRSS2 cells, in 50 µL DMEM containing 10% FBS and 50 U/mL P/S. Plates were incubated at 37 °C for 72 hours. The final total dilution of lung homogenates ranged from 50x-97656250x, and were all analyzed in eight replicas. Cytopathic effect was determined manually as present or absent in each well, using a light microscope, and used to calculate TCID50/ lung volume for the mice individually.

25

30

Results: The dose-response of mAb 31259 and mAb 31283 were investigated.

Treatment were given at doses; 4 µg, 40 µg, 400 µg and 700 µg to 3 mice in each group. The viral loads are displayed as TCID50/mg lung in Figure 7, for both mAbs 31259 and mAb 31283.

35

Conclusion: A dose-dependent reduction in viral loads is seen for both mAb 31259 and mAb 31283. mAb 31283 especially shows a significant reduction in viral copies at 40 µg and 400 µg, though with a break-through infection in both groups. This may be due to the injection route I.P. where intestines may be hit, influencing the uptake of the antibody. However, all mAb 31283 treated mice with a reduction had no detectable infectious virus, indicating protection the viral exposure administered. mAb 31259 treated mice display a partly reduction compared to that of mAb 31283, however, with a less potent IC50 than mAb 31283, this is to be expected, and higher doses would likely be needed to see the same effect as for mAb 31283.

Example 8: AAV design

Background: While vaccines result in the development of protective antibodies in the majority of the population, patients immunocompromised due to medication or genetic defects may have no response at all. AAV technology would enable delivery of neutralizing mAb genes to these patients' cells, resulting in them producing the protective antibody directly themselves.

Monoclonal antibody sequences of interest were cloned into the multiple cloning site of the vector AAV2ITR-EF1a_GOI_bGHpA , where expression is controlled by an EF1a promoter. The AAV2ITR-EF1a_GOI_bGHpA plasmid was sent to Genscript Biotech for synthesis of the four antibody expressing plasmids.

The final product was designed based on the layout:

HEAVY CHAIN LEADER SIGNAL- VARIABLE HEAVY CHAIN – CONSTANT HEAVY CHAIN - FURIN CLEAVAGE SITE– 2A PEPTIDE – LIGHT CHAIN LEADER SIGNAL – VARIABLE LIGHT CHAIN – CONSTANT LIGHT CHAIN

Constant amino acid sequences are summarized in Table 4 below:

Peptide	SEQ ID NO:
Heavy chain leader signal	139
Heavy constant chain	140
Furin cleavage site	141
2A Peptide	142
Light chain leader signal	143

Light constant chain	144
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Table 4: Constant amino acid sequences

The antibodies selected to be inserted in AAV2ITR-EF1a_GOI_bGHpA are:

- a) H4 Antibody (Wu et al Science 2020, PMID: 32404477)
- b) A23-58.1 Antibody (Wang et al Science 2021, PMID: 34210892)

The variable heavy chains (VH) and the variable light chains (VL) sequences are summarised in Table 5 below:

Antibody	VH SEQ ID NO:	VL SEQ ID NO:
H4 Antibody	145	146
A23-58.1 Antibody	149	150
31259 Antibody	29	30
29044 Antibody	129	130
31283 Antibody	37	38

Table 5: VH and VL sequences.

The two final product (FP) sequences inserted in AAV2ITR-EF1a_GOI_bGHpA, and the two resulting vectors are summarised in the Table 6 below:

Antibody	FP SEQ ID NO:	Vectors SEQ ID NO:
H4 Antibody	147	148
A23-58.1 Antibody	151	152
31259 Antibody	155	156
29044 Antibody	194	195
31283 Antibody	153	154

Table 6: Final product sequences.

Plasmid sequences were verified by sanger sequencing.

Example 9: Cell culture mAb expression

Background: To verify the vectors ability to express the desired mAbs, they were evaluated *in vitro*. Here, we show cell culture expression data on mAbs H4 and A23-58.1 known from the literature as a proof of concept.

Prior to cell culture expression, plasmids were amplified in NEB5 alpha competent bacteria and purified using MN midiprep endotoxin free plasmid purification kit. Plasmids were transfected into Expi293F cells using Polyethylenimine (PEI) and expression of mAbs in supernatant was followed over time. A small aliquot of each supernatant was isolated at days 1, 4, and 7 after which, mAb expression was visualized on a Western blot using anti-Human IgG antibody-HRP for detection.

Results: A small aliquot of each supernatant was isolated at days 1, 4, and 7 after which, mAb expression was visualized on a Western blot (WB) using anti-Human IgG antibody-HRP for detection in Figure 8.

Mock is used as negative control to identify unspecific protein bands. No unspecific bands are detected in lanes 1,4 and 7. mAb specific bands are detected in lanes 2, 3, 5, 6, 8, and 9 for H4 and A23-58.1 respectively. Bands are detected at 25 kDa, 50kDa and 75 kDa. Since this is a denatured blot, the 25kDa band represents mAb Light chain, the 50kDa band represents the heavy chain, and 75 kDa band represents antibodies that have not been denatured in the process.

Conclusion: WB shows that mAb expression accumulates over time with a relative minor higher expression of A23-58.1 compared to H4. The cloned vectors are successful in expressing the desired antibody sequence, which can in theory be swapped out for any desired sequence later, such as antibodies of the present disclosure.

Example 10: mAb supernatant pseudovirus neutralization

Background: To assess the functionality of the expressed mAbs we performed a SARS-CoV-2 pseudovirus neutralization assay. Eight 5-fold dilutions of supernatants from day 7 were mixed with either SARS-CoV-2 wt Spike (2S), -Alpha Spike, -Beta Spike, or -Delta Spike pseudoviruses. Supernatants and pseudoviruses incubated at 37°C for 1 hour before addition of Vero TRMPSS2 SARS-CoV-2 permissive cells and further incubated for 24 hours at 37°C. Due to pseudovirus expression of GFP, mAb neutralization capacity of pseudovirus can be analyzed using flow cytometry and frequency of infection can be determined and IC50 values calculated.

Results: Figure 9 displays curves from neutralization of pseudovirus SARS-CoV-2 WT, Alpha, Beta, and Delta, for mAbs supernatants with H4 and A23-58.1, isolated on day 7.

Conclusion: Both antibodies expressed display neutralization capabilities. mAb A23-58.1 show greater neutralization effect than H4 because infection is completely neutralized at the first supernatant dilution for all 4 SARS-CoV-2 variants. However, as protein concentrations are not standardized between the two mAbs in this assay, neutralization potency should not be compared between the two. It can be concluded however, that the antibodies expressed from the AAV vectors successfully retain their neutralization capabilities, serving as a proof of concept for expressing discovered antibodies of the disclosure in an identical way.

Example 11: Mesoscale ACE2 competition data for mAb 29044, mAb 31059 and sotrovimab against Omicron variants of concern (VoC)

Background: Antibodies 29044, 31059, and sotrovimab were screened for their ability to compete with ACE2 interaction to various SARS-CoV-2 Omicron Spike variants of concern (VoC), XBB.1, BQ.1, BA.2.75, BA.5. Antibody ability to compete with ACE2 binding were measured using the MSD Coronavirus panel 32. COVID-19 blocking antibody calibrator and mAbs in a five-fold dilution series from 20ug/ml – 0.256ng/ml antibody were incubated after plate blocking. SULFO-Tag conjugated ACE2 was added before washing, allowing ACE2 to compete with antibody binding to spike antigens immobilized on the plate. Bound ACE2 was measured on a MESO QuickPlex SQ 120 Reader after addition of GOLD Read Buffer B.

Results: Data from antibodies 29044 and 31259 are displayed in Figure 10, where they are compared to sotrovimab. Figure 10 displays curves from ACE2 competition % of SARS-CoV-2 spike from Omicron XBB.1, BQ.1, BA.2.75 and BA.5.

Conclusion: Here we tested the ACE2 competition capabilities from mAbs 29044, 31259 and sotrovimab against four SARS-CoV-2 Omicron Spike VoC, XBB.1, BQ.1, BA.2.75, BA.5. mAb 29044 retains the ability to compete with ACE2 for BA2.75 and BA.5 and mAb 31259 retains the ability to compete with ACE2 for all the omicron variants of concern, whereas sotrovimab do not have the ability to compete with ACE2 against either of the four variants of concern.

Example 12: Antigen binding to various SARS-CoV-2 Omicron Spike variants of concern (VoC)

Background: mAb 29044 and mAb 31059 were screened for their ability to bind various SARS-CoV-2 Omicron Spike variants of concern (VoC), XBB.1, BQ.1, BA.2.75, BA.5.

5 This was measured using the MSD Coronavirus Panel 32 (Meso Scale Discovery, Rockville, Maryland), following the manufacturers guidelines. Unspecific antibody binding was blocked using MSD Blocker A. MAbs were diluted in a five-fold dilution series from 20ug/ml – 0.256ng/ml in Diluent100, before application to the plates. After sample incubation, bound IgG was detected by incubation with MSD SULFO-TAG Anti-
10 Human IgG Antibody and subsequently measured on a MESO QuickPlex SQ 120 Reader after addition of GOLD Read Buffer B.

Results: The graph shows a dose-dependent binding of mAb 29044 and mAb 31259 to the four SARS-CoV-2 Omicron spike VoCs (Figure 11).

15

Conclusion: Both mAb 29044 and mAb 31259 bind SARS-CoV2 Omicron Spike variants of concern XBB.1, BQ.1, BA.2.75, BA.5 in a dose-dependent manner.

Example 13: mAb A23-58.1, mAb 29044 and mAb 31259 expression from AAV vectors

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Background: To verify the vectors ability to express the desired mAbs, they were evaluated *in vitro*. Here, we show cell culture expression data on mAb A23-58.1, mAb 29044 and mAb 31259.

25 AAV vectors comprising mAb A23, mAb 29044 and mAb 31259 were produced as described in Example 8 “AAV design”.

Prior to cell culture expression, plasmids were amplified in NEB5 alpha competent bacteria and purified using MN midiprep endotoxin free plasmid purification kit.

30 Plasmids were transfected into Expi293F cells using Polyethylenimine (PEI) and expression of mAbs in supernatant was followed over time. A small aliquot of each supernatant was isolated at days 3 and 6 after which, mAb expression was visualized on a Western blot using anti-Human IgG antibody-HRP for detection.

Results: A small aliquot of each supernatant was isolated at days 3 and 6 after which, mAb expression was visualized on a Western blot (WB) using anti-Human IgG antibody-HRP for detection as shown in Figure 12.

5 Mock is used as negative control to identify unspecific protein bands. No unspecific bands are detected in lanes 1 and 5. mAb specific bands are detected in lanes 2, 3, 4 and 6, 7, 8 for mAb 29044, mAb 31259 and mAb A23-58.1, respectively. Bands are detected at 25 kDa, 50kDa and 75 kDa. Since this is a denatured blot, the 25kDa band represents mAb Light chain, the 50kDa band represents the heavy chain, and 75 kDa
10 band represents antibodies that have not been denatured in the process.

Conclusion: Western Blot shows that mAb expression accumulates over time for all three antibodies. The cloned vectors are successful in expressing the desired antibody sequence.

15

Example 14: mAb A.23.58.1 expressed from AAV vector in mice protects against SARS-CoV-2 infection

Background: Mouse strains and AAV immunization.

Animal experiments were conducted under animal license 2020-15-0201-00726
20 approved by the Danish Animal Expectorate. 8-12 weeks old heterozygote B6.Cg-Tg(K18-ACE2)2Primn/J mice were obtained from the Jackson Laboratory. For intramuscular (i.m.) administration, mice were anesthetized by inhalation isoflurane and a single 10 µL dose of 1 x 10¹⁰ vector genomes (vg) in saline was injected to the right hind leg. For intravenous (i.v.) administration, a single 100 µL dose of 1 x 10¹⁰ vg in
25 saline was injected to the lateral tail vein.

An AAV vector comprising the A23-58.1 antibody (AAV8-A23) was produced as described in Example 8 "AAV design" and an AAV8 vector not encoding an antibody was used as control. The vectors were administered to mice as described above.

30

SARS-CoV2 challenge.

4 weeks after AAV treatment, mice were anesthetized and exposed to 11.8 TCID₅₀ SARS-CoV-2 (SARS-CoV-2/München-1.1/2020/929) intranasally. Animals were monitored daily following exposure. Four days after SARS-CoV-2 exposure the mice
35 were anesthetized, and lungs harvested and homogenized in RNase-free PBS. Lung

homogenate was weight and centrifuged, and an aliquot of supernatant was treated with RNA extraction buffer (Qiagen RNeasy) prior to freezing while the remaining lung homogenate was frozen without further treatment. Infectious viral units were estimated by a TCID₅₀ assay using untreated lung homogenate. Lung homogenate was diluted in five-fold serial dilutions and incubated with Vero76 cmv hTMPRSS2 cells for 72 hours. Cytopathic effect (CPE) was determined visually in each well with subsequent calculation of TCID₅₀/lung volume.

Results

Four weeks after AAV8-A23 administration, mice with sustained antibody expression were exposed to SARS-CoV-2. Four days after exposure, the mice were euthanized, and lungs harvested to quantify replication competent virus in a viral outgrowth assay. As shown in Figure 13B, there was a statistically significant reduction in the TCID₅₀ in a viral plaque assay for AAV8-A23 i.v.-treated mice (median 0.8 TCID₅₀/mg lung tissue, AAV8-control median 1100 TCID₅₀/mg lung tissue, $p = 0.0082$). Two of seven AAV8-A23 i.v.-treated mice had a higher TCID₅₀ indicating a breakthrough infection whereas 3 of 7 AAV8-A23i.v.-treated mice had no detectable viral outgrowth. Both AAV8-A23 i.m.-treated mice had no detectable viral outgrowth, but this reduction in TCID₅₀ compared to AAV8-control was not statistically significant (AAV8-A23 i.m. median 0.19 TCID₅₀/mg lung tissue, $p = 0.0741$) due to the low number of mice with sustained antibody expression in this group.

Conclusion

AAV immunization with AAV8-A23 protects against SARS-CoV-2 infection.

Example 15: *In vivo* studies on mAb 31259, mAb 31283 and mAb 29044

Background

To investigate the clinical potential of selected neutralizing antibodies discovered, *in vivo* prophylactic studies were performed. Heterozygous B6.Cg-Tg(K18-ACE2)²Primn/J mice, at least 8 weeks old were used for *in vivo* studies. Both males and females were included, the genders balanced between treatment groups. mAbs 31259, 31283 and 29044 were administered I.P. to the animals 18-24 hours prior to exposure to coronavirus. Saline water or a human IgG anti-tetanus antibody was administered to the control groups. 2 mg mAb 31259 ($n=6$), 400 μ g mAb 31283 ($n=8$) or 400 μ g mAb 29044 ($n=7$) was dosed to each animal for the survival study.

The day after antibody treatment, animals were exposed to coronavirus associated with 75 µg/g Ketamin, and 1 µg/g Medetomidin I.P. The mice were kept on a heating pad, and their eyes were covered with ophthalmological salve during the anesthesia period.

- 5 The starting weight of all mice was noted. 15 µl containing 82 PFU SARS-CoV-2 was placed gently in the nostril of each mouse. Post exposure 1 µg/g Atipamezol was administered prior to the mice being returned to their home cages to wake up. The animal's weight was monitored daily after viral exposure, with a maximum of 20% weight loss allowed, as rapid weight-loss is a characteristic symptom of coronavirus
- 10 infection in mice.

For survival studies, all mice were monitored daily until 20% weight loss occurred, or signs of inactivity and/or labored breathing was observed, after which they were euthanized. All remaining mice were euthanized 12 days post viral exposure.

- 15 Euthanization was carried out by initiating anesthesia with 5% isoflurane, followed by cervical dislocation.

Result

In vivo prophylaxis

- 20 Antibodies 31259, 31283 and 29044 were evaluated *in vivo* to determine their prophylactic potential. K18-hACE2 transgenic mice were used as a model of SARS-CoV-2 infection to study the disease course. The mAbs were administered 24 hours prior to SARS-CoV-2 exposure. The mice were monitored daily for up to 13 days after SARS-CoV-2 exposure, to determine if the observed reduction in virus observed in the
- 25 lungs, would translate to disease protection. During these studies, pre-defined welfare criteria were applied to score the disease severity of the mice and determine time of euthanization. A clear difference was observed in the weight stability of the animals between the mAb treated groups compared to the rapid weight loss observed in control mice between days five and eight post SARS-CoV-2 exposure (Figure 14B). This
- 30 translated into a highly significant increased rate of survival within mAb treated mice compared to control mice (mAb 31283 p=0.0002; mAb 31259 p=0.0004; mAb 29044 p=0.0003), as displayed in Figure 14C.

Conclusion

Treatment with mAb 31259, mAb 31283 and mAb 29044 resulted in weight stability and increased rate of survival compared to control treatment.

5 Sequence overview

SEQ ID NO:	Name/Identifier
1	31110 HCVR
2	31110 LCVR
3	31119 HCVR
4	31119 LCVR
5	31137 HCVR
6	31137 LCVR
7	31138 HCVR
8	31138 LCVR
9	31145 HCVR
10	31145 LCVR
11	31172 HCVR
12	31172 LCVR
13	31184 HCVR
14	31184 LCVR
15	31195 HCVR
16	31195 LCVR
17	31206 HCVR
18	31206 LCVR
19	31212 HCVR
20	31212 LCVR
21	31219 HCVR
22	31219 LCVR
23	31224 HCVR
24	31224 LCVR
25	31231 HCVR
26	31231 LCVR
27	31243 HCVR
28	31243 LCVR
29	31259 HCVR
30	31259 LCVR
31	31270 HCVR
32	31270 LCVR
33	31271 HCVR
34	31271 LCVR
35	31282 HCVR
36	31282 LCVR

37	31283 HCVR
38	31283 LCVR
39	31295 HCVR
40	31295 LCVR
41	31306 HCVR
42	31306 LCVR
43	31307 HCVR
44	31307 LCVR
45	31317 HCVR
46	31317 LCVR
47	31318 HCVR
48	31318 LCVR
49	31319 HCVR
50	31319 LCVR
51	31329 HCVR
52	31329 LCVR
53	31330 HCVR
54	31330 LCVR
55	31331 HCVR
56	31331 LCVR
57	31343 HCVR
58	31343 LCVR
59	31344 HCVR
60	31344 LCVR
61	31366 HCVR
62	31366 LCVR
63	31367 HCVR
64	31367 LCVR
65	31378 HCVR
66	31378 LCVR
67	31379 HCVR
68	31379 LCVR
69	31391 HCVR
70	31391 LCVR
71	31403 HCVR
72	31403 LCVR
73	31409 HCVR
74	31409 LCVR
75	31413 HCVR
76	31413 LCVR
77	31414 HCVR
78	31414 LCVR
79	31415 HCVR

80	31415 LCVR
81	31425 HCVR
82	31425 LCVR
83	31426 HCVR
84	31426 LCVR
85	31429 HCVR
86	31429 LCVR
87	31259 HCDR1
88	31259 HCDR2
89	31259 HCDR3
90	31259 LCDR1
91	31259 LCDR2
92	31259 LCDR3
93	31283 HCDR1
94	31283 HCDR2
95	31283 HCDR3
96	31283 LCDR1
97	31283 LCDR2
98	31283 LCDR3
99	31307 HCDR1
100	31307 HCDR2
101	31307 HCDR3
102	31307 LCDR1
103	31307 LCDR2
104	31307 LCDR3
105	31330 HCDR1
106	31330 HCDR2
107	31330 HCDR3
108	31330 LCDR1
109	31330 LCDR2
110	31330 LCDR3
111	31331 HCDR1
112	31331 HCDR2
113	31331 HCDR3
114	31331 LCDR1
115	31331 LCDR2
116	31331 LCDR3
117	31378 HCDR1
118	31378 HCDR2
119	31378 HCDR3
120	31378 LCDR1
121	31378 LCDR2
122	31378 LCDR3

123	31379 HCDR1
124	31379 HCDR2
125	31379 HCDR3
126	31379 LCDR1
127	31379 LCDR2
128	31379 LCDR3
129	29044 HCVR
130	29044 LCVR
131	31893 HCVR
132	31893 LCVR
133	31894 HCVR
134	31894 LCVR
135	31897 HCVR
136	31897 LCVR
137	31932 HCVR
138	31932 LCVR
139	Heavy chain leader signal
140	Heavy constant chain
141	Furin cleavage site
142	2A Peptide
143	Light chain leader signal
144	Light constant chain
145	H4-VH
146	H4-VL
147	H4 insertion in AAV2
148	AAV2ITR-EF1a-H4-bGHpA
149	A23-58.1-VH
150	A23-58.1-VL
151	A23-58.1 insertion in AAV2
152	AAV2ITR-EF1a-A23-58.1-bGHpA
153	31283 insertion in AAV2
154	AAV2ITR-EF1a-sym mAb 31283-bGHpA
155	31259 insertion in AAV2
156	AAV2ITR-EF1a-sym mAb 31259-bGHpA
157	29044 HCDR1
158	29044 HCDR2
159	29044 HCDR3
160	29044 LCDR1
161	29044 LCDR2
162	29044 LCDR3
163	31893 HCDR1
164	31893 HCDR2
165	31893 HCDR3

166	31893 LCDR1
167	31893 LCDR2
168	31893 LCDR3
169	31894 HCDR1
170	31894 HCDR2
171	31894 HCDR3
172	31894 LCDR1
173	31894 LCDR2
174	31894 LCDR3
175	31897 HCDR1
176	31897 HCDR2
177	31897 HCDR3
178	31897 LCDR1
179	31897 LCDR2
180	31897 LCDR3
181	31271 HCDR1
182	31271 HCDR2
183	31271 HCDR3
184	31271 LCDR1
185	31271 LCDR2
186	31271 LCDR3
187	31932 HCDR1
188	31932 HCDR2
189	31932 HCDR3
190	31932 LCDR1
191	31932 LCDR2
192	31932 LCDR3
193	29044 insertion in AAV2 (DNA)
194	29044 insertion in AAV2 (amino acid)
195	AAV2ITR-EF1a-sym mAb 29044-bGHpA

References

- 5 • Baum et al. *Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies*. Science 2020, 369, 1014-1018.
- Rogers et al. *Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model*. Science 2020, 369, 956-963.
- 10 • Hastie et al. *Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: A global consortium study*. Science 2021, 374, 472-478.

- Cao et al. *Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells*. Cell 2020, 182(1):73-84
- 5 • Lundgreen et al. *A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19*. New England Journal of Medicine 2021, 384 (10), 905-914.
- Chen et al. *SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19*. New England Journal of Medicine 2021, 384(3), 229-237.
- O'Brien et al. *Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19*. New England Journal of Medicine 2021, 385(13), 1184-1195.
- 10 • Viana et al. *Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa*. Nature 2022.
- Cao et al. *Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies*. Nature 2021.
- Carreno et al. *Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron*. Nature 2021.
- 15

20 Items

1. An isolated antibody or antigen-binding fragment thereof capable of binding a SARS-CoV-2 spike protein, wherein said isolated antibody or antigen-binding fragment thereof comprises:
 - 25 i) Three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) amino acid sequence set forth in any of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 129, 131, 133, 135 and 137, and
 - 30 ii) Three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) amino acid sequence set forth in in any of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52,

54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 130, 132, 134, 136 and 138.

2. The isolated antibody or antigen-binding fragment thereof according to item 1,
5 wherein said isolated antibody or antigen-binding fragment thereof comprises:
- 1) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 1 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 2, or
 - 10 2) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 3 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 4, or
 - 15 3) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 5 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 6, or
 - 20 4) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 7 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 8, or
 - 25 5) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 9 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 10, or
 - 30 6) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 11 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 12, or
 - 35 7) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 13 and LCDR1, LCDR2 and LCDR3
contained within the LCVR amino acid sequence set forth in SEQ ID
NO: 14, or
 - 8) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid
sequence set forth in SEQ ID NO: 15 and LCDR1, LCDR2 and LCDR3

- contained within the LCVR amino acid sequence set forth in SEQ ID NO: 16, or
- 5 9) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 17 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 18, or
- 10 10) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 19 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 20, or
- 15 11) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 21 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 22, or
- 20 12) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 23 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 24, or
- 25 13) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 25 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 26, or
- 30 14) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 27 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 28, or
- 15) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 29 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 30, or
- 16) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 31 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 32, or

- 17) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 33 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 34, or
- 5 18) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 35 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 36, or
- 10 19) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 37 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 38, or
- 15 20) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 39 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 40, or
- 20 21) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 41 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 42, or
- 25 22) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 43 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 44, or
- 30 23) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 45 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 46, or
- 24) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 47 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 48, or
- 25) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 49 and LCDR1, LCDR2 and LCDR3

- contained within the LCVR amino acid sequence set forth in SEQ ID NO: 50, or
- 5 26) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 51 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 52, or
- 10 27) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 53 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 54, or
- 15 28) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 55 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 56, or
- 20 29) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 57 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 58, or
- 25 30) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 59 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 60, or
- 30 31) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 61 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 62, or
- 32) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 63 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 64, or
- 33) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 65 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 66, or

- 34) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 67 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 68, or
- 5 35) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 69 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 70, or
- 10 36) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 71 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 72, or
- 15 37) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 73 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 74, or
- 20 38) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 75 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 76, or
- 25 39) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 77 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 78, or
- 30 40) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 79 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 80, or
- 41) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 81 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 82, or
- 42) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 83 and LCDR1, LCDR2 and LCDR3

- contained within the LCVR amino acid sequence set forth in SEQ ID NO: 84, or
- 5 43) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 85 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 86, or
- 10 44) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 129 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 130, or
- 15 45) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 131 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 132, or
- 20 46) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 133 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 134, or
- 25 47) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 135 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 136, or
- 48) HCDR1, HCDR2 and HCDR3 contained within the HCVR amino acid sequence set forth in SEQ ID NO: 137 and LCDR1, LCDR2 and LCDR3 contained within the LCVR amino acid sequence set forth in SEQ ID NO: 138.
3. The isolated antibody or antigen-binding fragment thereof according to any of the previous items selected from the group consisting of:
- 30 i) The antibody comprising a HCDR1 set forth in SEQ ID NO: 87, HCDR2 set forth in SEQ ID NO: 88, HCDR3 set forth in SEQ ID NO: 89, LCDR1 set forth in SEQ ID NO: 90, LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set forth in SEQ ID NO: 92, or
- 35 ii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 93, HCDR2 set forth in SEQ ID NO: 94, HCDR3 set forth in SEQ ID NO: 95, LCDR1 set

- forth in SEQ ID NO: 96, LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set forth in SEQ ID NO: 98, or
- 5 iii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 99, HCDR2 set forth in SEQ ID NO: 100, HCDR3 set forth in SEQ ID NO: 101, LCDR1 set forth in SEQ ID NO: 102, LCDR2 set forth in SEQ ID NO: 103, and LCDR3 set forth in SEQ ID NO: 104, or
- 10 iv) The antibody comprising a HCDR1 set forth in SEQ ID NO: 105, HCDR2 set forth in SEQ ID NO: 106, HCDR3 set forth in SEQ ID NO: 107, LCDR1 set forth in SEQ ID NO: 108, LCDR2 set forth in SEQ ID NO: 109, and LCDR3 set forth in SEQ ID NO: 110, or
- 15 v) The antibody comprising a HCDR1 set forth in SEQ ID NO: 111, HCDR2 set forth in SEQ ID NO: 112, HCDR3 set forth in SEQ ID NO: 113, LCDR1 set forth in SEQ ID NO: 114, LCDR2 set forth in SEQ ID NO: 115, and LCDR3 set forth in SEQ ID NO: 116, or
- 20 vi) The antibody comprising a HCDR1 set forth in SEQ ID NO: 117, HCDR2 set forth in SEQ ID NO: 118, HCDR3 set forth in SEQ ID NO: 119, LCDR1 set forth in SEQ ID NO: 120, LCDR2 set forth in SEQ ID NO: 121, and LCDR3 set forth in SEQ ID NO: 122, or
- 25 vii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 123, HCDR2 set forth in SEQ ID NO: 124, HCDR3 set forth in SEQ ID NO: 125, LCDR1 set forth in SEQ ID NO: 126, LCDR2 set forth in SEQ ID NO: 127, and LCDR3 set forth in SEQ ID NO: 128, or
- 30 viii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 157, HCDR2 set forth in SEQ ID NO: 158, HCDR3 set forth in SEQ ID NO: 159, LCDR1 set forth in SEQ ID NO: 160, LCDR2 set forth in SEQ ID NO: 161, and LCDR3 set forth in SEQ ID NO: 162, or
- ix) The antibody comprising a HCDR1 set forth in SEQ ID NO: 163, HCDR2 set forth in SEQ ID NO: 164, HCDR3 set forth in SEQ ID NO: 165, LCDR1 set forth in SEQ ID NO: 166, LCDR2 set forth in SEQ ID NO: 167, and LCDR3 set forth in SEQ ID NO: 168, or
- x) The antibody comprising a HCDR1 set forth in SEQ ID NO: 169, HCDR2 set forth in SEQ ID NO: 170, HCDR3 set forth in SEQ ID NO: 171, LCDR1 set forth in SEQ ID NO: 172, LCDR2 set forth in SEQ ID NO: 173, and LCDR3 set forth in SEQ ID NO: 174, or

- xi) The antibody comprising a HCDR1 set forth in SEQ ID NO: 175, HCDR2 set forth in SEQ ID NO: 176, HCDR3 set forth in SEQ ID NO: 177, LCDR1 set forth in SEQ ID NO: 178, LCDR2 set forth in SEQ ID NO: 179, and LCDR3 set forth in SEQ ID NO: 180, or
- 5 xii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 181, HCDR2 set forth in SEQ ID NO: 182, HCDR3 set forth in SEQ ID NO: 183, LCDR1 set forth in SEQ ID NO: 184, LCDR2 set forth in SEQ ID NO: 185, and LCDR3 set forth in SEQ ID NO: 186, or
- 10 xiii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 187, HCDR2 set forth in SEQ ID NO: 188, HCDR3 set forth in SEQ ID NO: 189, LCDR1 set forth in SEQ ID NO: 190, LCDR2 set forth in SEQ ID NO: 191, and LCDR3 set forth in SEQ ID NO: 192.
4. The isolated antibody or antigen-binding fragment thereof according to any of
- 15 the previous items selected from the group consisting of:
- 1) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 1 and the LCVR amino acid sequence set forth in SEQ ID NO: 2, or
- 2) The antibody comprising the HCVR amino acid sequence set forth in
- 20 SEQ ID NO: 3 and a LCVR amino acid sequence set forth in SEQ ID NO: 4, or
- 3) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 5 and the LCVR amino acid sequence set forth in SEQ ID NO: 6, or
- 25 4) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 7 and a LCVR amino acid sequence set forth in SEQ ID NO: 8, or
- 5) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 9 and a LCVR amino acid sequence set forth in SEQ ID
- 30 NO: 10, or
- 6) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 11 and the LCVR amino acid sequence set forth in SEQ ID NO: 12, or

- 7) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 13 and a LCVR amino acid sequence set forth in SEQ ID NO: 14, or
- 5 8) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 15 and the LCVR amino acid sequence set forth in SEQ ID NO: 16, or
- 9) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 17 and a LCVR amino acid sequence set forth in SEQ ID NO: 18, or
- 10 10) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 19 and a LCVR amino acid sequence set forth in SEQ ID NO: 20, or
- 11) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 21 and the LCVR amino acid sequence set forth in SEQ ID NO: 22, or
- 15 12) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 23 and a LCVR amino acid sequence set forth in SEQ ID NO: 24, or
- 13) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 25 and the LCVR amino acid sequence set forth in SEQ ID NO: 26, or
- 20 14) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 27 and a LCVR amino acid sequence set forth in SEQ ID NO: 28, or
- 25 15) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 29 and a LCVR amino acid sequence set forth in SEQ ID NO: 30, or
- 16) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 31 and the LCVR amino acid sequence set forth in SEQ ID NO: 32, or
- 30 17) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 33 and a LCVR amino acid sequence set forth in SEQ ID NO: 34, or

- 18) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 35 and the LCVR amino acid sequence set forth in SEQ ID NO: 36, or
- 5 19) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 37 and a LCVR amino acid sequence set forth in SEQ ID NO: 38, or
- 20) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 39 and a LCVR amino acid sequence set forth in SEQ ID NO: 40, or
- 10 21) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 41 and the LCVR amino acid sequence set forth in SEQ ID NO: 42, or
- 22) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 43 and a LCVR amino acid sequence set forth in SEQ ID NO: 44, or
- 15 23) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 45 and the LCVR amino acid sequence set forth in SEQ ID NO: 46, or
- 24) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 47 and a LCVR amino acid sequence set forth in SEQ ID NO: 48, or
- 20 25) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 49 and a LCVR amino acid sequence set forth in SEQ ID NO: 50, or
- 25 26) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 51 and the LCVR amino acid sequence set forth in SEQ ID NO: 52, or
- 27) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 53 and a LCVR amino acid sequence set forth in SEQ ID NO: 54, or
- 30 28) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 55 and the LCVR amino acid sequence set forth in SEQ ID NO: 56, or

- 29) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 57 and a LCVR amino acid sequence set forth in SEQ ID NO: 58, or
- 5 30) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 59 and a LCVR amino acid sequence set forth in SEQ ID NO: 60, or
- 31) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 61 and the LCVR amino acid sequence set forth in SEQ ID NO: 62, or
- 10 32) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 63 and a LCVR amino acid sequence set forth in SEQ ID NO: 64, or
- 33) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 65 and the LCVR amino acid sequence set forth in SEQ ID NO: 66, or
- 15 34) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 67 and a LCVR amino acid sequence set forth in SEQ ID NO: 68, or
- 35) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 69 and a LCVR amino acid sequence set forth in SEQ ID NO: 70, or
- 20 36) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 71 and the LCVR amino acid sequence set forth in SEQ ID NO: 72, or
- 25 37) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 73 and a LCVR amino acid sequence set forth in SEQ ID NO: 74, or
- 38) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 75 and the LCVR amino acid sequence set forth in SEQ ID NO: 76, or
- 30 39) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 77 and a LCVR amino acid sequence set forth in SEQ ID NO: 78, or

- 40) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 79 and a LCVR amino acid sequence set forth in SEQ ID NO: 80, or
- 5 41) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 81 and the LCVR amino acid sequence set forth in SEQ ID NO: 82, or
- 42) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 83 and a LCVR amino acid sequence set forth in SEQ ID NO: 84, or
- 10 43) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 85 and the LCVR amino acid sequence set forth in SEQ ID NO: 86, or
- 44) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 129 and the LCVR amino acid sequence forth in SEQ ID NO: 130, or
- 15 45) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 131 and the LCVR amino acid sequence forth in SEQ ID NO: 132, or
- 46) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 133 and the LCVR amino acid sequence forth in SEQ ID NO: 134, or
- 20 47) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 135 and the LCVR amino acid sequence forth in SEQ ID NO: 136, or
- 25 48) The antibody comprising the HCVR amino acid sequence set forth in SEQ ID NO: 137 and the LCVR amino acid sequence forth in SEQ ID NO: 138.
5. The isolated antibody or antigen-binding fragment thereof according to item 1,
- 30 the antibody comprising a HCDR1 set forth in SEQ ID NO: 87, HCDR2 set forth in SEQ ID NO: 88, HCDR3 set forth in SEQ ID NO: 89, LCDR1 set forth in SEQ ID NO: 90, LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set forth in SEQ ID NO: 92, the HCVR amino acid sequence set forth in SEQ ID NO: 29 and the LCVR amino acid sequence set forth in SEQ ID NO: 30.

- 5 6. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 93, HCDR2 set forth in SEQ ID NO: 94, HCDR3 set forth in SEQ ID NO: 95, LCDR1 set forth in SEQ ID NO: 96, LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set forth in SEQ ID NO: 98, the HCVR amino acid sequence set forth in SEQ ID NO: 37 and the LCVR amino acid sequence set forth in SEQ ID NO: 38.
- 10 7. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 99, HCDR2 set forth in SEQ ID NO: 100, HCDR3 set forth in SEQ ID NO: 101, LCDR1 set forth in SEQ ID NO: 102, LCDR2 set forth in SEQ ID NO: 103, and LCDR3 set forth in SEQ ID NO: 104, the HCVR amino acid sequence set forth in SEQ ID NO: 43 and the LCVR amino acid sequence set forth in SEQ ID NO: 44.
- 15 8. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 105, HCDR2 set forth in SEQ ID NO: 106, HCDR3 set forth in SEQ ID NO: 107, LCDR1 set forth in SEQ ID NO: 108, LCDR2 set forth in SEQ ID NO: 109, and LCDR3 set forth in SEQ ID NO: 110, the HCVR amino acid sequence set forth in SEQ ID NO: 53 and the LCVR amino acid sequence set forth in SEQ ID NO: 54.
- 20 9. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 111, HCDR2 set forth in SEQ ID NO: 112, HCDR3 set forth in SEQ ID NO: 113, LCDR1 set forth in SEQ ID NO: 114, LCDR2 set forth in SEQ ID NO: 115, and LCDR3 set forth in SEQ ID NO: 116, the HCVR amino acid sequence set forth in SEQ ID NO: 55 and the LCVR amino acid sequence set forth in SEQ ID NO: 56.
- 25 10. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 117, HCDR2 set forth in SEQ ID NO: 118, HCDR3 set forth in SEQ ID NO: 119, LCDR1 set forth in SEQ ID NO: 120, LCDR2 set forth in SEQ ID NO: 121, and LCDR3 set forth in SEQ ID NO: 122, the HCVR amino acid sequence set forth in SEQ ID NO: 65 and the LCVR amino acid sequence set forth in SEQ ID NO: 66.
- 30
- 35

11. The isolated antibody or antigen-binding fragment thereof according to item 1,
the antibody comprising a HCDR1 set forth in SEQ ID NO: 123, HCDR2 set
forth in SEQ ID NO: 124, HCDR3 set forth in SEQ ID NO: 125, LCDR1 set forth
in SEQ ID NO: 126, LCDR2 set forth in SEQ ID NO: 127, and LCDR3 set forth
in SEQ ID NO: 128, the HCVR amino acid sequence set forth in SEQ ID NO: 67
and the LCVR amino acid sequence set forth in SEQ ID NO: 68.
12. The isolated antibody or antigen-binding fragment thereof according to item 1,
the antibody comprising a HCDR1 set forth in SEQ ID NO: 157, HCDR2 set
forth in SEQ ID NO: 158, HCDR3 set forth in SEQ ID NO: 159, LCDR1 set forth
in SEQ ID NO: 160, LCDR2 set forth in SEQ ID NO: 161, and LCDR3 set forth
in SEQ ID NO: 162, the HCVR amino acid sequence set forth in SEQ ID NO:
129 and the LCVR amino acid sequence set forth in SEQ ID NO: 130.
13. The isolated antibody or antigen-binding fragment thereof according to item 1,
the antibody comprising a HCDR1 set forth in SEQ ID NO: 163, HCDR2 set
forth in SEQ ID NO: 164, HCDR3 set forth in SEQ ID NO: 165, LCDR1 set forth
in SEQ ID NO: 166, LCDR2 set forth in SEQ ID NO: 167, and LCDR3 set forth
in SEQ ID NO: 168, the HCVR amino acid sequence set forth in SEQ ID NO:
131 and the LCVR amino acid sequence set forth in SEQ ID NO: 132.
14. The isolated antibody or antigen-binding fragment thereof according to item 1,
the antibody comprising a HCDR1 set forth in SEQ ID NO: 169, HCDR2 set
forth in SEQ ID NO: 170, HCDR3 set forth in SEQ ID NO: 171, LCDR1 set forth
in SEQ ID NO: 172, LCDR2 set forth in SEQ ID NO: 173, and LCDR3 set forth
in SEQ ID NO: 174, the HCVR amino acid sequence set forth in SEQ ID NO:
133 and the LCVR amino acid sequence set forth in SEQ ID NO: 134.
15. The isolated antibody or antigen-binding fragment thereof according to item 1,
the antibody comprising a HCDR1 set forth in SEQ ID NO: 175, HCDR2 set
forth in SEQ ID NO: 176, HCDR3 set forth in SEQ ID NO: 177, LCDR1 set forth
in SEQ ID NO: 178, LCDR2 set forth in SEQ ID NO: 179, and LCDR3 set forth
in SEQ ID NO: 180, the HCVR amino acid sequence set forth in SEQ ID NO:
135 and the LCVR amino acid sequence set forth in SEQ ID NO: 136.

16. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 181, HCDR2 set forth in SEQ ID NO: 182, HCDR3 set forth in SEQ ID NO: 183, LCDR1 set forth in SEQ ID NO: 184, LCDR2 set forth in SEQ ID NO: 185, and LCDR3 set forth in SEQ ID NO: 186, the HCVR amino acid sequence set forth in SEQ ID NO: 33 and the LCVR amino acid sequence set forth in SEQ ID NO: 34.
17. The isolated antibody or antigen-binding fragment thereof according to item 1, the antibody comprising a HCDR1 set forth in SEQ ID NO: 187, HCDR2 set forth in SEQ ID NO: 188, HCDR3 set forth in SEQ ID NO: 189, LCDR1 set forth in SEQ ID NO: 190, LCDR2 set forth in SEQ ID NO: 191, and LCDR3 set forth in SEQ ID NO: 192, the HCVR amino acid sequence set forth in SEQ ID NO: 137 and the LCVR amino acid sequence set forth in SEQ ID NO: 138.
18. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the isolated antibody or antigen-binding fragment thereof comprises a heavy chain constant sequences as set forth in SEQ ID NO: 140 and/or a light chain constant sequences as set forth in SEQ ID NO: 144.
19. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises one or more amino acid substitutions, amino acid deletions or amino acid insertions.
20. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the HCVR amino acid sequence and/or LCVR amino acid sequence comprises one amino acid substitution, amino acid deletion or amino acid insertion, alternatively two amino acid substitutions, amino acid deletions or amino acid insertions, alternatively three amino acid substitutions, amino acid deletions or amino acid insertions, alternatively four amino acid substitutions, amino acid deletions or amino acid insertions, alternatively five amino acid substitutions, amino acid deletions or amino acid insertions.

21. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the one or more amino acid substitutions, amino acid deletions or amino acid insertions is not comprised in the CDR sequences.
- 5 22. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the isolated antibody or antigen-binding fragment thereof is an antibody.
- 10 23. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items, wherein the isolated antibody or antigen-binding fragment thereof is an antigen-binding fragment thereof.
- 15 24. The isolated antibody or antigen-binding fragment thereof according to any one of the previous items comprising an immunoglobulin constant region.
25. The isolated antibody or antigen-binding fragment thereof according to any of the previous items comprising an immunoglobulin constant region selected from IgG, IgM, IgA, IgD and IgE.
- 20 26. The isolated antibody or antigen-binding fragment thereof according to any of the previous items comprising an immunoglobulin constant region selected from IgG and IgA.
- 25 27. The isolated antibody or antigen-binding fragment thereof according to any of the previous items comprising an immunoglobulin constant region selected from IgG1, IgA1 and IgA2.
- 30 28. The isolated antibody or antigen-binding fragment thereof according to any of the previous items comprising an immunoglobulin constant region selected from IgG1, IgG2, IgG3 and IgG4.
- 35 29. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2.

30. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 10 µg/mL, alternatively between 0.001 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 5 µg/mL, alternatively between 0.01 µg/mL and 4 µg/mL, alternatively between 0.01 µg/mL and 3 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 1 µg/mL.
31. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 1 µg/mL, alternatively 0.001 µg/mL and 1 µg/mL, alternatively 0.01 µg/mL and 1 µg/mL, alternatively between 0.02 µg/mL and 1 µg/mL, alternatively between 0.03 µg/mL and 1 µg/mL, alternatively between 0.04 µg/mL and 1 µg/mL, alternatively between 0.05 µg/mL and 1 µg/mL, alternatively between 0.06 µg/mL and 1 µg/mL, alternatively between 0.07 µg/mL and 1 µg/mL, alternatively between 0.09 µg/mL and 1 µg/mL, alternatively between 0.1 µg/mL and 1 µg/mL.
32. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ below 1 µg/mL.
33. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ below 1 µg/mL, alternatively below 0.9 µg/mL, alternatively below 0.8 µg/mL, alternatively below 0.7 µg/mL, alternatively below 0.6 µg/mL, alternatively below 0.5 µg/mL, alternatively below 0.4 µg/mL, alternatively below 0.3 µg/mL, alternatively below 0.2 µg/mL, alternatively below 0.1 µg/mL, alternatively below 0.01 µg/mL, alternatively below 0.001 µg/mL, alternatively below 0.0001 µg/mL.

34. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ below 0.1 µg/mL.
- 5 35. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-2 with an IC₅₀ between 0.0001 µg/mL and 0.1 µg/mL, alternatively 0.001 µg/mL and 0.1 µg/mL, alternatively 0.01 µg/mL and 0.1 µg/mL, alternatively between 0.02 µg/mL and 0.1 µg/mL, alternatively between 10 0.03 µg/mL and 0.1 µg/mL, alternatively between 0.04 µg/mL and 0.1 µg/mL, alternatively between 0.05 µg/mL and 0.1 µg/mL, alternatively between 0.06 µg/mL and 0.1 µg/mL, alternatively between 0.07 µg/mL and 0.1 µg/mL, alternatively between 0.09 µg/mL and 0.1 µg/mL.
- 15 36. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof blocks interaction between Angiotensin-converting enzyme 2 (ACE2) and SARS- CoV-2 Spike protein.
- 20 37. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof blocks interaction between ACE2 and SARS- CoV-2 Spike protein receptor binding domain (RBD).
- 25 38. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant.
- 30 39. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.
- 35 40. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof

binds to at least two SARS-CoV-2 variant selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.

- 5 41. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least three SARS-CoV-2 variant selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.
- 10 42. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least four SARS-CoV-2 variant selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.
- 15 43. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to all five SARS-CoV-2 variant selected from the group consisting of Alpha strains, Beta strains, Gamma strains, Delta strains and Omicron strains.
- 20 44. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from an Alpha strain.
- 25 45. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Beta strain.
- 30 46. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Gamma strain.
- 35 47. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from a Delta strain.

48. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to at least one SARS-CoV-2 variant from an Omicron strain.

5 49. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof binds to a plurality of SARS-CoV-2 variants selected from the group consisting of:

- 10 i) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain, or
- ii) at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Gamma strain, or
- iii) at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Delta strain, or
- 15 iv) at least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from an Omicron strain, or
- v) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain, or
- 20 vi) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Delta strain, or
- vii) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from an Omicron strain, or
- 25 viii) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain, or
- 30 ix) At least one SARS-CoV-2 variant from an Alpha strain and at least one SARS-CoV-2 variant from a Beta strain and at least one SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-2 variant from a Delta strain and at least one SARS-CoV-2 variant from an Omicron strain, or

- 5 x) at least one SARS-CoV-2 variant from a Beta strain and at least one
 SARS-CoV-2 variant from a Gamma strain, or
- xi) at least one SARS-CoV-2 variant from a Beta strain and at least one
 SARS-CoV-2 variant from a Delta strain, or
- xii) at least one SARS-CoV-2 variant from a Beta strain and at least one
 SARS-CoV-2 variant from an Omicron strain, or
- xiii) At least one SARS-CoV-2 variant from a Beta strain and at least one
 SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-
 2 variant from a Delta strain, or
- 10 xiv) At least one SARS-CoV-2 variant from a Beta strain and at least one
 SARS-CoV-2 variant from a Gamma strain and at least one SARS-CoV-
 2 variant from a Delta strain and at least one SARS-CoV-2 variant from
 an Omicron strain, or
- xv) at least one SARS-CoV-2 variant from a Gamma strain and at least one
15 SARS-CoV-2 variant from a Delta strain, or
- xvi) at least one SARS-CoV-2 variant from a Gamma strain and at least one
 SARS-CoV-2 variant from an Omicron strain, or
- xvii) at least one SARS-CoV-2 variant from a Gamma strain and at least one
 SARS-CoV-2 variant from a Delta strain and at least one SARS-CoV-2
20 variant from an Omicron strain, or
- xviii) at least one SARS-CoV-2 variant from a Delta strain and at least one
 SARS-CoV-2 variant from an Omicron strain.
50. The isolated antibody or antigen-binding fragment thereof according to any of
25 the previous items, wherein said antibody or antigen-binding fragment thereof
 further binds to SARS-CoV-1.
51. The isolated antibody or antigen-binding fragment thereof according to any of
 the previous items, wherein said antibody or antigen-binding fragment thereof
30 further neutralizes SARS-CoV-1.
52. The isolated antibody or antigen-binding fragment thereof according to any of
 the previous items, wherein said antibody or antigen-binding fragment thereof
 has dual SARS-CoV-1 and SARS- CoV-2 neutralization.
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53. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between 0.01 µg/mL and 10 µg/mL, alternatively between 0.01 µg/mL and 5 µg/mL, alternatively between 0.01 µg/mL and 4 µg/mL, alternatively between 0.01 µg/mL and 3 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 2 µg/mL, alternatively between 0.01 µg/mL and 1 µg/mL.
54. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between 0.0001 µg/mL and 1 µg/mL, alternatively 0.001 µg/mL and 1 µg/mL, alternatively 0.01 µg/mL and 1 µg/mL, alternatively between 0.02 µg/mL and 1 µg/mL, alternatively between 0.03 µg/mL and 1 µg/mL, alternatively between 0.04 µg/mL and 1 µg/mL, alternatively between 0.05 µg/mL and 1 µg/mL, alternatively between 0.06 µg/mL and 1 µg/mL, alternatively between 0.07 µg/mL and 1 µg/mL, alternatively between 0.09 µg/mL and 1 µg/mL, alternatively between 0.1 µg/mL and 1 µg/mL.
55. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ below 1 µg/mL.
56. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ below 1 µg/mL, alternatively below 0.9 µg/mL, alternatively below 0.8 µg/mL, alternatively below 0.7 µg/mL, alternatively below 0.6 µg/mL, alternatively below 0.5 µg/mL, alternatively below 0.4 µg/mL, alternatively below 0.3 µg/mL, alternatively below 0.2 µg/mL, alternatively below 0.1 µg/mL.
57. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ below 0.1 µg/mL.

58. The isolated antibody or antigen-binding fragment thereof according to any of the previous items, wherein said antibody or antigen-binding fragment thereof neutralizes SARS-CoV-1 with an IC₅₀ between 0.0001 µg/mL and 0.1 µg/mL, alternatively 0.001 µg/mL and 0.1 µg/mL, alternatively 0.01 µg/mL and 0.1 µg/mL, alternatively between 0.02 µg/mL and 0.1 µg/mL, alternatively between 0.03 µg/mL and 0.1 µg/mL, alternatively between 0.04 µg/mL and 0.1 µg/mL, alternatively between 0.05 µg/mL and 0.1 µg/mL, alternatively between 0.06 µg/mL and 0.1 µg/mL, alternatively between 0.07 µg/mL and 0.1 µg/mL, alternatively between 0.09 µg/mL and 0.1 µg/mL.
59. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof according to any of items 1-58.
60. The pharmaceutical composition according to item 59 further comprising a pharmaceutically acceptable carrier or diluent.
61. A method of treating, alleviating or preventing a corona virus infection by administering the isolated antibody or antigen-binding fragment thereof according to any of items 1-58 or the pharmaceutical composition according to any of items 59-60 to a subject.
62. An isolated antibody or antigen-binding fragment thereof according to any of items 1-58 or the pharmaceutical composition according to any of items 59-60 for use in the treatment, alleviation or prevention of a corona virus infection.
63. A method of diagnosing a corona virus infection by detecting and/or measuring the presence of SARS-CoV-2 and/or SARS-CoV-1 in a sample using the isolated antibody or antigen-binding fragment thereof according to any of items 1-58.
64. The method according to claim 63, wherein the sample is obtained from a subject, such as a human, having a corona virus infection.
65. An isolated antibody or antigen-binding fragment thereof according to any of items 1-58 for use in a method of diagnosis of a corona virus infection.

66. The method or the isolated antibody or antigen-binding fragment thereof for use according to any of items 61-65, wherein the corona virus infection is caused by SARS-CoV-2 and/or SARS-CoV-1.
- 5
67. A diagnostic kit comprising the isolated antibody or antigen-binding fragment thereof according to any of items 1-58.
68. The diagnostic kit according to item 67, wherein the isolated antibody or antigen-binding fragment thereof is labeled with a detectable label or reporter molecule.
- 10
69. The diagnostic kit according to any of items 67-68, wherein the diagnostic kit further comprises a secondary antibody which is labeled with a detectable label or reporter molecule.
- 15
70. The diagnostic kit according to any of items 68-69, wherein the detectable label or reporter molecule is a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I .
71. The diagnostic kit according to any of items 68-69, wherein the detectable label or reporter molecule is a fluorescent moiety or chemiluminescent moiety, such as fluorescein isothiocyanate or rhodamine.
- 20
72. The diagnostic kit according to any of items 68-69, wherein the detectable label or reporter molecule is an enzyme such as alkaline phosphatase, β -galactosidase, horseradish peroxidase, or luciferase.
- 25
73. A method for detecting the presence of spike protein in a sample comprising contacting the sample with an isolated antibody or antigen-binding fragment thereof according to any of items 1-58 and detecting the presence of a complex between SARS-CoV-2 and/or SARS-CoV-1 and the antibody or antigen-binding fragment thereof, wherein the presence of the complex indicates the presence of SARS-CoV-2 and/or SARS-CoV-1.
- 30

74. A kit of parts comprising the isolated antibody or antigen-binding fragment thereof according to any of items 1-58 and instructions for use.
- 5 75. A polynucleotide encoding an isolated antibody or antigen-binding fragment thereof according to any of items 1-58.
76. The polynucleotide according to item 75, wherein said polynucleotide encodes the following elements:
- 10 i) A leader signal,
- ii) A heavy chain variable region (HCVR) sequence,
- iii) A constant heavy chain sequence,
- iv) A furin cleavage site,
- v) A 2A peptide sequence,
- vi) A leader signal,
- 15 vii) A light chain variable region (LCVR) sequence, and
- viii) A constant light chain sequence,
- optionally wherein said elements are arranged in the order from i) to viii).
77. A vector comprising the polynucleotide according to any of items 75-76.
- 20 78. The vector according to item 77, wherein said vector is an adeno-associated virus (AAV) vector.
79. The vector according to any of items 77-78, wherein said vector is a
- 25 recombinant vector.
80. The vector according to any of items 77-79, wherein said vector comprises inverted terminal repeats (ITRs).
- 30 81. The vector according to any of items 77-80, wherein said vector comprises a promoter selected from the group consisting of a CAG promoter, an UBC promoter and a MH promoter.
82. The vector according to any of items 77-80, wherein said vector comprises an
- 35 EF-1 α promoter.

83. The vector according to any of items 77-82, wherein said vector comprises:

- i) A left ITR,
- ii) An EF-1 α promoter,
- 5 iii) A polynucleotide according to any of items 75-76, and
- iv) A right ITR.

84. The vector according to any of items 77-83, wherein said vector comprises an origin of replication (ori) and/or a multicloning site, and/or a selectable marker.

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85. The vector according to any of items 77-84, wherein said vector comprises:

- i) A left ITR,
 - ii) An EF-1 α promoter,
 - iii) A T7 promoter,
 - 15 iv) The polynucleotide according to any of items 75-76,
 - v) A poly(A) signal,
 - vi) A right ITR,
 - vii) A F1 ori,
 - viii) An AmpR promoter,
 - 20 ix) An AmpR, and
 - x) An ori,
- optionally wherein said elements are arranged in the order from i) to viii).

86. Use of the vector according to any of items 77-85 for gene delivery of said anti-SARS-CoV-2 antibody to a subject in need thereof.

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87. Use of the vector according to any of items 77-85 for gene therapy.

88. A method of treating, alleviating or preventing coronavirus diseases, such as COVID-19 infections, by administering the vector according to any of items 77-85 to a subject in need thereof.

30

89. A vector according to any of items 77-85 for use in gene therapy.

90. A vector according to any of items 77-85 for use in the treatment, alleviation or prevention of coronavirus disease, such as COVID-19 infections.
- 5 91. The use, the method or the vector for use according to any of items 86-90, wherein the vector is delivered or administered to a subject having a coronavirus disease, such as a COVID-19 infection.
- 10 92. The use, the method or the vector for use according to any of items 86-91, wherein the subject is an immunocompromised subject, such as a moderately or severely immunocompromised subject.
- 15 93. The use, the method or the vector for use according to any of items 86-92, wherein the subject is an immunocompromised subject, such as a moderately or severely immunocompromised subject, selected from the group consisting of:
- 15 i) Subjects receiving active cancer treatment for tumors or cancers of the blood,
 - ii) Subjects having received an organ transplant and taking medicine to suppress the immune system,
 - 20 iii) Subjects having received a stem cell transplant within the last 2 years and/or subjects having received a stem cell transplant and taking medicine to suppress the immune system,
 - iv) Subjects having a severe autoimmune disease, such as lupus, rheumatoid arthritis, Crohn's disease and ulcerative colitis,
 - v) Subjects receiving B cell depletion therapy,
 - 25 vi) Subjects with moderate or severe primary immunodeficiency, such as DiGeorge syndrome or Wiskott-Aldrich syndrome, and/or
 - vii) Subjects receiving active treatment with high-dose corticosteroids or other immunosuppressive drugs.
- 30 94. The use, the method or the vector for use according to any of items 86-93, wherein the subjects receiving B cell depletion therapy is selected from the group consisting of:
- i) Patients receiving B cell antigen-targeting monoclonal antibodies to treat an underlying condition, such as for instance Rituximab, and/or

- ii) Patients receiving immunosuppressive treatment in relation to solid organ transplantation, and/or
- iii) Patients with primary antibody deficiencies such as agammaglobulemia and Common Variable Immunodeficiency (CVID).

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95. The use, the method or the vector for use according to item 94, wherein the underlying condition is selected from the group consisting of

- i) Malignancies, such as follicular lymphoma, diffuse large B cell lymphoma or chronic lymphocytic leukemia, and/or

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- ii) Autoimmune diseases, such as rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris.

96. A pharmaceutical composition comprising the vector according to any of items 77-85.

15

97. A kit of parts comprising the vector according to any of items 77-85 and instructions for use.

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Claims

1. An isolated antibody or antigen-binding fragment thereof capable of binding a
5 SARS-CoV-2 spike protein, wherein said isolated antibody or antigen-binding
fragment thereof binds to at least one SARS-CoV-2 variant from an Omicron strain.
2. The isolated antibody or antigen-binding fragment thereof according to claim 1,
wherein said isolated antibody or antigen-binding fragment thereof blocks
10 interaction between Angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2
Spike protein from an Omicron strain.
3. The isolated antibody or antigen-binding fragment thereof according to any of the
preceding claims wherein said isolated antibody or antigen-binding fragment
15 thereof neutralizes at least one SARS-CoV-2 variant from an Omicron strain.
4. The isolated antibody or antigen-binding fragment thereof according to any of the
preceding claims selected from the group consisting of:
 - i) An antibody comprising a HCDR1 set forth in SEQ ID NO: 157, HCDR2 set
20 forth in SEQ ID NO: 158, HCDR3 set forth in SEQ ID NO: 159, LCDR1 set
forth in SEQ ID NO: 160, LCDR2 set forth in SEQ ID NO: 161, and LCDR3
set forth in SEQ ID NO: 162, or
 - ii) An antibody comprising a HCDR1 set forth in SEQ ID NO: 87, HCDR2 set
25 forth in SEQ ID NO: 88, HCDR3 set forth in SEQ ID NO: 89, LCDR1 set
forth in SEQ ID NO: 90, LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set
forth in SEQ ID NO: 92, or
 - iii) The antibody comprising a HCDR1 set forth in SEQ ID NO: 93, HCDR2 set
30 forth in SEQ ID NO: 94, HCDR3 set forth in SEQ ID NO: 95, LCDR1 set
forth in SEQ ID NO: 96, LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set
forth in SEQ ID NO: 98.
5. The isolated antibody or antigen-binding fragment thereof according to any of the
preceding claims selected from the group consisting of:
 - i) An isolated antibody or antigen-binding fragment thereof comprises a
35 HCDR1 set forth in SEQ ID NO: 157, HCDR2 set forth in SEQ ID NO: 158,
HCDR3 set forth in SEQ ID NO: 159, LCDR1 set forth in SEQ ID NO: 160,

- LCDR2 set forth in SEQ ID NO: 161, and LCDR3 set forth in SEQ ID NO: 162, the HCVR amino acid sequence set forth in SEQ ID NO: 129 and the LCVR amino acid sequence set forth in SEQ ID NO: 130, or
- 5 ii) An isolated antibody or antigen-binding fragment thereof comprises a
HCDR1 set forth in SEQ ID NO: 87, HCDR2 set forth in SEQ ID NO: 88,
HCDR3 set forth in SEQ ID NO: 89, LCDR1 set forth in SEQ ID NO: 90,
LCDR2 set forth in SEQ ID NO: 91, and LCDR3 set forth in SEQ ID NO: 92,
the HCVR amino acid sequence set forth in SEQ ID NO: 29 and the LCVR
amino acid sequence set forth in SEQ ID NO: 30, or
- 10 iii) An isolated antibody or antigen-binding fragment thereof comprises a
HCDR1 set forth in SEQ ID NO: 93, HCDR2 set forth in SEQ ID NO: 94,
HCDR3 set forth in SEQ ID NO: 95, LCDR1 set forth in SEQ ID NO: 96,
LCDR2 set forth in SEQ ID NO: 97, and LCDR3 set forth in SEQ ID NO: 98,
the HCVR amino acid sequence set forth in SEQ ID NO: 37 and the LCVR
15 amino acid sequence set forth in SEQ ID NO: 38.
6. The isolated antibody or antigen-binding fragment thereof according to any of the
preceding claims, wherein the isolated antibody or antigen-binding fragment thereof
comprises a heavy chain constant sequences as set forth in SEQ ID NO: 140
20 and/or a light chain constant sequences as set forth in SEQ ID NO: 144.
7. The isolated antibody or antigen-binding fragment thereof according to any of the
preceding claims, wherein the HCVR amino acid sequence and/or LCVR amino
acid sequence comprises one amino acid substitution, amino acid deletion or
25 amino acid insertion, alternatively two amino acid substitutions, amino acid
deletions or amino acid insertions, alternatively three amino acid substitutions,
amino acid deletions or amino acid insertions, alternatively four amino acid
substitutions, amino acid deletions or amino acid insertions, alternatively five amino
acid substitutions, amino acid deletions or amino acid insertions.
30
8. The isolated antibody or antigen-binding fragment thereof according to claim 7,
wherein the one or more amino acid substitutions, amino acid deletions or amino
acid insertions is not comprised in the CDR sequence.

9. The isolated antibody or antigen-binding fragment thereof according to any of the preceding claims, wherein the isolated antibody or antigen-binding fragment thereof is an antibody.
- 5 10. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof according to any of claims 1-9 and further comprising a pharmaceutically acceptable carrier or diluent.
- 10 11. An isolated antibody or antigen-binding fragment thereof according to any of claims 1-9 or the pharmaceutical composition according to claim 10 for use in the treatment, alleviation or prevention of a corona virus infection.
- 15 12. A method of diagnosing a corona virus infection by detecting and/or measuring the presence of SARS-CoV-2 and/or SARS-CoV-1 in a sample using the isolated antibody or antigen-binding fragment thereof according to any of claims 1-9.
- 20 13. A polynucleotide encoding an isolated antibody or antigen-binding fragment thereof according to any of claims 1-9.
- 25 14. A vector comprising the polynucleotide according to claim 13, wherein said vector is an adeno-associated virus (AAV) vector.
- 30 15. A vector according to claim 14 for use in gene therapy, such as for use in the treatment, alleviation or prevention of coronavirus disease.
- 35 16. A vector according to claim 14 for use in the treatment, alleviation or prevention of coronavirus disease, such as COVID-19 infections.
17. The vector for use according to any of claims 15-16, wherein the vector is delivered or administered to a subject having a coronavirus disease, such as a COVID-19 infection.
18. The vector for use according to claim 17, wherein the subject is an immunocompromised subject, such as a moderately or severely immunocompromised subject.

19. The vector for use according to any of claims 17-18, wherein the subject is an immunocompromised subject, such as a moderately or severely immunocompromised subject, selected from the group consisting of:

- 5 i) Subjects receiving active cancer treatment for tumors or cancers of the blood,
- ii) Subjects having received an organ transplant and taking medicine to suppress the immune system,
- iii) Subjects having received a stem cell transplant within the last 2 years
10 and/or subjects having received a stem cell transplant and taking medicine to suppress the immune system,
- iv) Subjects having a severe autoimmune disease, such as lupus, rheumatoid arthritis, Crohn's disease and ulcerative colitis,
- v) Subjects receiving B cell depletion therapy,
- 15 vi) Subjects with moderate or severe primary immunodeficiency, such as DiGeorge syndrome or Wiskott-Aldrich syndrome, and/or
- vii) Subjects receiving active treatment with high-dose corticosteroids or other immunosuppressive drugs.

20 20. The vector for use according to any of claims 17-19, wherein the subjects receiving B cell depletion therapy is selected from the group consisting of:

- i) Patients receiving B cell antigen-targeting monoclonal antibodies to treat an underlying condition, such as for instance Rituximab, and/or
- ii) Patients receiving immunosuppressive treatment in relation to solid organ
25 transplantation, and/or
- iii) Patients with primary antibody deficiencies such as agammaglobulemia and Common Variable Immunodeficiency (CVID).

21. The vector for use according to claim 20, wherein the underlying condition is
30 selected from the group consisting of

- i) Malignancies, such as follicular lymphoma, diffuse large B cell lymphoma or chronic lymphocytic leukemia, and/or
- ii) Autoimmune diseases, such as rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris.

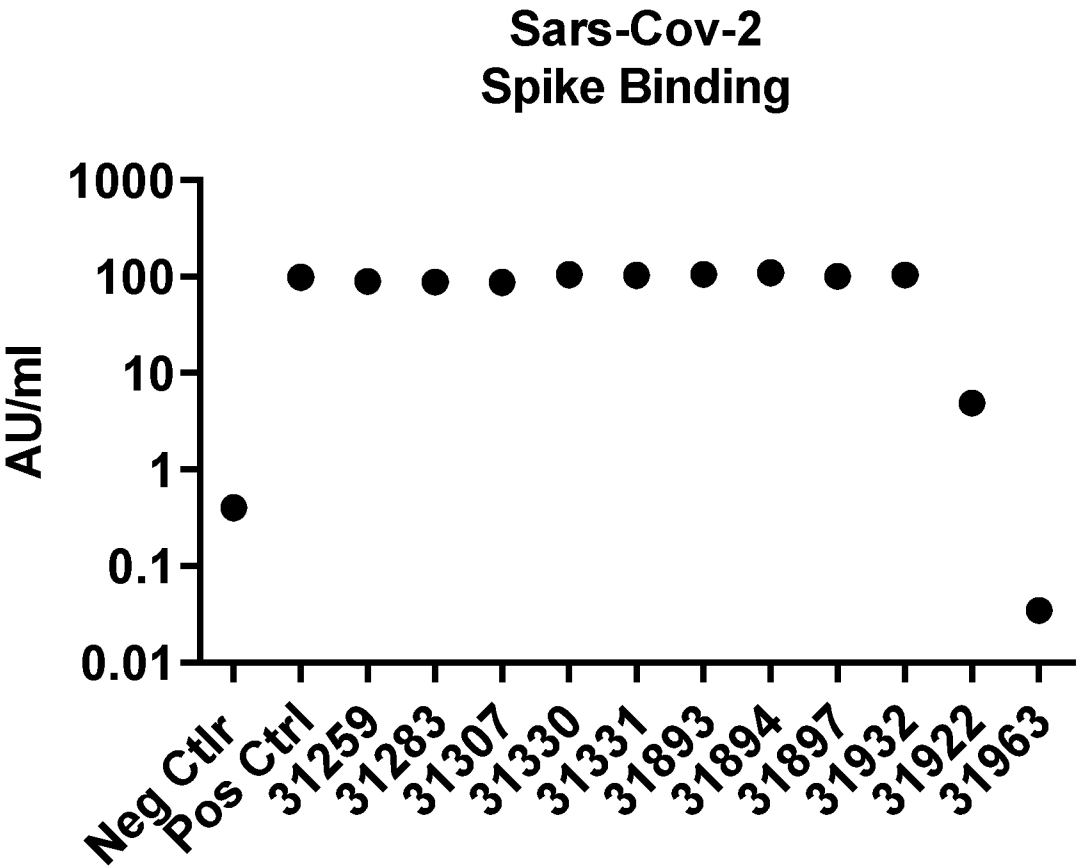


Fig. 1A

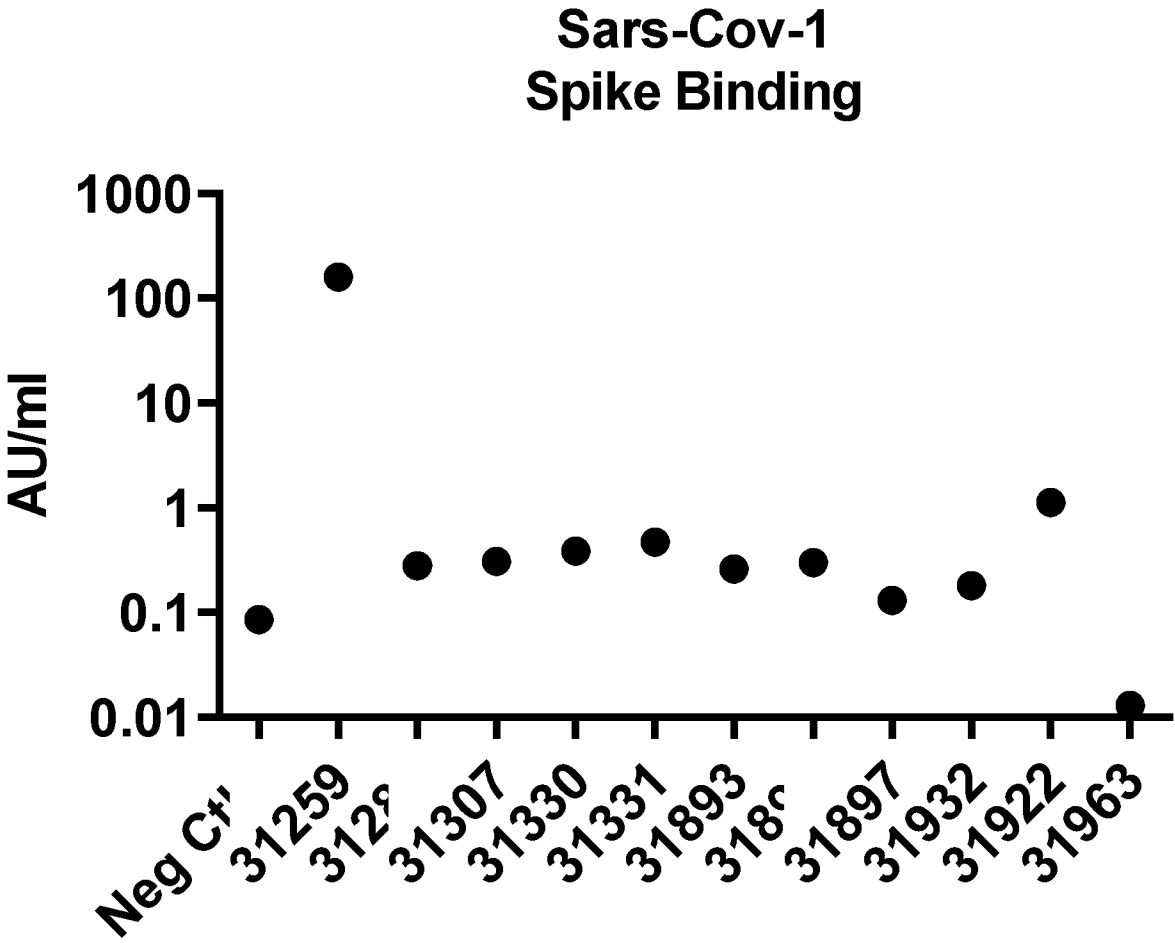


Fig. 1B

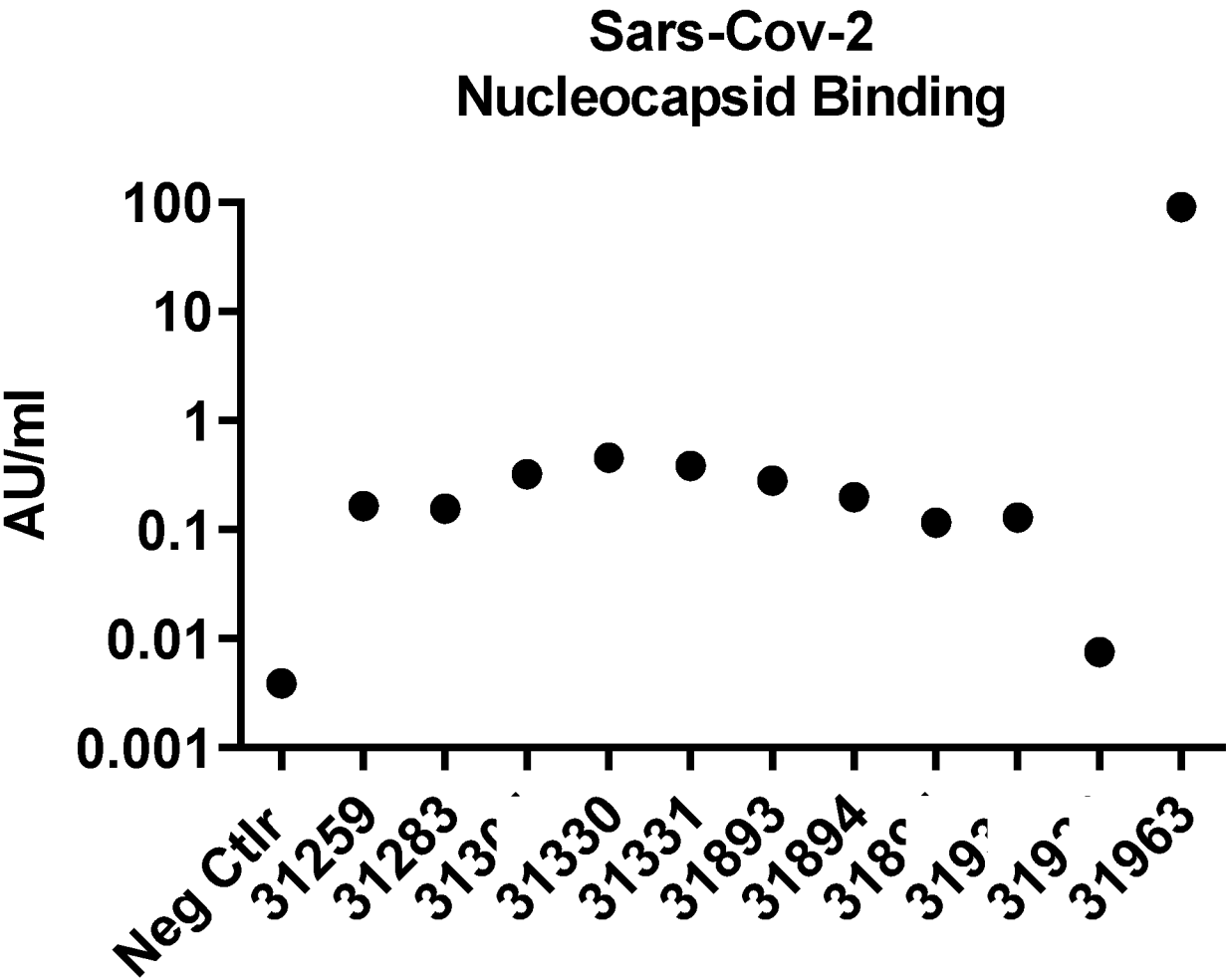


Fig. 1C

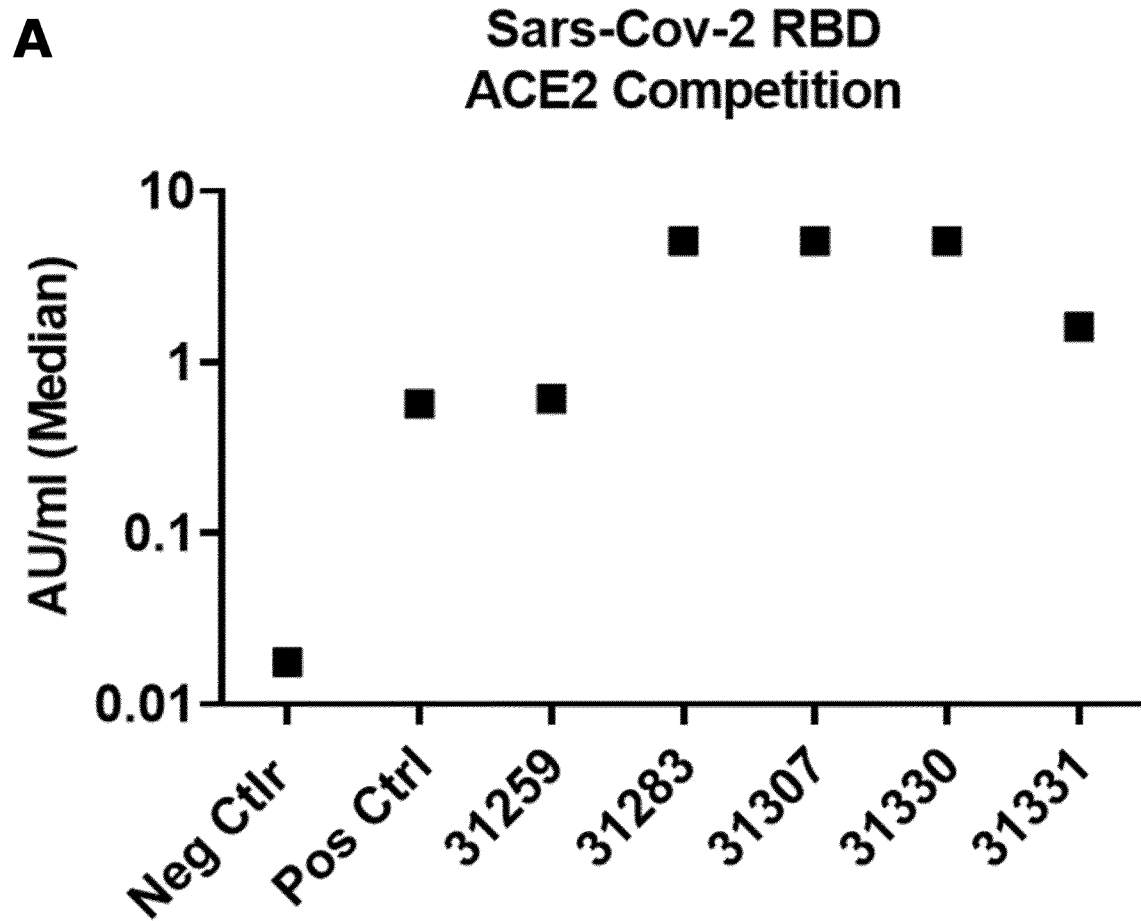


Fig. 2A

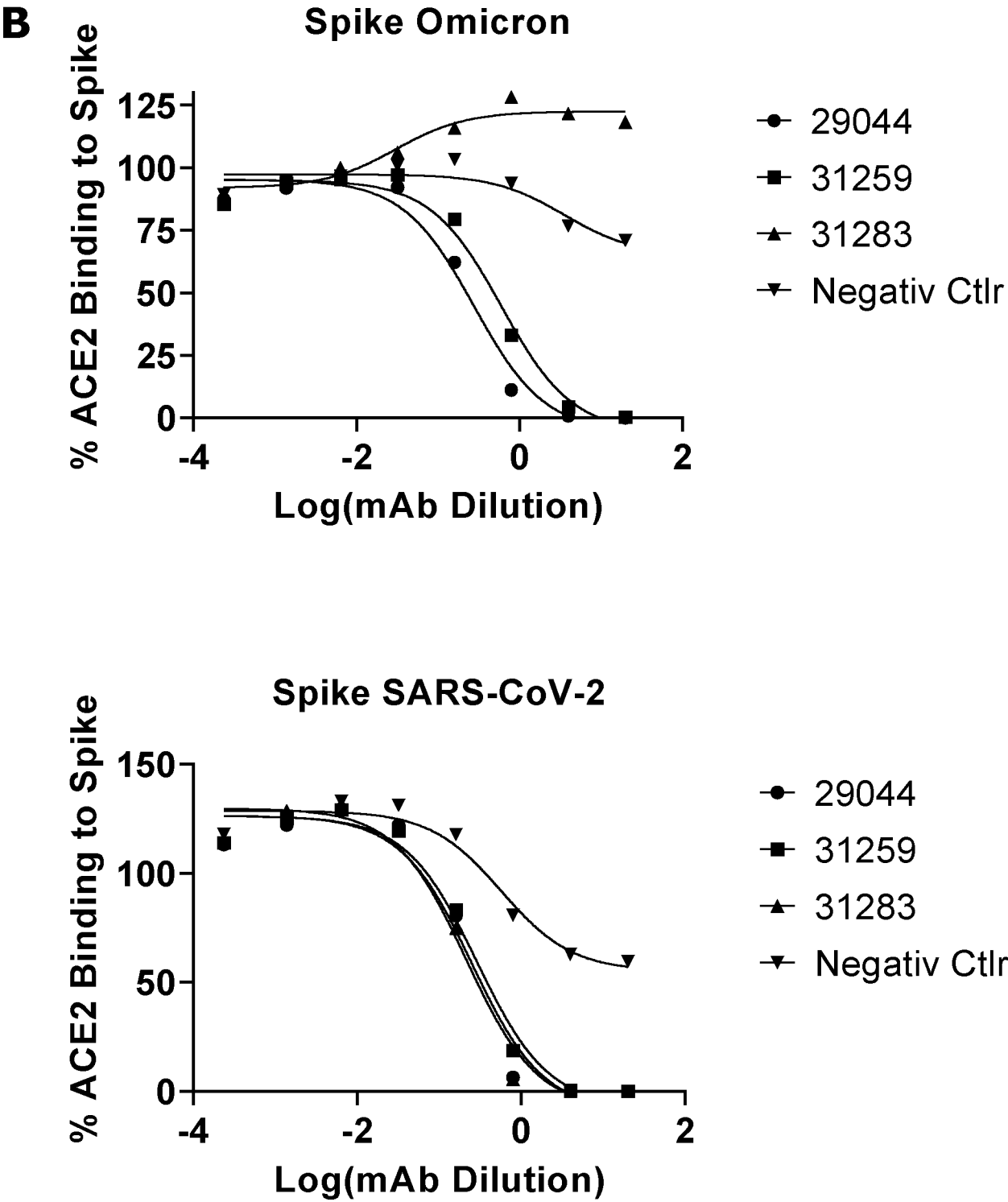


Fig. 2B

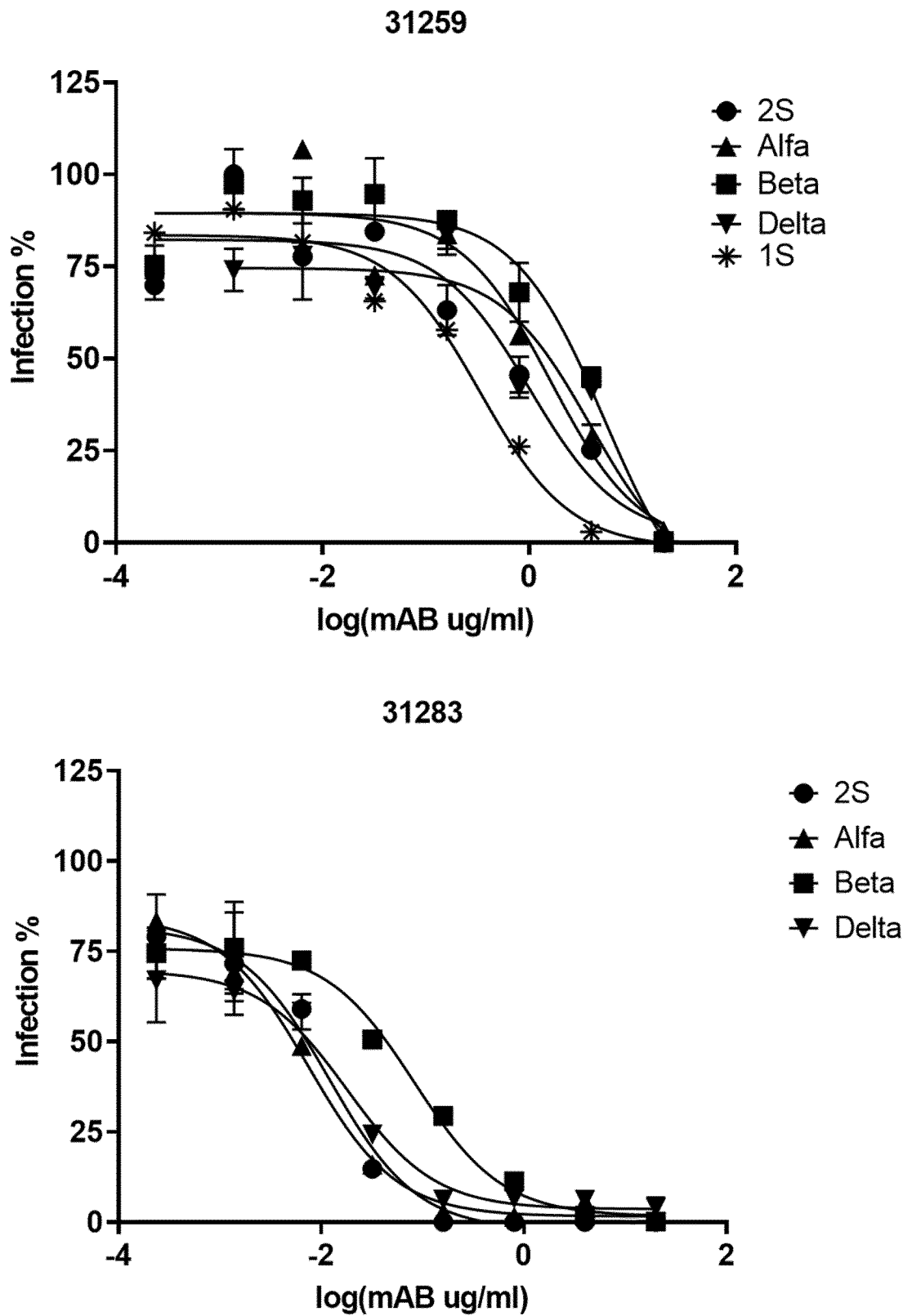


Fig. 3A

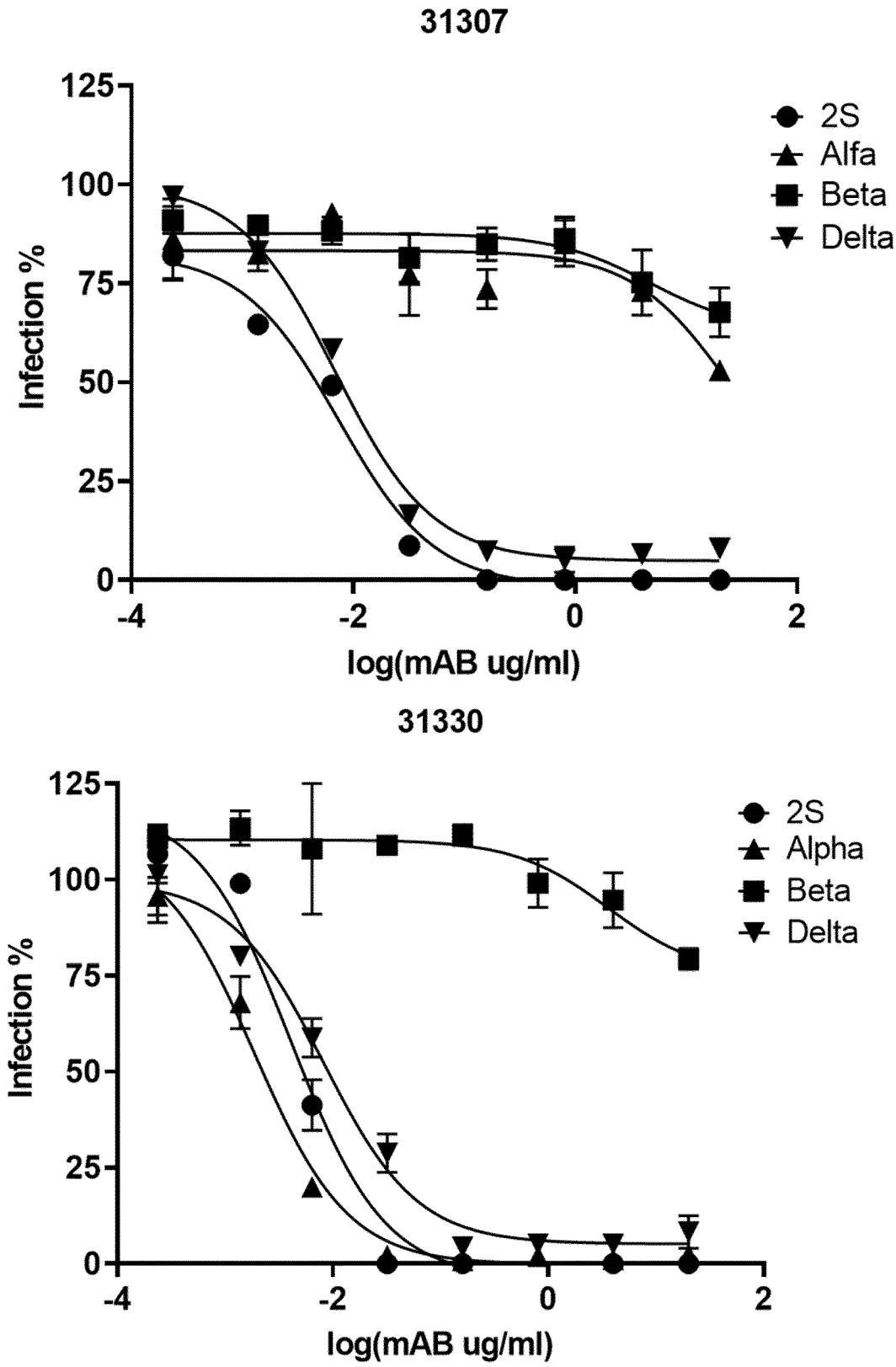


Fig. 3B

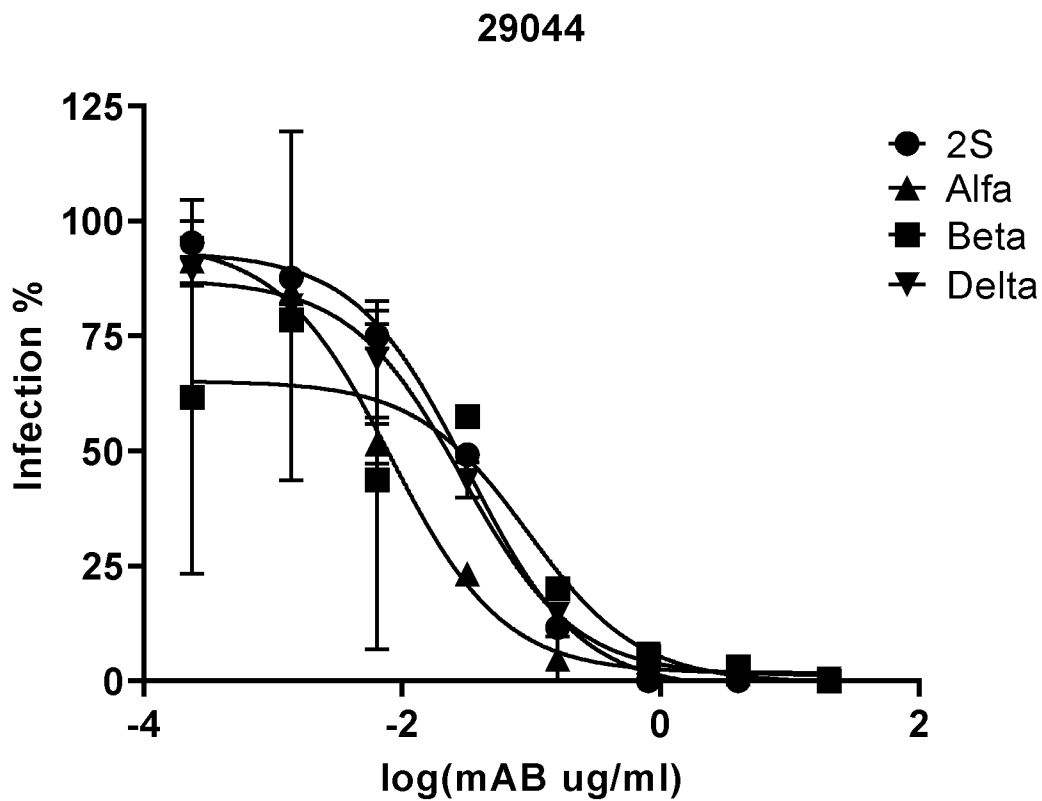
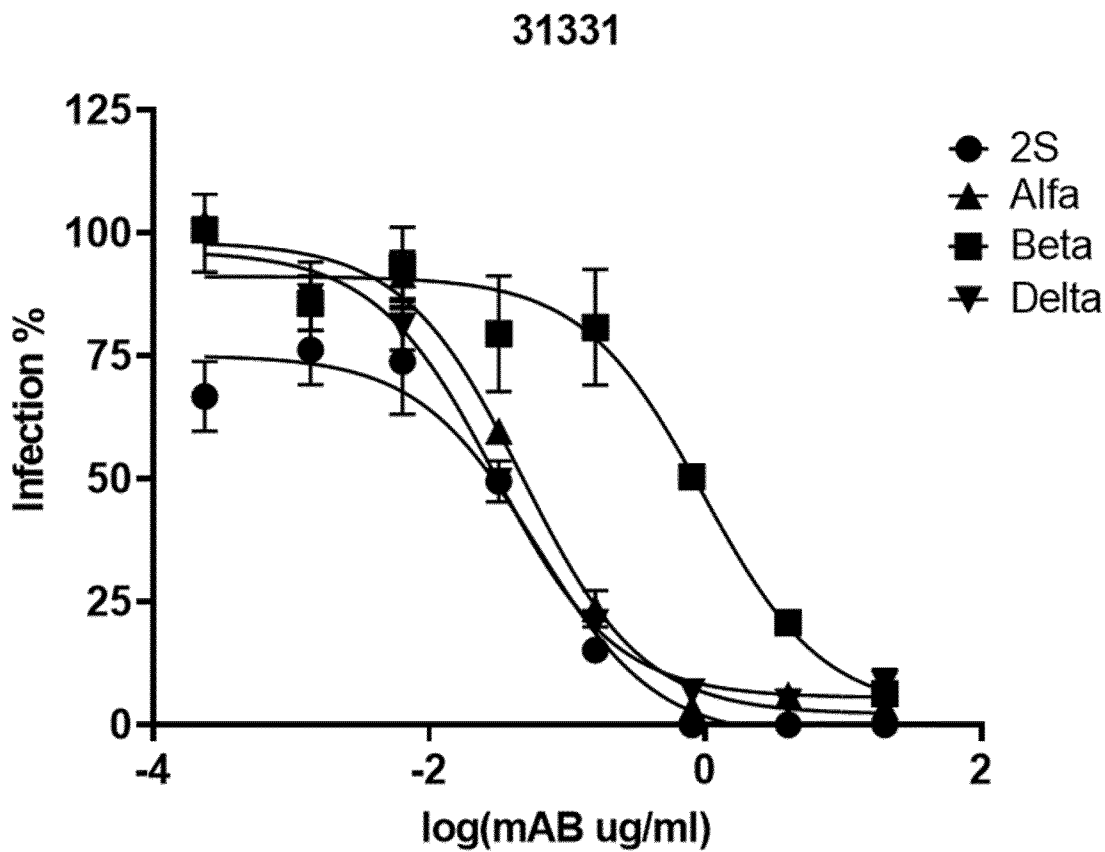


Fig. 3C

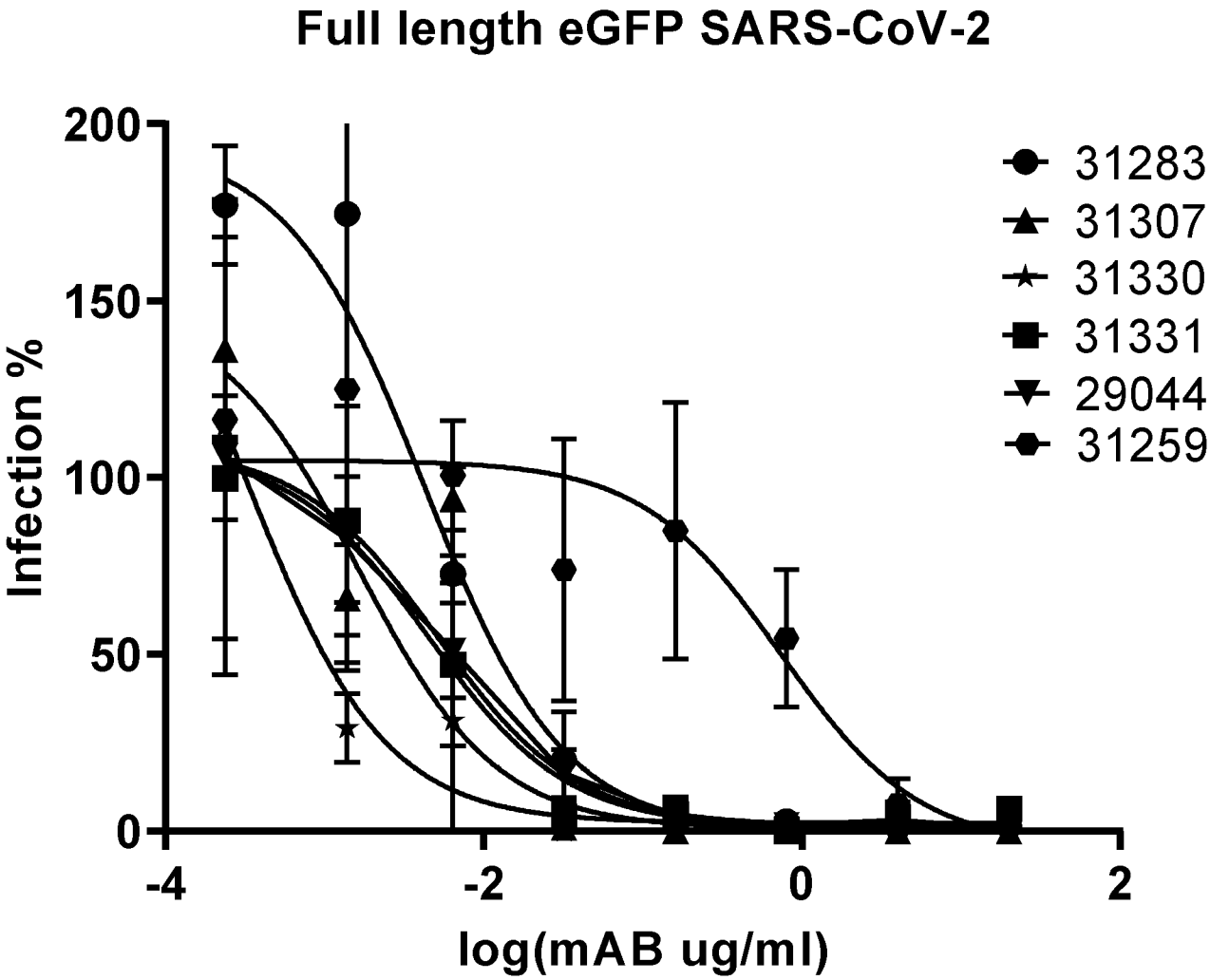


Fig. 4

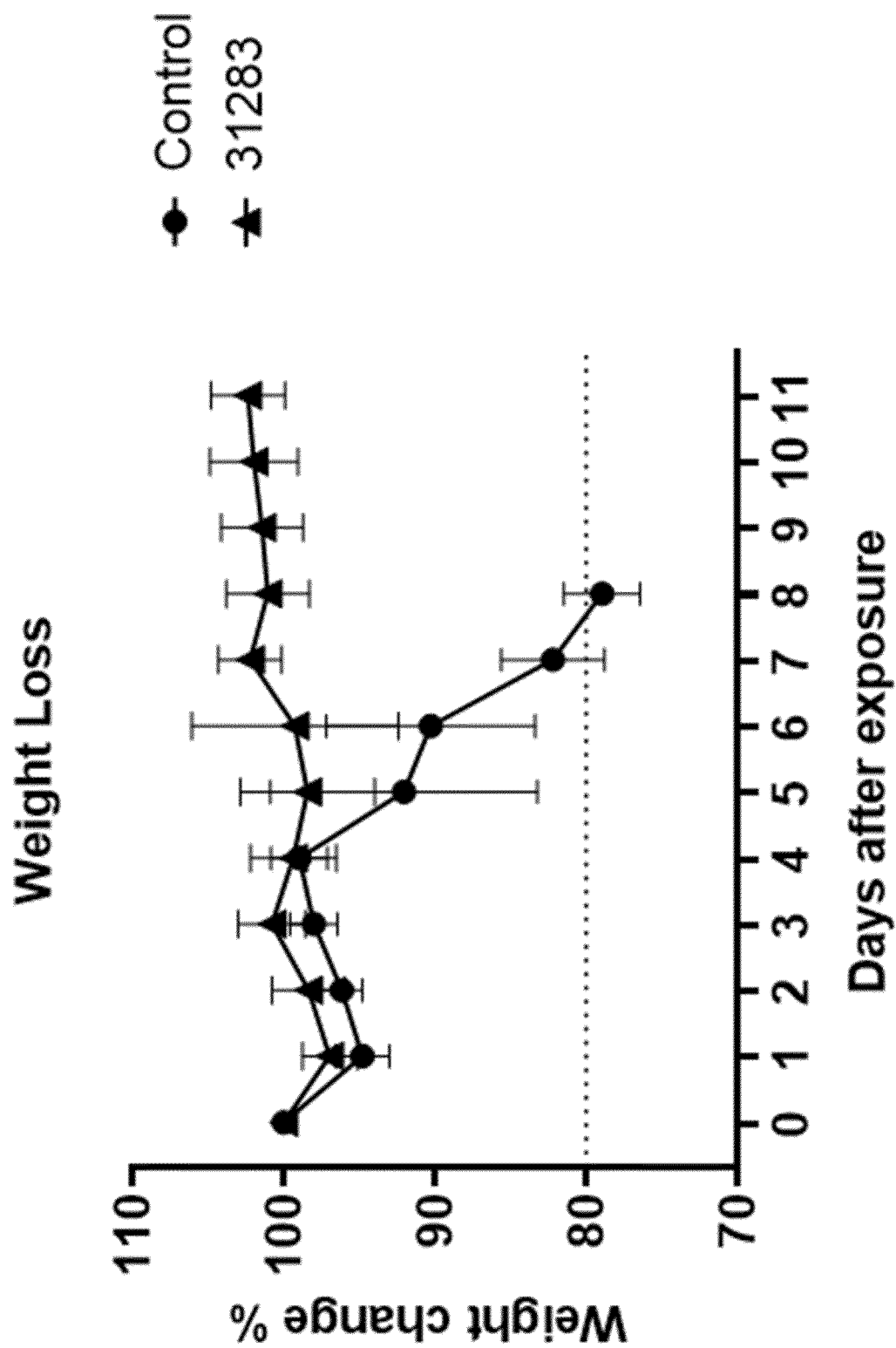


Fig. 5A

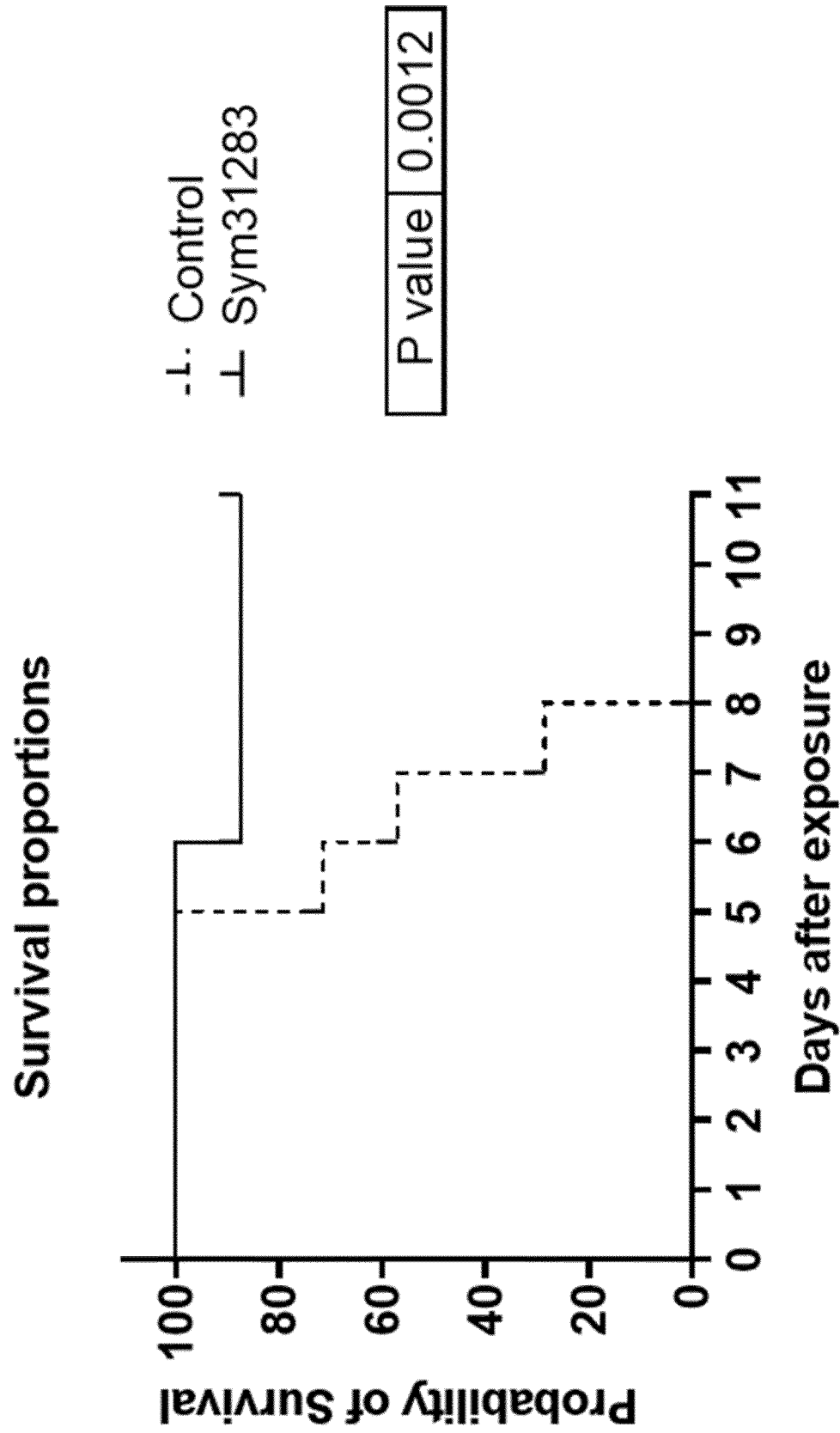


Fig. 5B

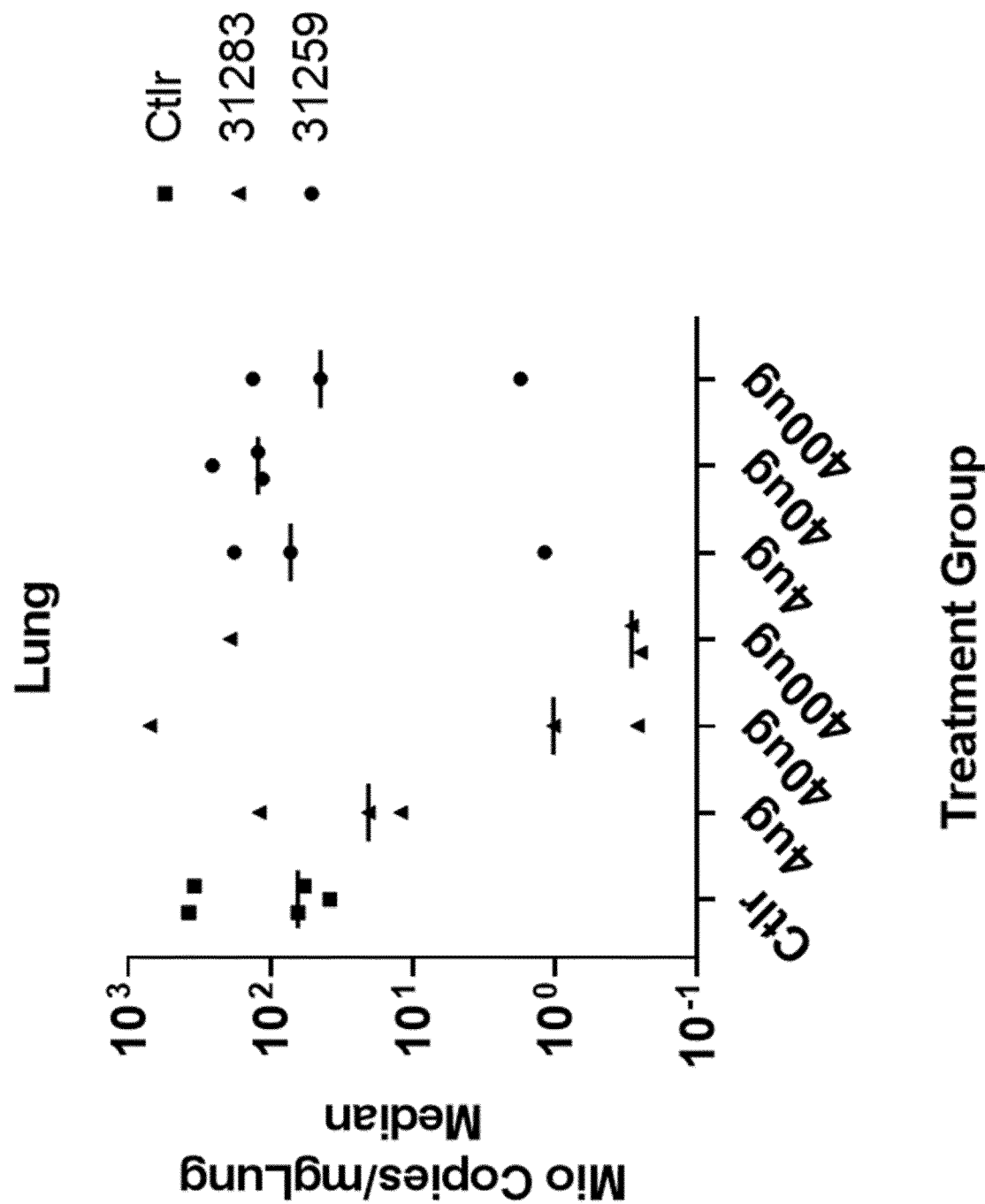


Fig. 6

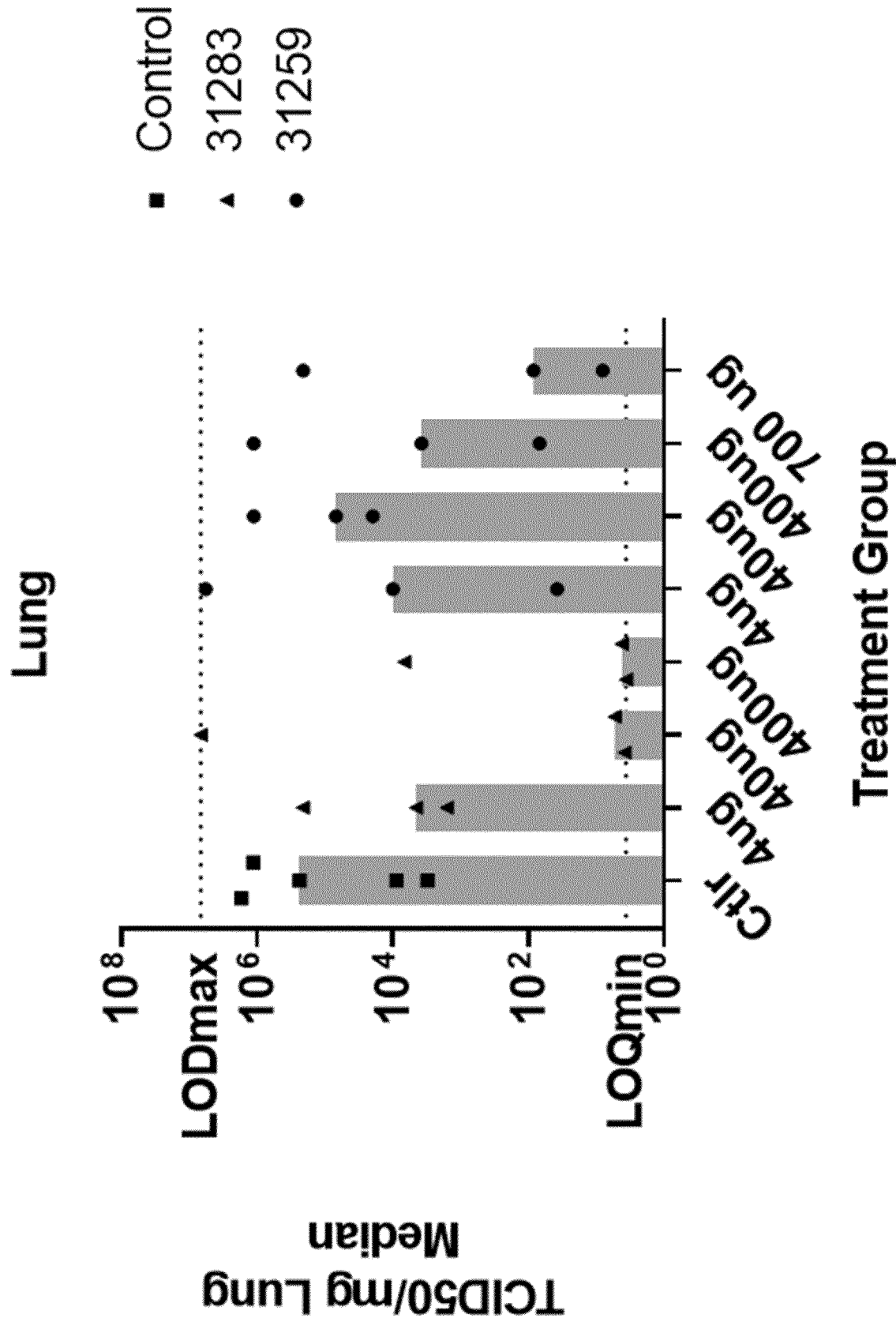


Fig. 7

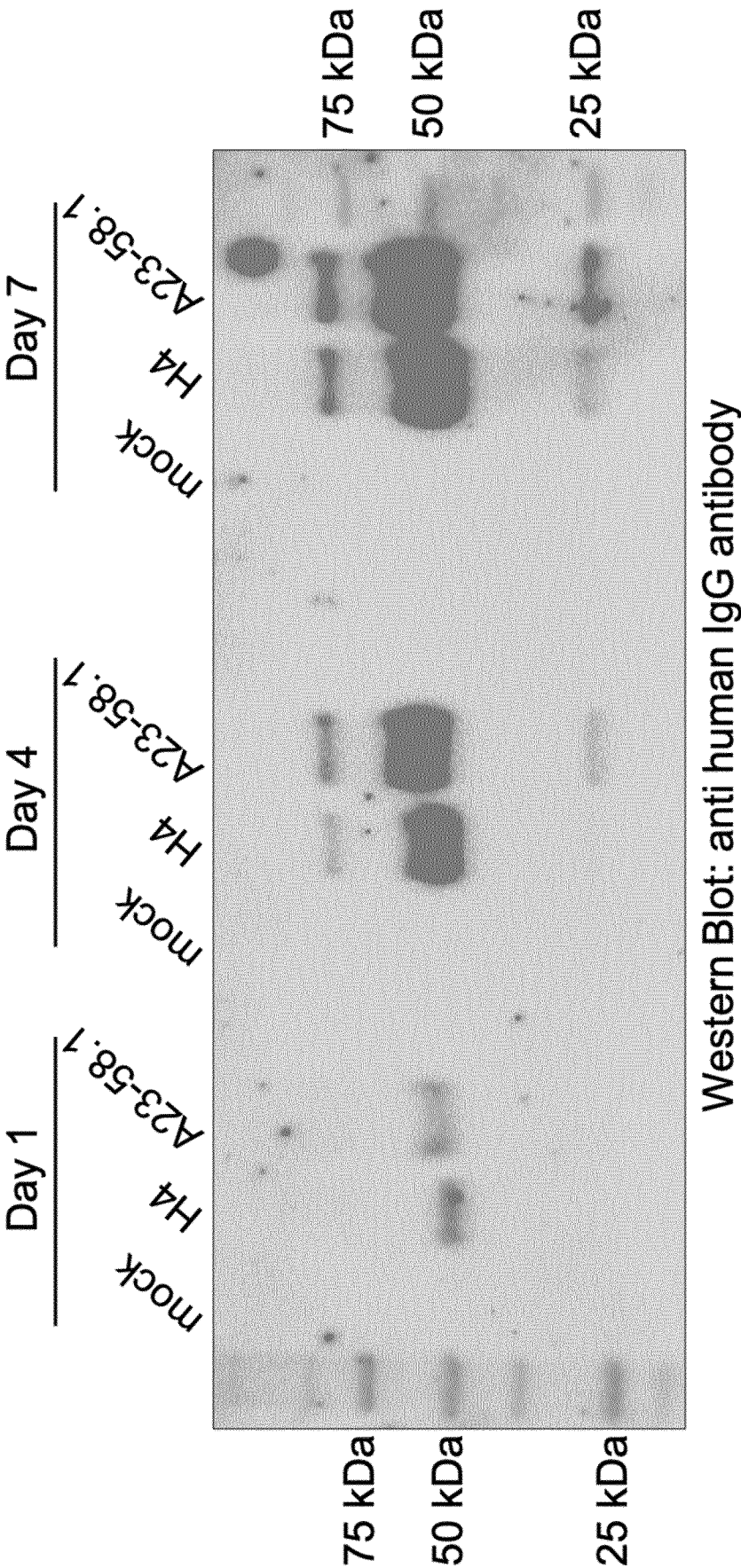


Fig. 8

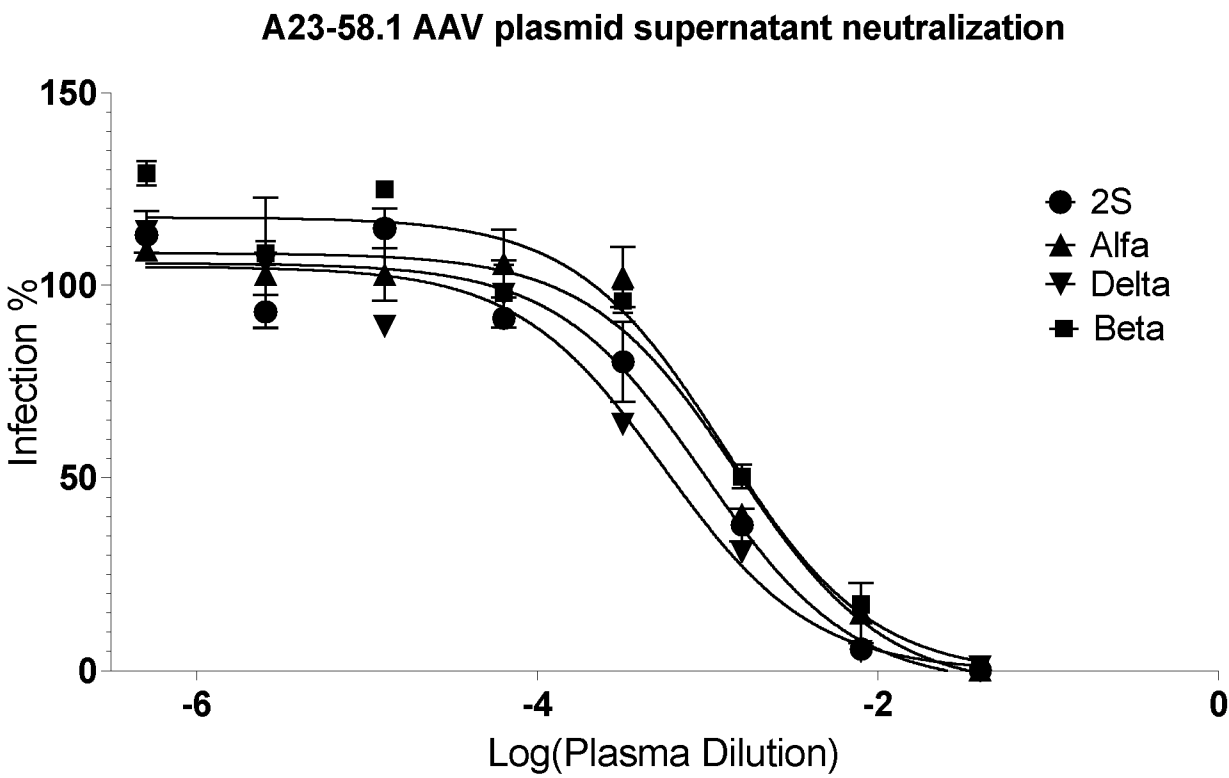
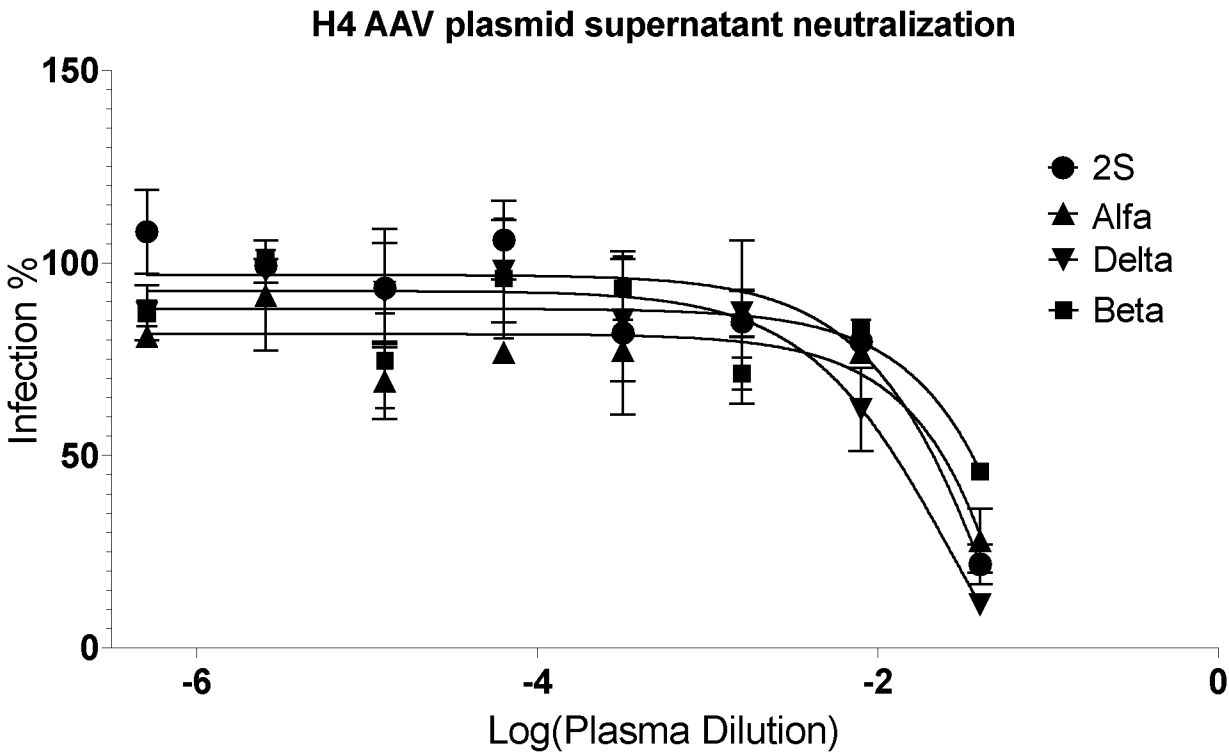


Fig. 9

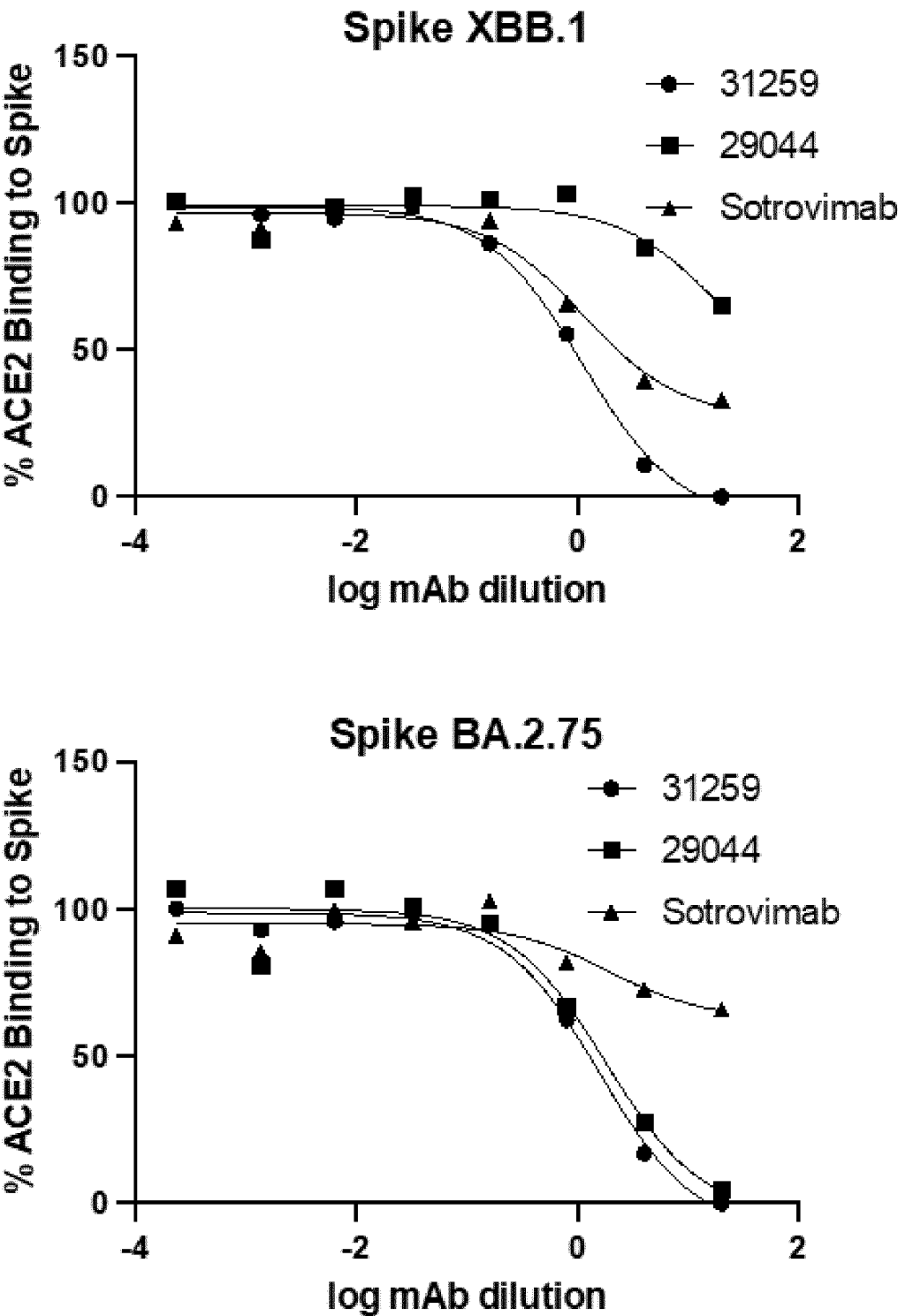


Fig. 10A

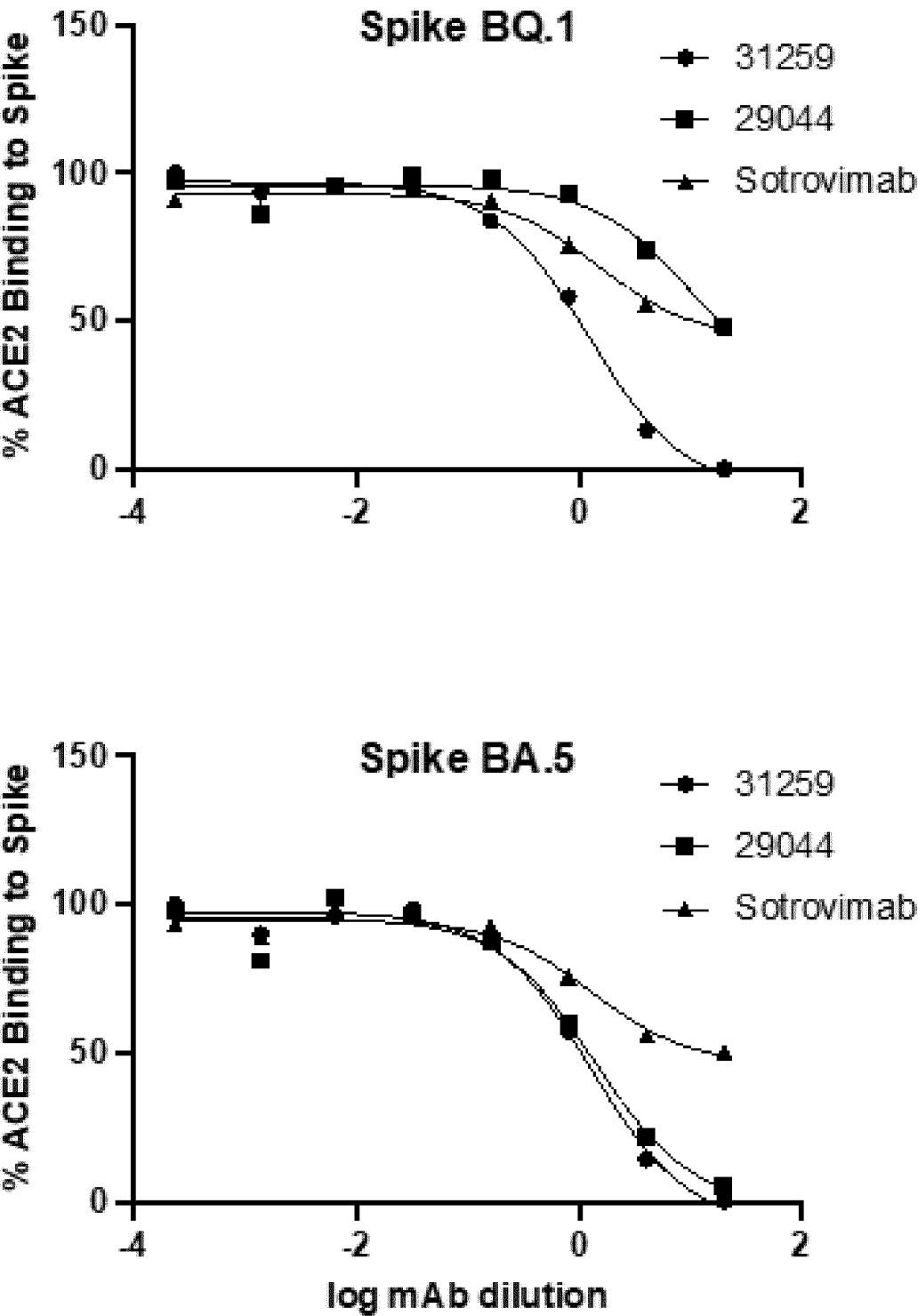


Fig. 10B

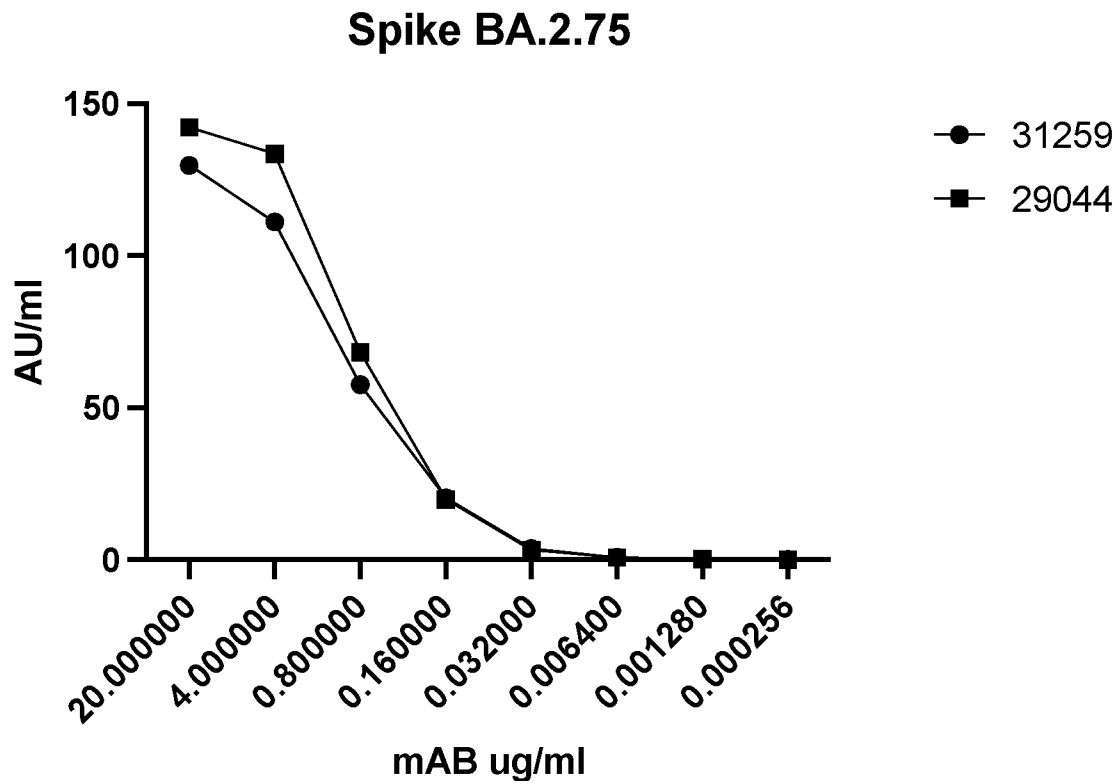
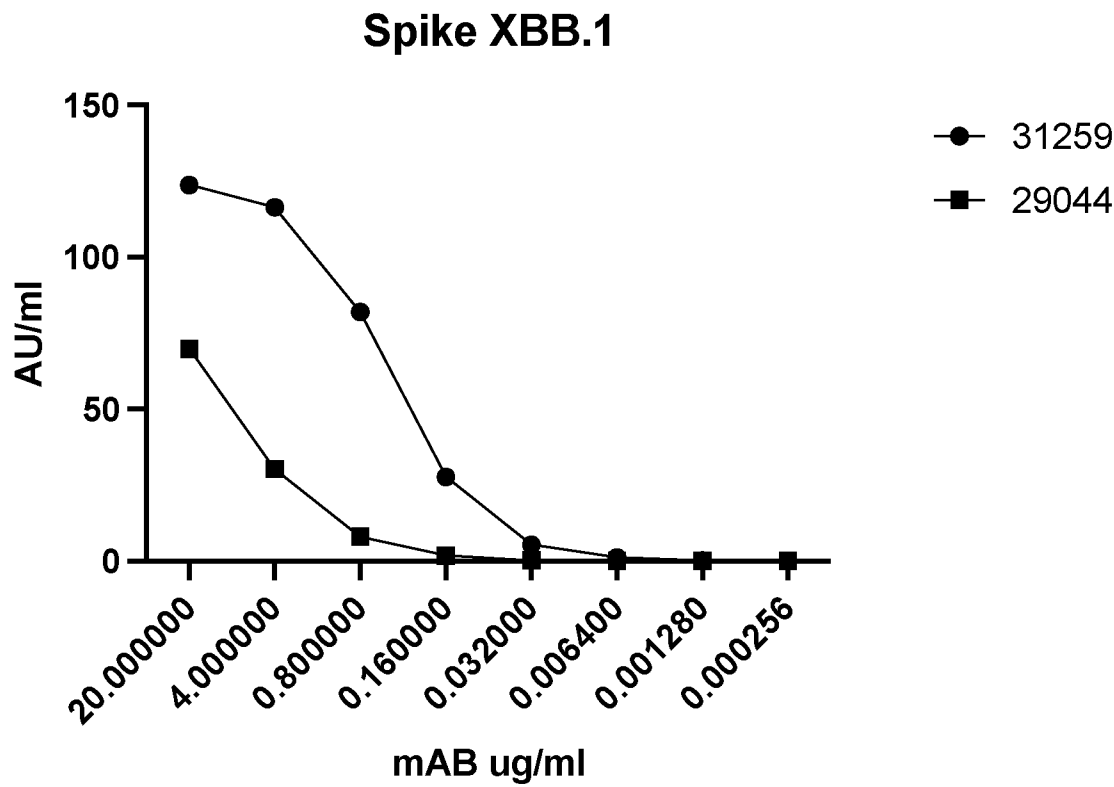


Fig. 11A

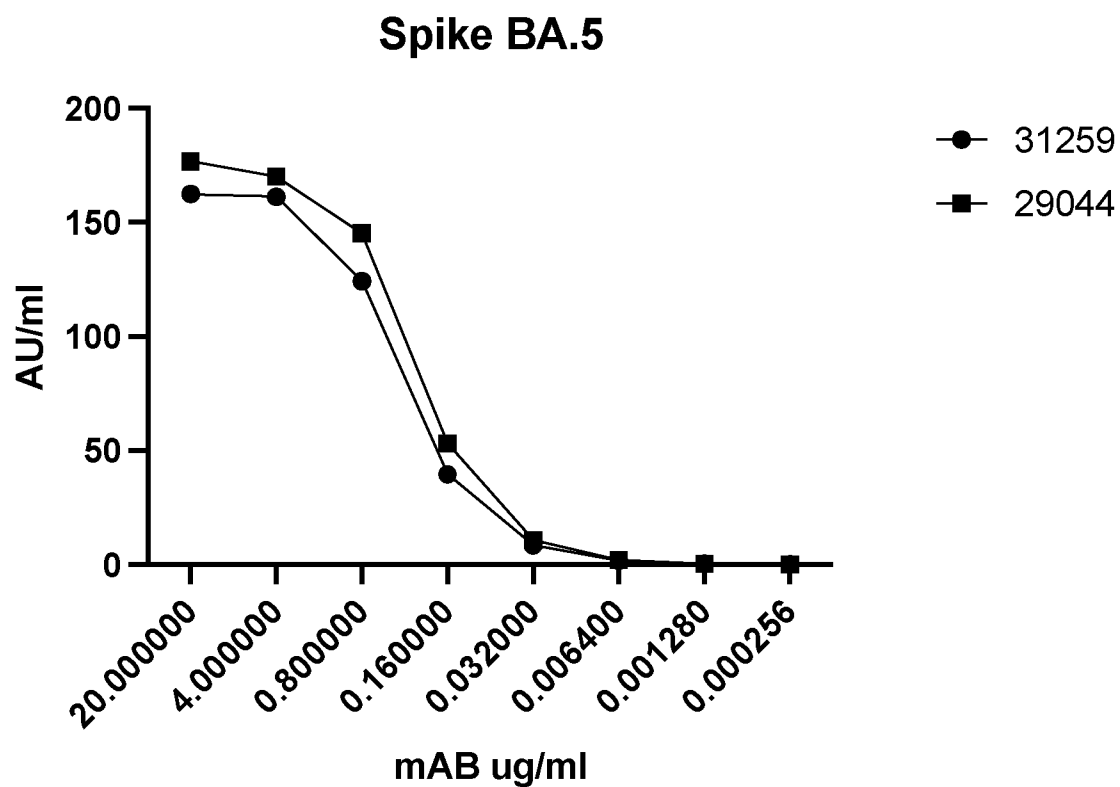
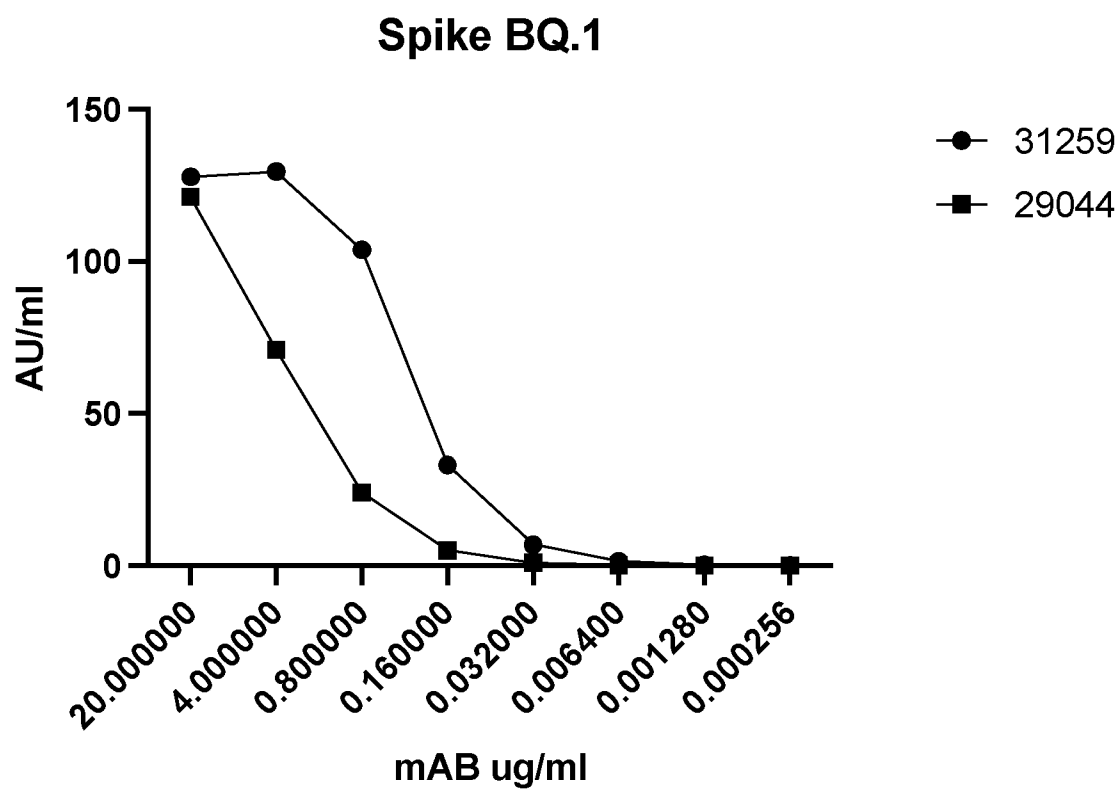


Fig. 11B

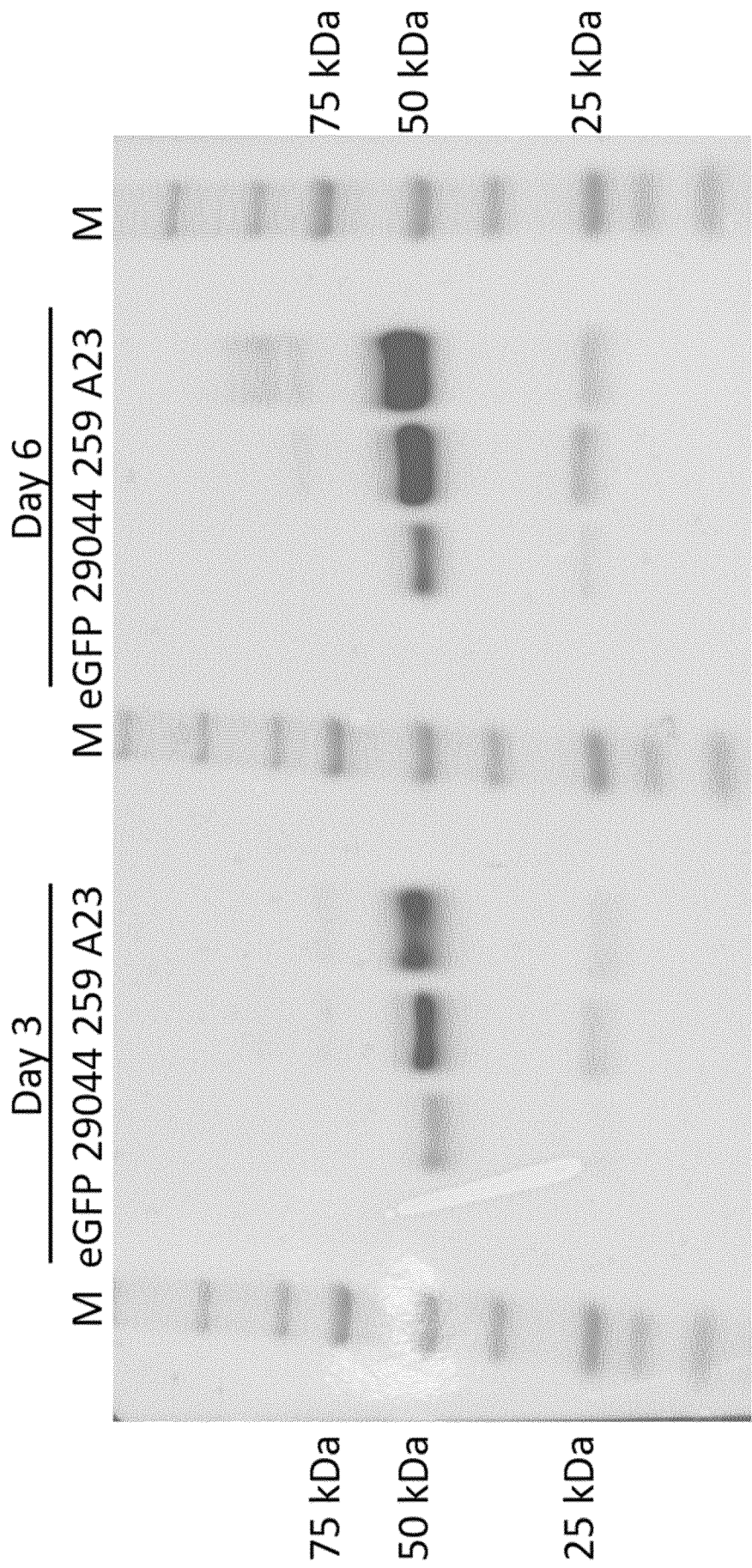


Fig. 12

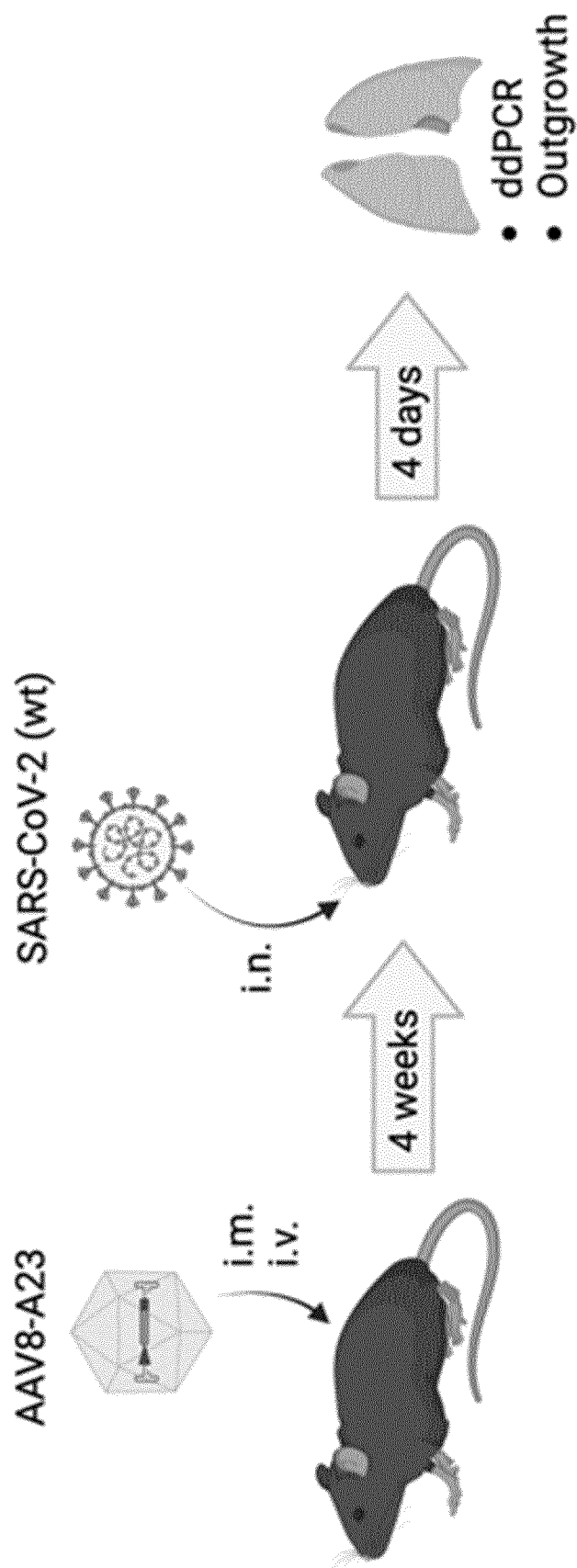


Fig. 13A

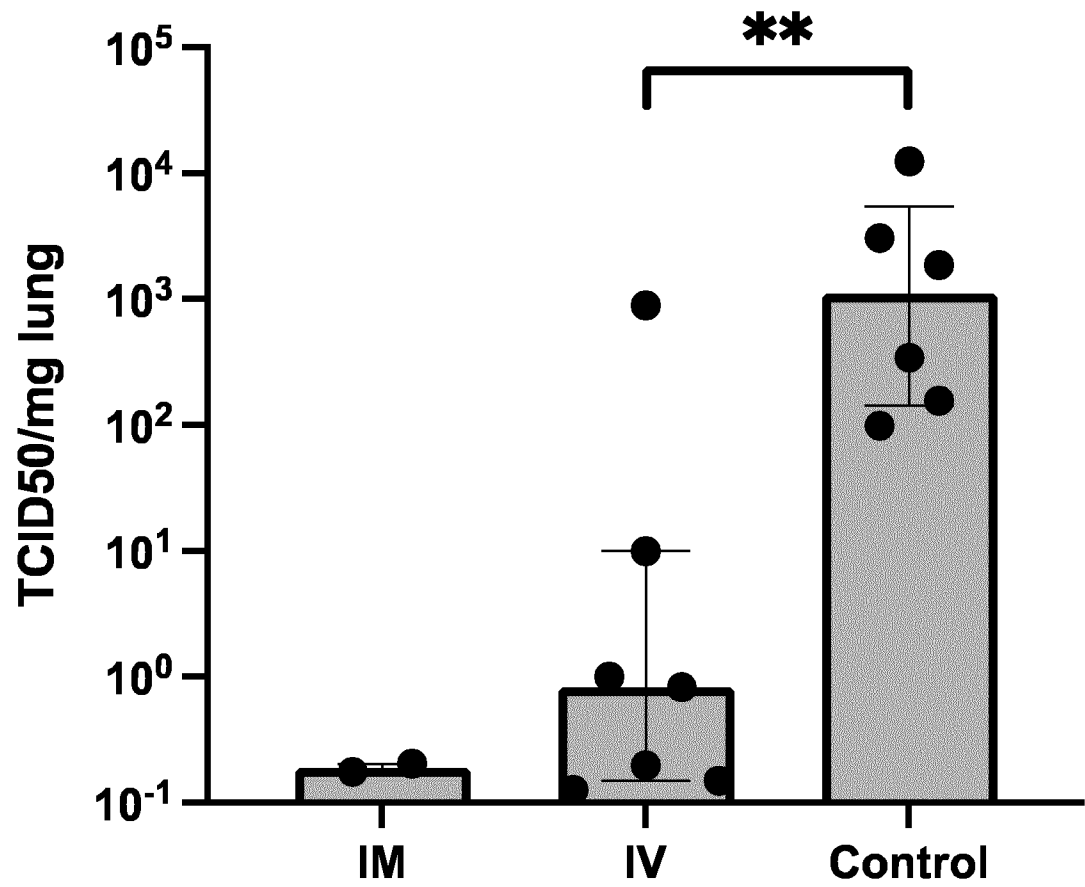


Fig. 13B

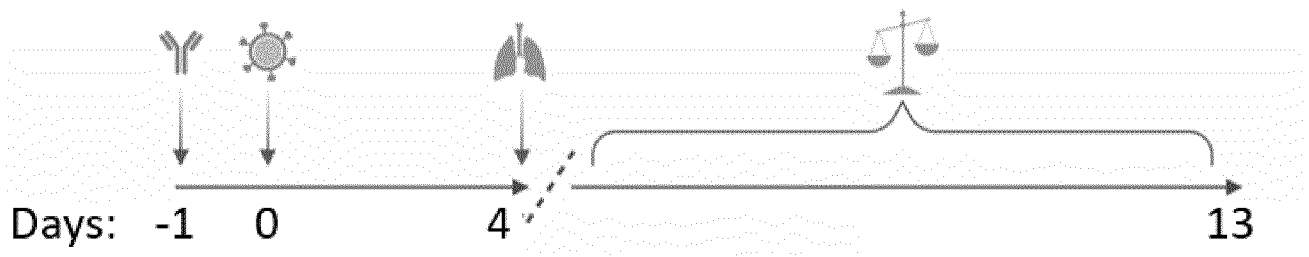


Fig. 14A

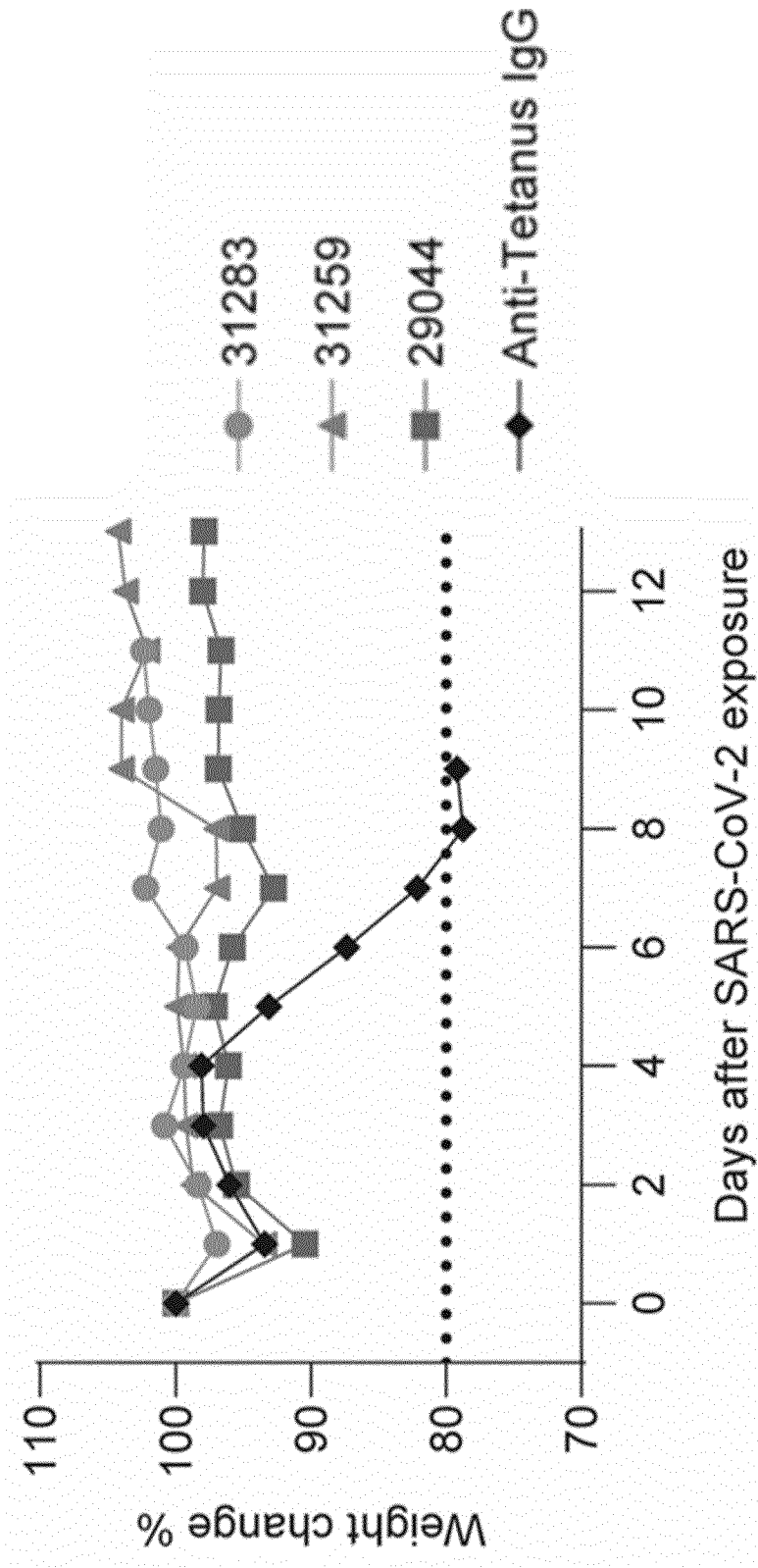


Fig. 14B

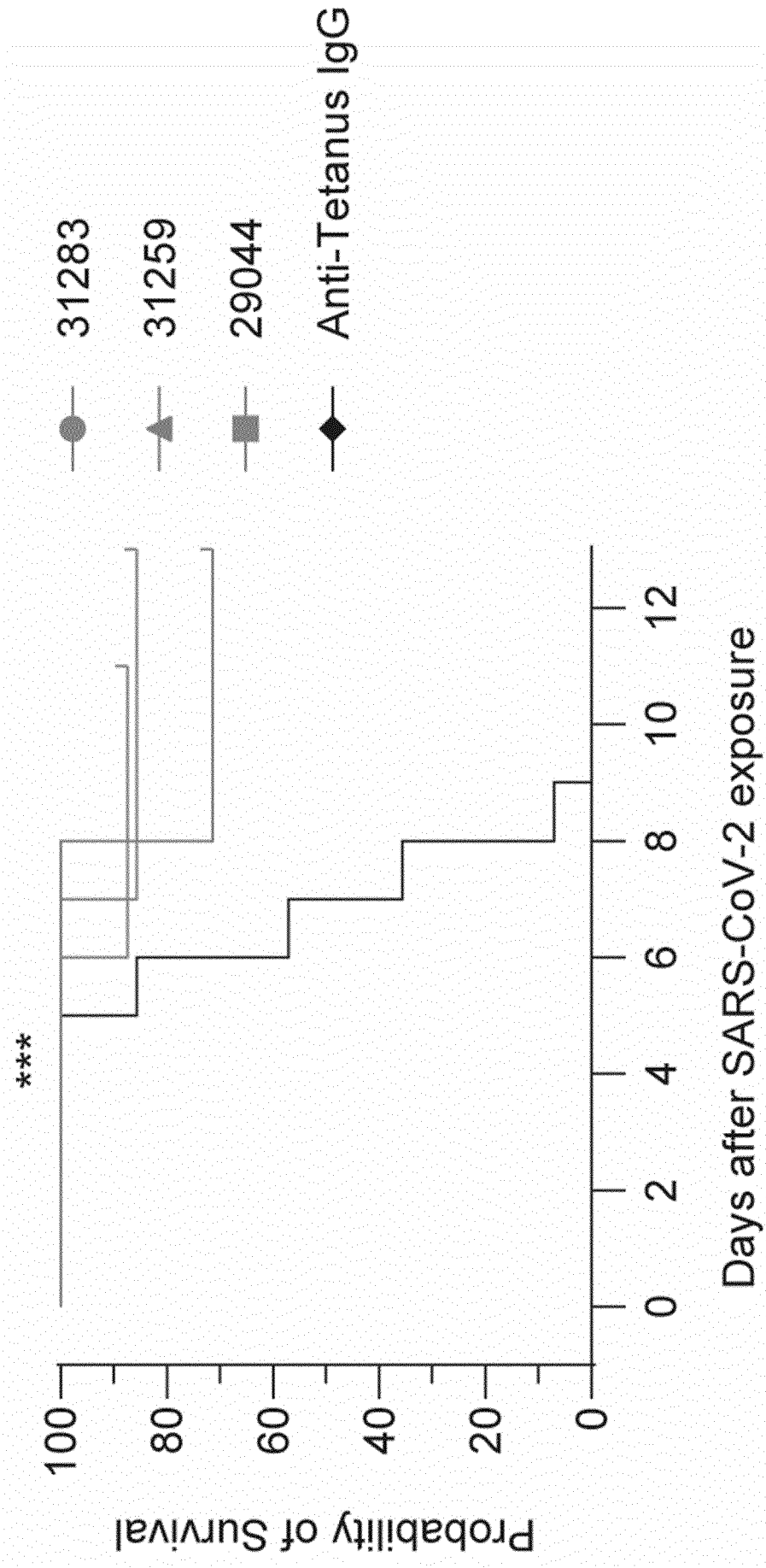


Fig. 14C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/061492

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/061492

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2023/061492

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/10 A61P31/14 C12N15/13 C12N15/864 G01N33/577 ADD.								
According to International Patent Classification (IPC) or to both national classification and IPC								
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07K C12N A61P								
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched								
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data								
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td> Zhou Biao ET AL: "An elite broadly neutralizing antibody protects SARS-CoV-2 Omicron variant challenge", bioRxiv, 5 January 2022 (2022-01-05), XP055880105, DOI: 10.1101/2022.01.05.475037 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2022.01.05.475037v1.full.pdf [retrieved on 2022-01-17] figures 2b, 2c, 4 ----- -/-- </td> <td>1-21</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	Zhou Biao ET AL: "An elite broadly neutralizing antibody protects SARS-CoV-2 Omicron variant challenge", bioRxiv, 5 January 2022 (2022-01-05), XP055880105, DOI: 10.1101/2022.01.05.475037 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2022.01.05.475037v1.full.pdf [retrieved on 2022-01-17] figures 2b, 2c, 4 ----- -/--	1-21
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
X	Zhou Biao ET AL: "An elite broadly neutralizing antibody protects SARS-CoV-2 Omicron variant challenge", bioRxiv, 5 January 2022 (2022-01-05), XP055880105, DOI: 10.1101/2022.01.05.475037 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2022.01.05.475037v1.full.pdf [retrieved on 2022-01-17] figures 2b, 2c, 4 ----- -/--	1-21						
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.								
* Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family				
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family							
Date of the actual completion of the international search		Date of mailing of the international search report						
1 August 2023		08/08/2023						
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Brouns, Gaby						

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAMERONI ELISABETTA ET AL: "Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift", NATURE, NATURE PUBLISHING GROUP UK, LONDON, vol. 602, no. 7898, 23 December 2021 (2021-12-23), pages 664-670, XP037700797, ISSN: 0028-0836, DOI: 10.1038/S41586-021-04386-2 [retrieved on 2021-12-23] figures 3b, ext. fig. 8 -----	1-21
X	Westendorf Kathryn ET AL: "LY-CoV1404 (bebtelovimab) potentially neutralizes SARS-CoV-2 variants", bioRxiv, 7 January 2022 (2022-01-07), XP055916038, DOI: 10.1101/2021.04.30.442182 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2021.04.30.442182v5.full.pdf [retrieved on 2022-04-27] tables 3B, 3C, 3D -----	1-21
X	CN 114 044 821 B (INST MILITARY MEDICINE ACADEMY MILITARY SCIENCES PLA) 25 March 2022 (2022-03-25) examples 3, 4 -----	1-21
A	US 11 312 760 B1 (LI YUANNIAN [CN] ET AL) 26 April 2022 (2022-04-26) example 3 -----	14-21
T	WANG QIAN ET AL: "Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants", CELL, ELSEVIER, AMSTERDAM NL, vol. 186, no. 2, 14 December 2022 (2022-12-14), page 279, XP087251258, ISSN: 0092-8674, DOI: 10.1016/J.CELL.2022.12.018 [retrieved on 2022-12-14]	
T	-& Wang Qian ET AL: "Suppl. Information: Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants", Cell, 14 December 2022 (2022-12-14), XP093067240, DOI: 10.1016/j.cell.2022.12.018 Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S0092867422015318?via%3Dihub [retrieved on 2023-07-25] -----	
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2023/061492

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	Anonymous: "FDA updates Sotrovimab emergency use authorization", , 4 May 2022 (2022-05-04), XP093067103, Retrieved from the Internet: URL:https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization#:~:text=This%20EUA%20authorizes%20sotrovimab%20for,19%2C%20including%20hospitalization%20or%20death.[retrieved on 2023-07-25] -----	
T	HE QINGWEN ET AL: "An updated atlas of antibody evasion by SARS-CoV-2 Omicron sub-variants including BQ.1.1 and XBB", CELL REPORTS MEDICINE, vol. 4, no. 4, 18 April 2023 (2023-04-18), page 100991, XP093067182, ISSN: 2666-3791, DOI: 10.1016/j.xcrm.2023.100991 Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S2666379123000976?via%3Dihub figure 1 -----	
A	Khanna Nina ET AL: "Position paper on the use of monoclonal antibodies against SARS-CoV-2 as passive immunisation treatments in severely immunocompromised persons in Switzerland", , 26 April 2022 (2022-04-26), XP093067471, Retrieved from the Internet: URL:https://www.bag.admin.ch/dam/bag/de/dokumente/mt/i-und-b/ekif/positionspapier-ss-i-ekif-praeexpositionsprophylaxe-sars-cov-2.pdf.download.pdf/220421_position%20paper_mAK%20Pr%C3%A4v_COVID_final_de.pdf [retrieved on 2023-07-26] -----	18-21
A	WO 2021/169167 A1 (NANJING GENSCRIPT BIOTECH CO LTD [CN] ET AL.) 2 September 2021 (2021-09-02) -----	14-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2023/061492

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CN 114044821	B	25-03-2022	NONE	

US 11312760	B1	26-04-2022	AU 2021209287 B1	24-03-2022
			US 11312760 B1	26-04-2022
			WO 2022156653 A1	28-07-2022

WO 2021169167	A1	02-09-2021	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-21

Anti-SARS CoV-2 spike protein (S) monoclonal antibodies (mAb)

1.1. claims: 1-21 (partially)

Anti-SARS CoV-2 S mAb 29044 comprising CDRs defined by SEQ ID NO:157-162, and subject-matter related thereto.

1.2. claims: 1-21 (partially)

Anti-SARS CoV-2 S mAb 31259 comprising CDRs defined by SEQ ID NO:87-92, and subject-matter related thereto.

1.3. claims: 1-21 (partially)

Anti-SARS CoV-2 S mAb 31283 comprising CDRs defined by SEQ ID NO:93-98, and subject-matter related thereto.
