

METHOD FOR PREVENTION OR TREATMENT OF CORONAVIRUS INFECTION

FIELD OF THE INVENTION

5 The invention is in the field of medical treatment and relates to a method for treating β -coronavirus infections in animals and humans, including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

In particular, the present invention relates to methods for prophylactic and/or therapeutic
10 treatment of SARS-CoV-2 by means of mucosal administration, especially intranasal and/or oral inhalation of antibodies against β -coronavirus, in particular SARS-CoV-2.

BACKGROUND OF THE INVENTION

The SARS-CoV-2 virus causes the disease COVID-19 in humans and is widespread having
15 a significant impact on human society. We should expect the SARS-CoV-2 virus and its variants of concern to continue to cause frequent infections, as well as severe disease and death. As of January 2023, the ongoing COVID-19 pandemic caused by SARS-CoV-2, has resulted in more than 6.7 million worldwide deaths since 2019.

20 In recent years, outbreaks of other coronaviruses have caused severe illness and deaths. As scientists develop therapeutic antibodies and vaccines against SARS-CoV-2, the danger remains of future novel variants of SARS-CoV-2 and novel coronaviruses emerging. These novel coronaviruses can lead to morbidity, mortality, and could cause pandemics. It remains vitally important to identify broadly protective therapies that can
25 combat current and emerging coronaviruses in the future.

In addition to SARS-CoV-2, four other betacoronaviruses are known to cause disease in humans: the betacoronaviruses HCoV-OC43 (human coronavirus OC43), HCoV-HKU1 (human coronavirus HKU1), SARS-CoV (severe acute respiratory syndrome coronavirus)
30 and MERS-CoV (Middle East respiratory syndrome coronavirus). Spillover events, where humans get infected with coronaviruses that circulate in animal reservoirs, are common. Recently, three betacoronaviruses crossed over from animals to humans, including SARS-CoV-2 causing serious outbreaks.

Furthermore, two coronaviruses previously linked only to animal infection were recently detected in humans who presented with flu-like symptoms.

5 Coronaviruses derive their name from their crown-like appearance. Coronaviruses are a large group of viruses that have spike proteins on their surface, resembling crown-like thorns. The antibodies elicited by natural infection or by COVID-19 vaccines used for mass immunization between 2020-2023 primarily target the variable receptor binding domain (RBD) of these spike proteins.

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Structure of the spike protein

Coronavirus infection is a multistep process that involves enzymatic cleavage and rearrangement of the surface spike protein. The spike protein has an S1 subunit with the receptor-binding domain (RBD) and an S2 subunit involved in fusion of the viral and
15 (host) cell membranes thereby facilitating cell entry.

The viral spike protein of SARS-CoV-2 facilitates viral entry by binding primarily to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells.

20 The SARS-CoV-2 spike contains two cleavage sites: a furin cleavage site at the boundary of the S1 and S2 subunits, and an S2' site that is highly conserved among different coronaviruses.

S1 subunit

25 The SARS-CoV-2 spike protein uses the RBD on the S1 subunit to engage the target cell's ACE2 receptor.

The S1 subunit is more accessible and remains the main target of many neutralizing antibodies. The S1 subunit, however, is more genetically variable than the S2 subunit;
30 especially when subjected to selective pressure from antibodies. This propensity towards genetic variability can lead to viral variants with the predominant changes occurring on the S1 subunit. Changes in the receptor-binding domain in SARS-CoV-2 variants of

concern have resulted in frequent reinfections, as protection by the antibodies elicited by previous infection and/or vaccines dramatically reduced.

S2 subunit

- 5 The viral spike components essential to infection also involve the structurally complex S2 subunit. The S2 subunit contains dynamic elements essential for fusion with the host cell. Once the receptor has bound, the S1 subunit is discarded and the membrane enzyme transmembrane serine protease 2 (TMPRSS2) or endosomal cathepsins cleave the S2 site.
- 10 This cleaving leads to insertion of the fusion peptide into the cell membrane culminating in viral fusion.

These S2 subunit elements are less disposed towards genetic variability than the RBD, which so far has been capable of retaining or even increasing binding capabilities to ACE2

15 despite a variety of mutations.

The S2 domain sites yield poorly accessible targets for novel therapeutics to protect against a wider range of coronaviruses.

The stem helix

20 The stem helix at the base of the viral spike protein is even more difficult to access than elements on the S2 subunit but historically benefits from better-preserved amino acid sequencing.

Treatments and prevention

- 25 Limited options for the viral treatment of SARS-CoV-2 exist in the form of small molecule or antibody antiviral drugs. For prevention of SARS-CoV-2 infection, few interventions exist. Most are non-pharmaceutical interventions such as social distancing and mask wearing. These methods are non-specific, and efficacy largely depends on compliance.
- 30 Thus, there is a need for different treatments, especially treatments that simultaneously target the multitude of SARS-CoV-2 variants of concern such as, for example, broad-neutralizing antibodies (bnAbs).

Although treatment of SARS-CoV-2 infection with one, two or more antibodies is a possibility, a treatment comprising a single antibody or combination of antibodies would be considerably more cost-efficient. The currently dominant SARS-CoV-2 Omicron subvariant BA.5 is resistant to most monoclonal antibody therapeutics.
5 Betacoronaviruses, including SARS-CoV-2, also infect a range of species know to have frequent human contact, thus increasing the risk of zoonotic transfer and new outbreaks with SARS-CoV-2 variants or viruses that previously have not infected humans and for which no therapies exist.

10 There is therefore an urgent need to develop therapeutic mAbs that broadly target β -coronaviruses, as well as new SARS-CoV-2 variants of concern that are not neutralized by antibodies elicited by immunization and/or natural infection.

It remains vitally important to identify broadly protective therapies that can combat novel
15 coronaviruses. We have surprisingly developed a novel array of broadly protective antibodies which are disclosed herein.

SUMMARY OF THE INVENTION

The inventors have discovered that an antibody having complementarity-determining
20 regions (CDR) as disclosed herein can advantageously be used in the treatment of a coronavirus infection, especially in the prophylactic treatment of coronavirus infection.

The inventors have surprisingly established when treating a coronavirus infection, mucosal administration of an antibody having CDRs as disclosed herein is a more potent
25 prophylactic route of administration method compared with intraperitoneal administration.

The inventors have surprisingly established when treating a coronavirus infection, intranasal administration of an antibody having CDRs as disclosed herein is a more
30 potent prophylactic route of administration method compared with intraperitoneal administration.

Significantly, the mucosal administration method of treatment of the present invention is effective against SARS-Cov-2 and variants of concern and does not require the use of additional antibodies.

- 5 A mucosal administration treatment method of the invention is effective even at low dosages and prevents body weight loss.

Complementarity-determining regions (CDRs)

Preferably, CDR regions are according to Kabat *et al.*, (1991) as described in Sequences of
10 Proteins of Immunological Interest.

In a preferred embodiment, the invention provides an antibody that comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy
15 chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of
20 SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

In a preferred embodiment, the invention provides an antibody comprising a heavy chain
25 variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of
30 SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of

SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to mucosal epithelium.

In a preferred embodiment, the invention provides a method for the treatment of a coronavirus infection in an individual, the method comprising administering to an individual in need thereof an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to mucosal epithelium.

In a preferred embodiment, the invention provides a mucosal composition comprising an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

In a preferred embodiment, the invention provides an antibody for use in a method for treatment of a coronavirus infection in an individual, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any

one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to mucosal epithelium.

In a preferred embodiment, the invention provides an antibody, or a method or composition comprising the antibody, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising SEQ ID NO: 046, a heavy chain CDR2 region comprising SEQ ID NO: 114, and a heavy chain CDR3 region comprising SEQ ID NO: 254, a light chain variable domain that comprises a light chain CDR1 region comprising SEQ ID NO: 367, a light chain CDR2 region comprising SEQ ID NO: 430, and a light chain CDR3 region comprising SEQ ID NO: 545.

In a preferred embodiment, the invention provides an antibody, or a method or composition comprising the antibody, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region consisting of SEQ ID NO: 046, a heavy chain CDR2 region consisting of SEQ ID NO: 114, and a heavy chain CDR3 region consisting of SEQ ID NO: 254, a light chain variable domain that comprises a light chain CDR1 region consisting of SEQ ID NO: 367, a light chain CDR2 region consisting of SEQ ID NO: 430, and a light chain CDR3 region consisting of SEQ ID NO: 545.

In a preferred embodiment, an antibody is disclosed herein for use in a method for the prophylactic treatment of a coronavirus infection, in an individual, the antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259,

280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3
5 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, and wherein between 0.1 mg and 20 mg of the antibody is administered to the mucosa.

In a preferred embodiment, an antibody is disclosed herein for use in a method for the
10 prophylactic treatment of a coronavirus infection, in an individual, the antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3
15 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3
20 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, and wherein between 0.1 mg and 20 mg of the antibody is administered intranasally.

In a preferred embodiment, an antibody is disclosed herein for use in a method for the
25 prophylactic treatment of a coronavirus infection, in an individual, the antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3
30 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3

region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, and wherein between 0.1 mg and 20 mg of the antibody is administered by oral inhalation.

5 In a preferred embodiment, a composition comprising an antibody is disclosed herein, the antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain
10 CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light
15 chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, for use in a method of prevention or treatment of a coronavirus infection, wherein the administration route comprises at least one of pulmonary administration, nasal administration and oropharyngeal administration and wherein the nominal dose of the antibody is between 0.1 mg and 20 mg.

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Preferably, an antibody as disclosed herein comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to
25 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296.

Preferably, an antibody as disclosed herein comprises a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising
30 any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

Preferably, in a method for treatment of the invention, the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296.

Preferably, in a method for treatment of the invention, the antibody comprises a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

In an alternative preferred embodiment, the invention provides an antibody that comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 047 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 255 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 368 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 431 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 546 to 550, 584 to 589, 595 to 600, 617 to 622.

Embodiments having > 1 CDRs

Preferably, an antibody as disclosed herein comprises a heavy chain variable domain that comprises a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196.

Route of administration

In a preferred embodiment, the invention provides an antibody as disclosed herein, or a method or composition comprising the antibody as disclosed herein, wherein the antibody is administered by mucosal administration.

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In a preferred embodiment, the invention provides an antibody as disclosed herein, or a method or composition comprising the antibody as disclosed herein, wherein the antibody is administered by intravenous administration.

10 In a preferred embodiment, the invention provides an antibody as disclosed herein, or a method or composition comprising the antibody as disclosed herein, wherein the antibody is administered by at least one of oral inhalation, nasal administration, ocular administration, vaginal administration, rectal administration and oropharyngeal administration.

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In a preferred embodiment, the antibody as disclosed herein is administered intranasally.

Such an antibody is useful for the treatment of coronavirus infection in an individual. Preferably, the method for treatment of coronavirus infection is a method for prophylactic and/or therapeutic treatment of a coronavirus infection. Preferably, the antibody is
20 provided to an individual infected with coronavirus. Preferably, the antibody is provided to the individual prophylactically. Preferably, the antibody is provided to the individual after infection but prior to onset of symptoms.

25 In a preferred embodiment, the disclosure provides a method of treating coronavirus infection in an individual, said method comprising mucosal administration, preferably administering intranasally and/or by oral inhalation, to an individual in need thereof an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051,
30 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain

CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

In a preferred embodiment, the individual is infected with coronavirus or at risk of coronavirus infection.

In a preferred embodiment, the disclosure provides an antibody as disclosed herein for use in the manufacture of a medicament for use in the treatment of a coronavirus infection.

Clauses

The following numbered clauses each represent preferred embodiments of the invention and are part of the description.

Clause 1:

A method for the treatment of a coronavirus infection in an individual, the method comprising administering to an individual in need thereof an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to the mucosa.

Clause 2:

A mucosal composition comprising an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region
5 comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2
10 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.

Clause 3:

15 An antibody for use in a method of prevention or treatment of a coronavirus infection in an individual, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to
20 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468,
25 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to mucosa.

Clause 4:

30 A method, composition or antibody according to any preceding Clause, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising SEQ ID NO: 046, a heavy chain CDR2 region comprising SEQ ID NO: 114, and a heavy chain CDR3 region comprising SEQ ID NO: 254, a light chain variable domain that comprises a light chain CDR1 region comprising SEQ ID NO: 367, a light

chain CDR2 region comprising SEQ ID NO: 430, and a light chain CDR3 region comprising SEQ ID NO: 545.

Clause 5:

5 A method, composition or antibody according to any preceding Clause, wherein the method for treatment of coronavirus virus infection is a method for prophylactic and/or therapeutic treatment of a coronavirus, preferably wherein the method for treatment is for the prophylactic treatment of a SARS-COV-2 infection.

10 **Clause 6:**

A method, composition or antibody according to any preceding Clause, wherein the antibody comprises a heavy chain variable domain having the sequence of SEQ ID NO:629 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid insertions, deletions, substitutions which are not in the heavy chain CDRs.

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Clause 7:

A method, composition or antibody according to any preceding Clause, wherein the antibody comprises a light chain variable domain having the sequence of SEQ ID NO:630 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid insertions, deletions, substitutions which are not in the light chain CDRs.

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Clause 8:

A method, composition or antibody according to any preceding Clause, wherein the antibody is an IgG antibody, preferably an IgG1 antibody.

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Clause 9:

A method, composition or antibody according to any preceding Clause, wherein the antibody is provided to the individual prophylactically.

Clause 10:

A method, composition or antibody according to any preceding Clause, wherein the administration route comprises at least one of oral inhalation, nasal administration, ocular administration and oropharyngeal administration.

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Clause 11:

A method, composition or antibody according to any preceding Clause, wherein the antibody is administered at least once or at least twice monthly.

10 **Clause 12:**

A method, composition or antibody according to any preceding Clause, wherein the antibody is administered to the individual at a dosage of between 0.01 mg and 20 mg.

Clause 13:

15 A composition according to any preceding Clause, comprising an antibody in a single dose unit of between 0.01 mg and 20 mg, preferably between 0.1 mg and 15 mg or preferably 0.5 mg and 10 mg, wherein the antibody is as defined in any one of Clauses 1 to 12.

Clause 14:

20 A composition according to any preceding Clause, wherein the composition is self-administered.

Clause 15:

25 A medicament delivery device comprising a composition according to any preceding Clause.

Dosing

Preferably, between 0.01 mg and 20 mg of the antibody is administered to an individual,
30 more preferably between 0.1 mg and 20 mg of the antibody is administered to an individual.

The flat dose, or nominal dose, of the antibody is preferably between 0.01 mg and 17 mg, preferably between 0.011 mg and 16 mg, preferably between 0.012 mg and 15 mg, preferably between 0.013 mg and 14 mg, preferably between 0.014 mg and 13 mg, preferably between 0.015 mg and 12 mg, preferably between 0.016 mg and 11 mg, preferably between 0.017 mg and 10 mg, preferably between 0.018 mg and 9 mg, preferably between 0.020 mg and 8 mg, preferably between 0.023 mg and 7 mg, preferably between 0.025 mg and 6 mg, preferably between 0.030 mg and 5 mg, preferably between 0.040 mg and 4 mg, preferably between 0.050 mg and 3 mg, preferably between 0.075 mg and 2 mg, or preferably between 0.10 mg and 1 mg.

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The flat dose, or nominal dose, of the antibody is preferably between 0.010 mg and 5.0 mg, preferably between 0.020 mg and 4.5 mg, preferably between 0.030 mg and 4.0 mg, preferably between 0.040 mg and 3.5 mg, preferably between 0.050 mg and 3.0 mg, preferably between 0.060 mg and 2.5 mg, preferably between 0.070 mg and 2.0 mg, preferably between 0.080 mg and 1.5 mg, preferably between 0.090 mg and 1.0 mg, or preferably between 0.100 mg and 0.5 mg.

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The flat dose, or nominal dose, of the antibody is preferably between 0.010 mg and 15.0 mg, preferably between 0.020 mg and 14.5 mg, preferably between 0.030 mg and 4.0 mg, preferably between 0.040 mg and 13.5 mg, preferably between 0.050 mg and 13.0 mg, preferably between 0.060 mg and 12.5 mg, preferably between 0.070 mg and 12.0 mg, preferably between 0.080 mg and 11.5 mg, preferably between 0.090 mg and 11.0 mg, or preferably between 0.100 mg and 10.5 mg.

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The flat dose, or nominal dose, of the antibody to be delivered to a human subject is preferably between 0.1 μ g and 10 μ g, preferably between 0.2 μ g and 9 μ g, preferably between 0.3 μ g and 8 μ g, preferably between 0.4 μ g and 7 μ g, preferably between 0.5 μ g and 6 μ g, preferably between 0.6 μ g and 5 μ g, preferably between 0.7 μ g and 4 μ g, preferably between 0.8 μ g and 3 μ g, preferably between 0.9 μ g and 2 μ g or preferably around 1 μ g.

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The flat dose, or nominal dose, of the antibody to be delivered to a human subject is preferably between 1 mg and 11 mg, preferably between 2 mg and 12 mg, preferably between 3 mg and 13 mg, preferably between 4 mg and 14 mg, preferably between 5 mg

and 15 mg, preferably between 6 mg and 16 mg, preferably between 7 mg and 17 mg, preferably between 8 mg and 18 mg, preferably between 9 mg and 19 mg, or preferably between 10 mg and 20 mg.

5 The flat dose, or nominal dose, of the antibody to be delivered to a human subject is preferably between 1 mg and 20 mg, preferably between 2 mg and 19 mg, preferably between 3 mg and 18 mg, preferably between 4 mg and 17 mg, preferably between 5 mg and 16 mg, preferably between 6 mg and 15 mg, preferably between 7 mg and 14 mg, preferably between 8 mg and 13 mg, preferably between 9 mg and 12 mg, or preferably
10 between 10 mg and 11 mg.

The flat dose, or nominal dose, of the antibody to be delivered to a human subject is preferably between 11 mg and 20 mg, preferably between 10 mg and 19 mg, preferably between 9 mg and 18 mg, preferably between 8 mg and 17 mg, preferably between 7 mg
15 and 16 mg, preferably between 6 mg and 15 mg, preferably between 5 mg and 14 mg, preferably between 4 mg and 13 mg, preferably between 3 mg and 12 mg, preferably between 2 mg and 11 mg, or preferably between 1 mg and 10 mg.

In a preferred embodiment, the disclosure further provides a composition formulated for
20 mucosal administration comprising an antibody as disclosed herein in a single dose unit of between 0.1 mg and 20 mg, preferably between 5 mg and 15 mg or preferably 7.5 mg and 12.5 mg.

In a preferred embodiment, the disclosure further provides a composition formulated for
25 intranasal administration comprising an antibody as disclosed herein in a single dose unit of between 0.1 mg and 20 mg, preferably between 5 mg and 15 mg or preferably 7.5 mg and 12.5 mg.

In a preferred embodiment, the disclosure further provides a composition formulated for
30 oral inhalation comprising an antibody as disclosed herein in a single dose unit of between 0.1 mg and 20 mg, preferably between 5 mg and 15 mg or preferably 7.5 mg and 12.5 mg.

Timing and intervals

Preferably, the antibody is administered at least once or at least twice per month.

Preferably, the antibody is administered at least once or at least twice per week.

5 The weekly flat dose, or nominal dose, of the antibody is between 0.010 mg and 17 mg, preferably between 0.011 mg and 16 mg, preferably between 0.012 mg and 15 mg, preferably between 0.013 mg and 14 mg, preferably between 0.014 mg and 13 mg, preferably between 0.015 mg and 12 mg, preferably between 0.016 mg and 11 mg, preferably between 0.017 mg and 10 mg, preferably between 0.018 mg and 9 mg,
10 preferably between 0.020 mg and 8 mg, preferably between 0.023 mg and 7 mg, preferably between 0.025 mg and 6 mg, preferably between 0.030 mg and 5 mg, preferably between 0.040 mg and 4 mg, preferably between 0.050 mg and 3 mg, preferably between 0.075 mg and 2 mg, or preferably between 0.10 mg and 1 mg.

15 The weekly flat dose, or nominal dose, of the antibody is between 0.010 mg and 5.0 mg, preferably between 0.020 mg and 4.5 mg, preferably between 0.030 mg and 4.0 mg, preferably between 0.040 mg and 3.5 mg, preferably between 0.050 mg and 3.0 mg, preferably between 0.060 mg and 2.5 mg, preferably between 0.070 mg and 2.0 mg, preferably between 0.080 mg and 1.5 mg, preferably between 0.090 mg and 1.0 mg, or
20 preferably between 0.100 mg and 0.5 mg.

Preferably, the antibody is administered at least once or at least twice per day. Preferably, the antibody is administered daily. Preferably, the antibody is administered twice daily.

25 Preferably, the daily flat dose, or nominal dose, is between 0.001 mg and 17 mg, preferably between 0.011 mg and 16 mg, preferably between 0.012 mg and 15 mg, preferably between 0.013 mg and 14 mg, preferably between 0.014 mg and 13 mg, preferably between 0.015 mg and 12 mg, preferably between 0.016 mg and 11 mg, preferably between 0.017 mg and 10 mg, preferably between 0.018 mg and 9 mg, preferably between 0.020 mg and 8 mg,
30 preferably between 0.023 mg and 7 mg, preferably between 0.025 mg and 6 mg, preferably between 0.030 mg and 5 mg, preferably between 0.040 mg and 4 mg, preferably between 0.050 mg and 3 mg, preferably between 0.075 mg and 2 mg, or preferably between 0.10 mg and 1 mg.

Framework regions

Preferably, the antibody comprises a heavy chain variable domain having the sequence of SEQ ID NO: 629 and/or a light chain variable domain having the sequence of SEQ ID NO: 630.

Preferably, the heavy chain variable domain of said antibody further comprises a heavy chain framework region FR1 of SEQ ID NO: 631, a heavy chain framework region FR2 of SEQ ID NO: 632, a heavy chain framework region FR3 of SEQ ID NO: 633, and/or a heavy chain framework region FR4 of SEQ ID NO: 634.

Preferably, said light chain variable domain further comprises a light chain framework region FR1 of SEQ ID NO: 635, a light chain framework region FR2 of SEQ ID NO: 636, a light chain framework region FR3 of SEQ ID NO: 637, and/or a light chain framework region FR4 of SEQ ID NO: 638.

Combination compositions

In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 639, 640, 641, 642, 643 or SEQ ID NO.: 644. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622. More preferably wherein the First fragment comprises any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 645, 646, 647, 648, 649 or SEQ ID NO.: 650. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

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In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 651, 652, 653, 654, 655 or SEQ ID NO.: 656. Preferably, the fragment is selected from anyone of the the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

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In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191

to 196, 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622. More preferably wherein the First fragment comprises a sequence
5 comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 and 545. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 657, 658, 659, 660, 661 or SEQ ID NO.: 662. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv,
10 diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

Bispecific antibodies

In a preferred embodiment, we disclose a bispecific antibody, wherein the bispecific antibody is capable of binding to the stem helix of a coronavirus. In a preferred
15 embodiment, we disclose a bispecific antibody, wherein the bispecific antibody is capable of binding to the stem helix of SARS-CoV-2.

In a preferred embodiment, we disclose an anti- coronavirus bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix
20 of a coronavirus and a second Fab capable of binding to the fusion peptide of a coronavirus. In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2.

25 In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545; alternatively wherein the first Fab comprises
30 a sequence comprising any one or more of preferred SEQ ID Numbers: 651, 652, 653, 654, 655 or 656; or alternatively wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 657, 658, 659, 660, 661 to 662, and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 639, 640, 641, 642, 643 to 644; or alternatively wherein the second Fab

comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 645, 646, 647, 648, 649 to 650.

5 In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 639, 640, 641, 642, 10 643 to 644. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

15 In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 645, 646, 647, 648, 20 649 to 650. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

25

In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab also capable of binding to the stem helix of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 651, 652, 653, 654, 30 655 to 656. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain

antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

5 In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab also capable of binding to the stem helix of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 657, 658, 659, 660, 10 661 to 662. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

15

In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 046, 114 or 254, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 660, 661, or 662.

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In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 046, 114 or 254, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 642, 643, or 644.

25

In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 046, 114 or 254, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 648, 649, or 650.

30

In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in

preferred SEQ ID Numbers: 046, 114 or 254, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 654, 655, or 656.

5 In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 657, 658, or 659, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 367, 430 or 545.

10 In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 639, 640, or 641, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 367, 430 or 545.

15 In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 645, 646, or 647, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 367, 430 or 545.

20 In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 651, 652 or 653, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 367, 430 or 545.

25 The present invention also provides construction, expression, purification methods for a bispecific antibody having a function of binding to the stem helix of SARS-CoV-2, and use of the bispecific antibody in the field of medicine and especially in the prevention and/or treatment of SARS-CoV-2 infections.

Clauses

30 The following numbered clauses each represent preferred embodiments of the invention and are part of the description.

Clause 26:

An anti-coronavirus, preferably anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 639, 640, 641, 642, 643 to 644.

Clause 27:

A bispecific antibody or an antigen binding fragment thereof according to Clause 26, comprising a first Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and a second Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 and/or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 639, 640, 641, 642, 643 and/or 644.

Clause 28:

A bispecific antibody or an antigen binding fragment thereof according to Clauses 26 or 27, comprising a first Fab specifically binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and a second Fab specifically binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, characterized in that:

- a.) the first Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and
- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 639, a Heavy Chain CDR2 region of SEQ ID NO: 640 and a Heavy Chain CDR3 region of SEQ ID NO: 641 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 642, a Light Chain CDR2 region of SEQ ID NO: 643 and a Light Chain CDR3 region of SEQ ID NO: 644.

Clause 29:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 28, comprising:

- a) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody or an antigen binding fragment thereof, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and
 - b) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody or an antigen binding fragment thereof, capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2,
- wherein the constant domains CL and CH1 from the antibody or an antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, are replaced by each other.

Clause 30:

- A bispecific antibody or an antigen binding fragment thereof according to Clause 29, wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and the VL domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and
- wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2 comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 639, a Heavy Chain CDR2 region of SEQ ID NO: 640 and a Heavy Chain CDR3 region of SEQ ID NO: 641 and the VL domain of the antibody or the antigen binding fragment thereof that is capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 642, a Light Chain CDR2 region of SEQ ID NO: 643 and a Light Chain CDR3 region of SEQ ID NO: 644.

Clause 31:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 28, comprising:

- a) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2; and
- b) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein constant domains CL and CH1 from the antibody that is capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2 are replaced by each other.

Clause 32:

A bispecific antibody or an antigen binding fragment thereof according to Clause 31,

- wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and the VL domain of the antibody capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and

- wherein the VH domain of the antibody capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 639, a Heavy Chain CDR2 region of SEQ ID NO: 640 and a Heavy Chain CDR3 region of SEQ ID NO: 641 and the VL domain of the antibody capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 642, a Light Chain CDR2 region of SEQ ID NO: 643 and a Light Chain CDR3 region of SEQ ID NO: 644.

Clause 33:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 28, comprising:

a) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2; and

5 b) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein domains VL-CL and VH-CH1 from the antibody that specifically binds to the fusion peptide of a coronavirus, preferably SARS-CoV-2, are replaced by each other.

10 **Clause 34:**

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 33, wherein the first Fab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, 15 at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 629.

Clause 35:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 20 26 to 33, wherein the second Fab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 663.

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Clause 36:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 33, wherein the first Fab comprises a light chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, 30 at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 630.

Clause 37:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 33, wherein the second Fab comprises a light chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 664.

Clause 38:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 33, wherein the bispecific antibody or an antigen binding fragment thereof is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

Clause 39:

A method for the production of a bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 38, comprising a) culturing a host cell, comprising an expression vector, comprising a polynucleotide encoding a bispecific antibody or an antibody fragment according to any one of the preceding Clauses under conditions which permit the production of said bispecific antibody or an antigen binding fragment thereof, and b) isolating said bispecific antibody or an antigen binding fragment thereof.

Clause 40:

A nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleic acid sequence encodes the bispecific antibody or antigen binding fragment thereof, a heavy chain variable region and/or a light chain variable region of the bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 38, preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.

Clause 41:

A nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleic acid sequence encodes the bispecific antibody or antigen binding fragment thereof, a heavy chain variable region and/or light chain variable region of the bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 38 and Clause 40,
5 wherein the nucleic acid sequence comprises at least anyone of:

- (i) a first nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 046, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 046,
- 10 (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 114, or a second nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 114,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 254, or a third nucleic acid sequence encoding the amino acid sequence having at
15 most 1, 2 or 3 amino acids different from SEQ ID NO. 254,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 367, or a fourth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3 or 4 amino acids different from SEQ ID NO. 367,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID
20 NO. 430, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 430,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 545, or a sixth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, or 4 amino acids different from SEQ ID NO. 545,
- 25 (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 639, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 639,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 640, or an eighth nucleic acid sequence encoding the amino acid sequence
30 having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 640,
- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 641, or a ninth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, or 4 amino acids different from SEQ ID NO. 641,

(x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 642, or a tenth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, or 4 amino acids different from SEQ ID NO. 642,

5 (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 643, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 643, and

(xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 644, or a twelfth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, or 3 amino acids different from SEQ ID NO. 644.

10

Clause 42:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 38 for use in a method of treating a coronavirus infection in a subject.

15 **Clause 43:**

A composition comprising the bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 38.

Clause 44:

20 A composition according to Clause 43 further comprising a second medicament, for simultaneous, separate, or sequential administration.

Clause 45:

25 A composition according to Clause 44, wherein the second medicament comprises a second antibody or antigen binding fragment thereof.

Clause 46:

A composition according to Clause 44, wherein the second medicament comprises a bispecific antibody or bispecific antigen binding fragment thereof.

30

Clause 47:

A composition according to Clause 43, wherein the composition further comprises a pharmaceutically acceptable excipient or carrier.

5 **Clause 48:**

A composition according to Clause 43, for use in inhibiting and /or treating a coronavirus infection in a subject, preferably, a SARS-CoV-1 or SARS-CoV-2 infection in a subject, comprising an effective amount of the bispecific antibody or an antigen binding fragment thereof, nucleic acid molecule, or vector, and optionally a pharmaceutically acceptable
10 excipient or carrier.

Clause 49:

The composition of Clause 43, for use as a medicament.

15 **Clause 50:**

An inhaler device comprising the composition of Clause 43.

Clause 51:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses
20 26 to 38, wherein the bispecific antibody or an antigen binding fragment thereof is bivalent.

Clause 52:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses
25 26 to 38, wherein the bispecific antibody or antigen-binding fragment thereof is capable of binding to the stem helix and/or the fusion peptide of at least one of an α -coronavirus, β -coronavirus, γ -coronavirus, and δ -coronavirus, preferably at least an α -coronavirus and/or a β -coronavirus.

30 Clauses

The following numbered clauses each represent preferred embodiments of the invention and are part of the description.

Clause 53:

An anti-coronavirus, preferably anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 645, 646, 647, 648, 649 to 650.

10

Clause 54:

A bispecific antibody or an antigen binding fragment thereof according to Clause 53, comprising a first Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and a second Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 046, 114, 254, 367, 430 and/or 545 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 645, 646, 647, 648, 649 and/or 650.

Clause 55:

A bispecific antibody or an antigen binding fragment thereof according to Clauses 53 or 54, comprising a first Fab specifically binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and a second Fab specifically binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, characterized in that:

- a.) the first Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and
- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 645, a Heavy Chain CDR2 region of SEQ ID NO: 646 and a Heavy Chain CDR3 region of SEQ ID NO: 647 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 648, a Light Chain CDR2 region of SEQ ID NO: 649 and a Light Chain CDR3 region of SEQ ID NO: 650.

Clause 56:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 55, comprising:

- 5 a) A light chain comprising VL-CL domains and heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody or an antigen binding fragment thereof, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, and
- b) A light chain comprising VL-CL domains and heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody or an antigen binding fragment thereof, capable of binding
- 10 to the fusion peptide of a coronavirus, preferably SARS-CoV-2,

wherein constant domains CL and CH1 from the antibody or an antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, are replaced by each other.

15 **Clause 57:**

A bispecific antibody or an antigen binding fragment thereof according to Clause 56, wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region

20 of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and the VL domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and

- 25 wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 645, a Heavy Chain CDR2 region of SEQ ID NO: 646 and a Heavy Chain CDR3 region of SEQ ID NO: 647 and the VL domain of the antibody or the antigen binding fragment thereof that is capable of
- 30 binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 648, a Light Chain CDR2 region of SEQ ID NO: 649 and a Light Chain CDR3 region of SEQ ID NO: 650.

Clause 58:

A bispecific antibody, or an antigen binding fragment thereof according to any of Clauses 53 to 55, comprising:

- a) A light chain comprising VL-CL domains and heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2; and
- b) A light chain comprising VL-CL domains and heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein constant domains CL and CH1 from the antibody that is capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2 are replaced by each other.

Clause 59:

A bispecific antibody or an antigen binding fragment thereof according to Clause 58,

- wherein the VH domain of the antibody or the antigen binding fragment thereof that is capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 046, a Heavy Chain CDR2 region of SEQ ID NO: 114 and a Heavy Chain CDR3 region of SEQ ID NO: 254 and the VL domain of the antibody capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 367, a Light Chain CDR2 region of SEQ ID NO: 430 and a Light Chain CDR3 region of SEQ ID NO: 545, and

- wherein the VH domain of the antibody capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 645, a Heavy Chain CDR2 region of SEQ ID NO: 646 and a Heavy Chain CDR3 region of SEQ ID NO: 647 and the VL domain of the antibody capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 648, a Light Chain CDR2 region of SEQ ID NO: 649 and a Light Chain CDR3 region of SEQ ID NO: 650.

Clause 60:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 55, comprising:

a) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2; and

5 b) A light chain comprising VL-CL domains and a heavy chain comprising VH-CH1-CH2-CH3 domains of an antibody, capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, wherein domains VL-CL and VH-CH1 from the antibody that specifically binds to the fusion peptide of a coronavirus, preferably SARS-CoV-2, are replaced by each other.

10 **Clause 61:**

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 60, wherein the first Fab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical,
15 at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 629.

Clause 62:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses
20 53 to 60, wherein the second Fab comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 665.

25

Clause 63:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 60, wherein the first Fab comprises a light chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical,
30 at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 630.

Clause 64:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 60, wherein the second Fab comprises a light chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 666.

Clause 65:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 60, wherein the bispecific antibody or antigen binding fragment thereof is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

Clause 66:

A method for the production of a bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 65, comprising a) culturing a host cell, comprising an expression vector, comprising a polynucleotide encoding a bispecific antibody or an antibody fragment according to any one of the preceding Clauses under conditions which permit the production of said bispecific antibody or an antigen binding fragment thereof, and b) isolating said bispecific antibody or an antigen binding fragment thereof.

Clause 67:

A nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleic acid sequence encodes the bispecific antibody or antigen binding fragment thereof, a heavy chain variable region and/or a light chain variable region of the bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 65, preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.

Clause 68:

A nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleic acid sequence encodes the bispecific antibody or antigen binding fragment thereof, a heavy chain variable region and/or light chain variable region of the bispecific antibody or the antigen binding fragment thereof according to any of Clauses 53 to 65 and Clause 67,
5 wherein the nucleic acid sequence comprises at least anyone of:

- (i) a first nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 046, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 046,
- 10 (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 114, or a second nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 114,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 254, or a third nucleic acid sequence encoding the amino acid sequence having at
15 most 1, 2 or 3 amino acids different from SEQ ID NO. 254,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 367, or a fourth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3 or 4 amino acids different from SEQ ID NO. 367,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID
20 NO. 430, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 430,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 545, or a sixth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, or 4 amino acids different from SEQ ID NO. 545,
- 25 (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 645, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 645,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 646, or an eighth nucleic acid sequence encoding the amino acid sequence
30 having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 646,
- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 647, or a ninth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 647,

(x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 648, or a tenth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, or 3 amino acids different from SEQ ID NO. 648,

5 (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 649, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 649, and

(xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 650, or a twelfth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, or 3 amino acids different from SEQ ID NO. 650.

10

Clause 69:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 65 for use in a method of treating a coronavirus infection in a subject.

15 **Clause 70:**

A composition comprising the bispecific antibody and/or an antigen binding fragment thereof according to any of Clauses 53 to 65.

Clause 71:

20 A composition according to Clause 70 further comprising a second medicament, for simultaneous, separate, or sequential administration.

Clause 72:

25 A composition according to Clause 71, wherein the second medicament comprises a second antibody or antigen binding fragment thereof.

Clause 73:

A composition according to Clause 71, wherein the second medicament comprises a bispecific antibody or bispecific antigen binding fragment thereof.

30

Clause 74:

A composition according to Clause 70, wherein the composition further comprises a pharmaceutically acceptable excipient or carrier.

5 **Clause 75:**

A composition according to Clause 70, for use in inhibiting and /or treating a coronavirus infection in a subject, preferably, a SARS-CoV-1 or SARS-CoV-2 infection in a subject, comprising an effective amount of the bispecific antibody or an antigen binding fragment thereof, nucleic acid molecule, or vector, and optionally a pharmaceutically acceptable
10 excipient or carrier.

Clause 76:

The composition of Clause 70, for use as a medicament.

15 **Clause 77:**

An inhaler device comprising the composition of Clause 70.

Clause 78:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses
20 53 to 65, wherein the bispecific antibody or an antigen binding fragment thereof is bivalent.

Clause 79:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses
25 53 to 65, wherein the bispecific antibody or antigen binding fragment thereof is capable of binding to the stem helix and/or the fusion peptide of at least one of an α -coronavirus, β -coronavirus, γ -coronavirus, and δ -coronavirus, preferably at least an α -coronavirus and/or a β -coronavirus.

30

DESCRIPTION OF THE DRAWINGS

Figure 1. Survival after lethal challenge - CV3-25.

Kaplan-Meier survival curves of the intraperitoneal prophylactic treatment group. Animals (n=10 per group), treated with a dose titration with the control antibody, CV3-25, at day -1. At day 0, animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Lines are nudged relative to the Y-axis to improve visual representation.

Figure 2. Survival after lethal challenge - CV3-25.

Kaplan-Meier survival curves of the intranasal prophylactic treatment group. Animals (n=10 per group, except 15 mg/kg where n=8), treated with a dose titration with the control antibody, CV3-25, at day -1. At day 0, animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Lines are nudged relative to the Y-axis to improve visual representation.

Figure 3. Bodyweight change - CV3-25.

Bodyweight change (%) relative to day 0, for the intraperitoneal prophylactic treatment group. Animals (n=10 per group) were treated with a dose titration of the control antibody, CV3-25, at day -1 intranasally. At day 0 animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Bars represent the 95% CI. of the mean. If a mouse died / was euthanized during follow-up of the study, the last observed bodyweight was carried forward.

Figure 4. Bodyweight change - CV3-25.

Bodyweight change (%) relative to day 0, for the intranasal prophylactic treatment group. Animals (n=10 per group, except 15 mg/kg where n=8) were treated with a dose titration of the control antibody, CV3-25, at day -1 intranasally. At day 0 animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Bars represent the 95% CI. of the mean. If a mouse died / was euthanized during follow-up of the study, the last observed bodyweight was carried forward.

Figure 5. Survival and bodyweight change for the intraperitoneal administration – antibody according to invention

Survival and bodyweight change for the intraperitoneal administration of the antibody according to invention in a pre-exposure efficacy study in K18-hACE2 mice upon lethal SARS-CoV-2 Delta challenge. Animals (n=10 per group) were treated with a dose titration of the antibody intraperitoneally or vehicle control. Figure 5A: Kaplan-Meier survival curves of the treatment groups is shown. Lines are nudged relative to the Y-axis to improve visual representation. Figure 5B: Bodyweight change (%) relative to Day 0 is shown. Error bars represent the 95% confidence interval (CI.) of the mean. If a mouse died/ was euthanized during follow-up of the study, the last observed bodyweight was carried forward. Asterisk indicates significance compared to vehicle control group.

Figure 6. Survival and bodyweight change for the intranasal administration – antibody according to invention

Survival and bodyweight change for the intranasal administration of the antibody according to invention in a pre-exposure efficacy study in K18-hACE2 mice upon lethal SARS-CoV-2 Delta challenge. Animals (n=10 per group) were treated with a dose titration of the antibody intranasally or vehicle control. Figure 6A: Kaplan-Meier survival curves of the treatment groups is shown. Lines are nudged relative to the Y-axis to improve visual representation. Figure 6B: Bodyweight change (%) relative to Day 0 is shown. Error bars represent the 95% confidence interval (CI.) mean. If a mouse died/ was euthanized during follow-up of the study, the last observed bodyweight was carried forward. Asterisk indicates significance compared to vehicle control group.

Figure 7. Linear epitope mapping against Spike helix domain of alpha and beta coronaviruses.

Grey highlighted amino acids were identified as the epitope where the antibody is binding the Spike protein. Target sequences for the 7 tested strains are aligned by Clustal. *may contain multiple smaller parts of the epitope.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of clarity and a concise description, features may be described herein as part of the same or separate embodiments, however, it will be appreciated that the disclosure includes embodiments having combinations of all or some of the features described. References to “method for treatment”, “treatment method”, “antibody for use” and “use of an antibody in the manufacture of a medicament” can be used interchangeably and embodiments disclosed in relation to any one of those aspects also applies in relation to said other aspects. In other words, they all refer to medical treatments involving an antibody as disclosed herein.

Prophylactic treatment

The term ‘**prophylactic treatment**’, as used herein, includes reference to a treatment for preventing infection of an individual with a coronavirus, or preventing symptoms after infection with a coronavirus, or preventing severe symptoms after known infection with a coronavirus with or without symptoms, or preventing hospitalization and death after infection with a coronavirus.

Prevention of an infection is preferably performed by administration of an antibody as disclosed herein prior to coronavirus exposure *i.e.* pre-exposure prophylaxis.

‘Prophylactically’ therefore preferably means prior to virus exposure. Nonetheless, it may also involve administration after infection, for example for reducing the replication or spread, or increasing clearance of the virus *i.e.* post-exposure prophylaxis.

Infected individuals may present with no symptoms. Alternatively, infected individuals may present with symptoms.

Preferably, post-exposure prophylaxis involves administering an antibody as disclosed herein after coronavirus exposure to prevent symptomatic disease.

Preferably, post-exposure prophylaxis involves administering an antibody as disclosed herein after coronavirus exposure to prevent severe disease, in particular hospitalization.

In a treatment method of the invention, prophylactic treatment involves administration of antibodies against coronavirus at a point in time when the individual is not infected with coronavirus. Preferably, said antibodies bind to a conserved epitope of the spike protein of a coronavirus virion. In some embodiments, an individual in need thereof is not
5 (yet) infected with coronavirus.

Therapeutic treatment

The term '**therapeutic treatment**', as used herein, includes reference to treatment of a viral infection (including coronavirus disease) after viral infection has taken place. A viral
10 infection involves the entry of the virus into the body, and/or the replication of the virus in the body and/or the spreading of the virus to cells, tissues or locations in the body that were previously uninfected. A viral infection may cause one or more diseases, but may also be latent, in other words may reside in the body without causing symptoms or disease.

Coronavirus

The term '**coronavirus**', as used herein, includes reference to a positive-sense single-stranded RNA virus belonging to the family of Coronaviridae.

Preferably, an antibody as disclosed herein is capable of specifically binding to the stem
20 helix of a coronavirus, in particular SARS-CoV-2.

Preferably, an antibody as disclosed herein is capable of specifically binding to the stem helix of SARS-CoV-2 variants of concern.

Preferably, the antibody as disclosed herein is capable of neutralizing a coronavirus, in
25 particular SARS-CoV-2.

Preferably, an antibody as disclosed herein is capable of neutralizing at least one or more, preferably two or more, preferably three or more, preferably four or more, even more
30 preferably five or more coronavirus subtypes.

The phrase "is capable of" as used in, means the ability of an antibody or an antigen-binding fragment thereof as described herein is enough to bind to at least a part of an

antigen, such as the stem helix of a coronavirus, in particular SARS-CoV-2 and/or the fusion protein of a coronavirus, in particular SARS-CoV-2. The binding affinity or the binding ability of the antibody and/or the antigen-binding fragment thereof as described herein can be measured using any methods known by a person skilled in the art. The
5 phrase “is capable of” as used here, encompasses but not limited to the phrase “specifically binding” or “specifically bind to”.

Coronavirus infection

The term ‘**coronavirus infection**’, as used herein, includes reference to the pathological
10 or non-pathological, preferably pathological, entrance and residence of a coronavirus of any type in a human host. The infecting virus may replicate within the host, its cells or the cells of its microbiome. The infecting virus may or may not cause a disease, for example COVID-19. The infection may or may not be able to be detected by methods for virus infection detection known in the art. The infected individual may or may not be
15 aware of the infection. Typical, but non-exclusive locations of the human body where, for example SARS-CoV-2, may be located in an infected individual, are the respiratory system and/or cells thereof and the cardiovascular system and/or cells thereof. The term ‘coronavirus infection’, as used herein, further includes reference to the entrance and residence of a part of a coronavirus of any type that is able to cause viral replication in a
20 human host. The term ‘**coronavirus infection**’ encompasses symptoms or disease following the infection, e.g. COVID-19. The term ‘coronavirus infection’ encompasses ‘SARS-CoV-2 infection’.

Epitope

25 An “epitope”, as used herein, includes reference to a moiety that is capable of binding to an antibody as disclosed herein with sufficiently high affinity to form a detectable antigen-antibody complex.

Individual

30 The term ‘**individual**’, as used herein, includes reference to a mammal or human that is subject to, or a risk of suffering from viral infection. Infection may take place in any system, tissue or cell belonging to the host, including the host’s microbiome. Coronavirus infection and the disease coronavirus may occur in individuals of all age groups and sexes. Nonetheless, preferably, the individual is a human, in particular an elderly human such

as a human that is at least 60, 65, 70, 75, 80, or at least 85 years old, or that has an increased risk of infection because of occupation or living environment. Preferably, the individual is at risk of suffering from severe illness, for example COVID-19, once infected. In preferred embodiments, the individual has an underlying disease such as (i) a
5 respiratory disease such as asthma, COPD, chronic bronchitis and lung emphysema, (ii) cardiovascular disease such as cardiac arrhythmia or individuals that have received cardiac surgery, (iii) diabetes, (iv) renal failure and/or (v) a disease affecting the immune system, for instance immunocompromised individuals, or higher risk of viral infection because of occupation.

10

The phrase '**an individual**', as used herein, includes reference to a mammal such as a but not limited to a human that benefits from a specified therapy, for example, the phrase '**an individual**' may encompass Non-human primates (NHP).

15 Preferably, the individual is a mammal, more preferably a human.

Administering and Administration

The terms '**administering**' and '**administration**', as used herein, include reference to the provision of one or more drug and optionally one or more adjuvant with the aim to
20 treat, cure, reduce, or prevent a disease or its symptoms in an individual, or to promote the individual's well-being. Preferred methods of administration of the antibody as disclosed herein include mucosal administration, preferably intranasal administration and oral inhalation.

An individual in need thereof

25 The phrase '**an individual in need thereof**', as used herein, includes reference to a mammal such as a human that benefits from a specified therapy. A treatment method of the invention may be used prophylactically, the exhibition of symptoms or indications for coronavirus infection are not required. Individuals that are especially in need of the
30 method or antibody for use of the invention, are individuals with an elevated risk of coronavirus infection, individuals with an elevated risk of developing severe symptoms (illness), for example COVID-19, and/or individuals with an elevated risk of dying from COVID-19. The person skilled in the art is aware of the risk factors for an elevated risk

of coronavirus infection, an elevated risk of developing severe symptoms of coronavirus infection, and an elevated risk of dying from coronavirus infection.

Antibody

5 The term '**antibody**', as used herein, includes reference to an intact immunoglobulin, including monoclonal antibodies, such as chimeric, humanized or human monoclonal antibodies, or to a binding molecule comprising an antigen-binding domain (such as heavy chain CDRs 1-3 of a variable domain) of an antibody as disclosed herein or an antibody that competes with an antibody as disclosed herein for specific binding to the binding
10 partner of the immunoglobulin.

In other words, functional fragments of antibodies are also encompassed by the term 'antibody'. Antibodies are generally Y-shaped proteins. Within the antibody, constant domain and variable domains are generally present. The variable domain facilitates
15 antigen binding. An antibody generally comprises two heavy chains and two light chains. Both the heavy chains and the light chains are partially constant and partially variable. Antibodies occur in a few classes: IgA, IgD, IgE, IgG and IgM. Preferably, the antibody of the invention is of the IgG, preferably IgG1, class. Some classes may be further subdivided into subclasses or isotypes. For example, the IgG class is subdivided into the subclasses
20 IgG1, IgG2, IgG3 and IgG4. Preferably, the antibody of the invention is of the IgG, preferably IgG1, class. Antigen-binding regions, or antigen-binding fragments of an antibody, which are encompassed by the term 'antibody' and which are therefore part of the present invention, may include, for example, Fab, F(ab'), F(ab')₂, dAb, Fv, Fd, CDR fragments, diabodies, triabodies, tetrabodies, single-chain antibodies (scFv, scFv-Fc),
25 bivalent single-chain antibodies, single-chain phage antibodies, (poly)peptides that contain at least a fragment of an immunoglobulin that is sufficient to confer specific antigen binding to the (poly)peptide, etc. The above fragments may be produced synthetically or by enzymatic or chemical cleavage of intact immunoglobulins or they may be genetically engineered by recombinant DNA techniques. The methods for production
30 of antibodies and antigen-binding fragments are well-known to a person skilled in the art. The antibody may be conjugated or unconjugated. The antibody may be conjugated, linked, or otherwise physically or functionally associated with an effector moiety or tag, such as inter alia an enzyme, a liposome, a radioactive substance, a fluorophore, a toxic

substance. Antibodies may have been stabilized, multimerized, humanized or otherwise manipulated.

Antibodies may be neutralizing, which includes reference to inhibition of a virus as
5 measured by an *in vitro* neutralization assay, for instance in terms of viral host cell entry
and/or viral replication. Neutralization can for example be achieved by inhibiting the
attachment or adhesion of the virus to the cell surface, or by inhibition of the fusion of
viral and cellular membranes following attachment of the virus to the target cell or by
inhibiting viral egress from cells. Neutralization does not specify the method of
10 neutralization. Preferably, the antibody is cross-neutralizing, which includes reference to
the ability of the antibodies of the invention to bind a set of different molecules, preferably
different molecules of different subtypes belonging to the Coronaviridae family.

The term “domain” or “region” as used herein, with reference to a part of an antibody,
15 bispecific antibody, or an antigen binding fragment thereof, can be used interchangeably
herein.

The phrase “antigen-binding fragments”, “antigen binding fragments”, “antigen
fragment”, “a fragment of an antibody” or “antigen-binding molecule” as used herein,
20 means a protein, polypeptide or molecular complex comprising or consisting of at least
one complementarity determining region (CDR) that alone, or in combination with one or
more additional CDRs and/or framework regions (FRs), as described herein, is capable of
binding to a part of an antigen, including the stem helix of a coronavirus, in particular
SARS-CoV-2, and/or the stem helix of a coronavirus, in particular SARS-CoV-2 and its
25 variants of concern. The phrases “antigen-binding fragments”, “antigen binding
fragments”, “antigen fragment”, “a fragment of an antibody” or “antigen-binding
molecule” as used herein, can be used interchangeably. For instance, the phrase “antigen
binding fragments” as used herein is to be used interchangeably with the phrase “antibody
fragments” as used herein.

30

Antibodies comprise complementarity determining regions situated on the variable
domains of the heavy chain and the light chain. The CDRs contribute to a large extent to
the antigen binding site. Three CDRs can be distinguished, namely CDR1, CDR2 and
CDR3. As each CDR can be located on either the light chain or the heavy chain, there are

generally six CDRs for each antigen receptor that collectively contact the antigen: the light chain CDR1, the light chain CDR2, the light chain CDR3, the heavy chain CDR1, the heavy chain CDR2 and the heavy chain CDR3. The CDRs of type CDR3 are the most variable. The CDRs can be specific for linear epitopes, discontinuous epitopes, or
5 conformational epitopes of proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured or activated. Epitopes may also consist of or comprise post-translational modifications of proteins. Antibodies of the invention that are of particular interest, are antibodies comprising CDRs that recognize coronavirus antigens, such as the spike protein and in
10 particular the stem helix of the spike protein. The antibody as disclosed herein binds to a conserved epitope in the stem helix at the base of the spike protein of the SARS-CoV-2 virion. The epitope of the antibody as disclosed herein uses light and heavy chain CDR loops.

15 The antibody as disclosed herein can be used in isolated or non-isolated form.

Preferably, the compositions of the invention comprise a single anti-coronavirus antibody as disclosed herein.

20 Preferably, the antibody of the invention as disclosed herein can cross-neutralize coronavirus, in particular SARS-CoV-2.

Furthermore, the antibody as disclosed herein can be used alone or in a mixture comprising the antibody (or variant, fragment or bispecific thereof) as disclosed herein,
25 and/or with other antibodies that bind to a coronavirus and have a coronavirus inhibiting effect. In other words, the antibody as disclosed herein can be used in combination, e.g., as a pharmaceutical composition or co-administration of compositions comprising two or more antibodies that specifically bind coronavirus. For example, antibodies having different, but complementary activities can be combined in a single therapy to achieve a
30 desired therapeutic or prophylactic effect, but alternatively, antibodies having identical activities can also be combined in a single therapy to achieve a desired prophylactic or therapeutic effect. Optionally, the mixture further comprises at least one other therapeutic agent.

Preferably, the antibody as disclosed herein are a bispecific antibody and/or an antigen binding fragment thereof, wherein the bispecific antibody is capable of binding to the stem helix of a coronavirus and/or capable of binding to fusion peptide of coronavirus. The phrase “capable of binding” encompasses the phrase “specifically binds to”, in other words,
5 an antibody, a bispecific antibody and/or an antigen binding fragment thereof as disclosed herein are that is capable of binding to an epitope may also be capable of binding the other epitopes.

Preferably, the coronavirus as described herein includes SARS-CoV-2 and variants.

10

The phrase “are replaced by each other”, “are mutually interchanged”, “swap places with each other”, or “are traded for one another” as used herein, includes reference to at least a part of the heavy chain domains of an antibody or an antigen-binding fragment as described herein such as when a CH1 and/or VH, is substituted by at least a part of the
15 light chain domains such as CL and/or VL to which said at least a part of the heavy chain domains are paired, and at the same instant, said at least a part of the light chain domains is substituted by said at least a part of the heavy chain domains. The phrase “are replaced by each other”, “are mutually interchanged”, “swap places with each other”, or “are traded for one another” are to be used interchangeably herein.

20

Preferably, the antibody as disclosed herein is a human antibody.

Framework regions

25 Antibodies also comprise framework regions, generally four framework regions (FR1, FR2, FR3 and FR4) on each of the variable heavy chain domain and variable light chain domain. The CDRs are situated between the framework regions (preferably in the order FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and both the CDRs and framework regions together define a heavy chain variable domain (or region) and light chain variable domain
30 (or region) which may also be referred to as an antigen-binding region or domain.

IgG antibody

The term 'IgG antibody', as used herein, includes reference to an antibody comprising two antigen-binding sites. IgG is the most common antibody in human serum. Heavy chains of IgG antibodies are of type γ , which can be subdivided in $\gamma 1$, $\gamma 2$, $\gamma 3$ and $\gamma 4$. Preferably, the antibodies described herein are $\gamma 1$ heavy chains. Light chains of IgG antibodies are of type λ or κ . Preferably, the antibodies described herein are λ light chains.

Preferably, the antibody is an IgG antibody, preferably an IgG1 antibody.

IgA antibody

The term 'IgA antibody', as used herein, includes reference to an antibody comprising two to four antigen-binding sites. IgA is the most abundant antibody in mucosal secretions. An IgA antibody can be produced in monomeric, dimeric or secretory form, with two or four antigen-binding sites, respectively, and can exist as an IgA1 or IgA2 isotype. [Heavy chains of IgA antibodies are of type α , which can be subdivided in $\alpha 1$ and $\alpha 2$. Light chains of IgA antibodies are of type λ or κ .

Preferably, the antibody is an IgA antibody.

IgM antibody

The term 'IgM antibody', as used herein, includes reference to an antibody comprising ten to twelve antigen-binding sites. An IgM antibody can be produced in pentameric or hexameric form. Heavy chains of IgM antibodies are of type μ . Light chains of IgM antibodies are of type λ or κ .

Preferably, the antibody is an IgM antibody.

Anti-Coronavirus antibody

The term 'anti-coronavirus antibody', as used herein, includes reference to an antibody as disclosed herein, *i.e.* an antibody that can be used in a treatment method of the invention. Preferably, the anti-coronavirus antibody of the invention is able to treat different subtypes of coronavirus.

For the avoidance of doubt, the term 'anti-coronavirus antibody', can be used interchangeably with 'coronavirus antibody'.

A composition

5 In a preferred embodiment, an antibody disclosed herein is the sole active ingredient in a composition administered for treatment, e.g., the antibody is provided in a composition as the sole active ingredient.

In a preferred embodiment, the active ingredients comprise an antibody disclosed herein,
10 e.g., the antibody is provided either as a composition as the sole active ingredient in a composition administered for treatment or in a combination with another antibody.

In a preferred embodiment, a first antibody as disclosed herein is provided as a composition in combination with a second antibody, wherein the first antibody comprises
15 a CDR sequence comprising any one of SEQ ID NO: 001 to 006, 012 to 017, 023 to 028, 033 to 038, 042 to 047, 050 to 055, 077 to 082, 088 to 093, 099 to 104, 110 to 115, 121 to 126, 132 to 137, 197 to 202, 208 to 213, 219 to 224, 230 to 235, 241 to 246, 252 to 257, 303 to 308, 314 to 319, 325 to 330, 336 to 341, 347 to 352, 358 to 363, 421 to 426, 432 to 437, 443 to 448, 454 to 459, 465 to 470, 475 to 480, 514 to 519, 525 to 530, 536 to 541, 547 to
20 552, 558 to 563, 569 to 574. More preferably wherein the first antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545, and the second antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 639, 640, 641, 642, 643 or SEQ ID NO.: 644. Preferably wherein the composition is administered for prophylactic and/or therapeutic treatment.

25

In a preferred embodiment, a first antibody as disclosed herein is provided as a composition in combination with a second antibody, wherein the first antibody comprises a CDR sequence comprising any one of SEQ ID NO: 001 to 006, 012 to 017, 023 to 028, 033 to 038, 042 to 047, 050 to 055, 077 to 082, 088 to 093, 099 to 104, 110 to 115, 121 to
30 126, 132 to 137, 197 to 202, 208 to 213, 219 to 224, 230 to 235, 241 to 246, 252 to 257, 303 to 308, 314 to 319, 325 to 330, 336 to 341, 347 to 352, 358 to 363, 421 to 426, 432 to 437, 443 to 448, 454 to 459, 465 to 470, 475 to 480, 514 to 519, 525 to 530, 536 to 541, 547 to 552, 558 to 563, 569 to 574. More preferably wherein the first antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545, and

the second antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 645, 646, 647, 648, 649 or SEQ ID NO.: 650. Preferably wherein the composition is administered for prophylactic and/or therapeutic treatment.

5 In a preferred embodiment, a first antibody as disclosed herein is provided as a composition in combination with a second antibody, wherein the first antibody comprises a CDR sequence comprising any one of SEQ ID NO: 001 to 006, 012 to 017, 023 to 028, 033 to 038, 042 to 047, 050 to 055, 077 to 082, 088 to 093, 099 to 104, 110 to 115, 121 to 126, 132 to 137, 197 to 202, 208 to 213, 219 to 224, 230 to 235, 241 to 246, 252 to 257, 303
10 to 308, 314 to 319, 325 to 330, 336 to 341, 347 to 352, 358 to 363, 421 to 426, 432 to 437, 443 to 448, 454 to 459, 465 to 470, 475 to 480, 514 to 519, 525 to 530, 536 to 541, 547 to 552, 558 to 563, 569 to 574. More preferably wherein the first antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545, and the second antibody comprises CDR sequences comprising any one or more of SEQ ID NO:
15 651, 652, 653, 654, 655 or SEQ ID NO.: 656. Preferably wherein the composition is administered for prophylactic and/or therapeutic treatment.

In a preferred embodiment, a first antibody as disclosed herein is provided as a composition in combination with a second antibody, wherein the first antibody comprises
20 a CDR sequence comprising any one of SEQ ID NO: 001 to 006, 012 to 017, 023 to 028, 033 to 038, 042 to 047, 050 to 055, 077 to 082, 088 to 093, 099 to 104, 110 to 115, 121 to 126, 132 to 137, 197 to 202, 208 to 213, 219 to 224, 230 to 235, 241 to 246, 252 to 257, 303 to 308, 314 to 319, 325 to 330, 336 to 341, 347 to 352, 358 to 363, 421 to 426, 432 to 437, 443 to 448, 454 to 459, 465 to 470, 475 to 480, 514 to 519, 525 to 530, 536 to 541, 547 to
25 552, 558 to 563, 569 to 574. More preferably wherein the first antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 046, 114, 254, 367, 430 or 545, and the second antibody comprises CDR sequences comprising any one or more of SEQ ID NO: 657, 658, 659, 660, 661 or SEQ ID NO.: 662. Preferably wherein the composition is administered for prophylactic and/or therapeutic treatment.

30

Preferably, the composition of the invention is a water-based composition such as an aqueous liquid. Preferably, the composition of the invention further comprises one or more salts, for example sodium chloride. The composition of the invention may further comprise one or more buffering agents, for example sodium acetate. The composition of the

invention may further comprise one or more carbohydrates, such as sucrose, or other active ingredients, such as other antibodies, neuraminidase inhibitors, endonuclease inhibitors, and adjuvants such as oils, cytokines, emulsifiers, or combinations thereof. The pH of the composition of the invention can be between 4 and 8, more preferably the pH is
5 around 5.5. Preferably the pH is around 7.4.

Mucosal composition

The term '**mucosal composition**', as used herein, refers to any pharmaceutical formulation that may be topically applied to a mucosal surface and delays or resists the
10 mucosal flushing or removal action.

The term '**mucosal composition**', may be used in reference to a route of administration in which an antibody, as disclosed herein, is provided into the nasal cavity, oropharyngeal region or upper respiratory tract, preferably through the nostrils, as part of a prophylactic
15 and/or therapeutic treatment as disclosed herein.

Mucosally

The mucosa comprises membranes that line cavities in the human body, covering internal organs, and consist of one or more layers of epithelial cells and loose
20 connective tissue, which may produce mucus. The term 'mucosally', as used herein, may also be referred to as 'mucosal administration', and includes reference to a route of administration in which a drug is prophylactically and/or therapeutically provided to the mucosa, for example, mucosa found in the nose, mouth, lungs, vagina, rectum or stomach. The mucous membrane lubricates and protects these organs and cavities from
25 abrasive particles and bodily fluids, as well as invasive pathogens.

Preferably, the antibodies of the invention are administered mucosally.

Intranasally

30 The term 'intranasally', as used herein, may also be referred to as 'nasal administration', and includes reference to a route of administration in which a drug is provided into the upper respiratory tract and/or lower respiratory tract, preferably through the nostrils, as part of a prophylactic and/or therapeutic treatment as disclosed herein. Preferably, the

administration provides for drug in the nasal cavity. The back section of the nasal cavity is also referred to as the pharynx. Nasal administration preferably provides for delivery of antibodies as disclosed herein in the mucous membrane lining the nasal cavity. Intranasal administration can be performed using, for instance, a nasal spray or nose
5 drops. In some embodiments, the drug is delivered to the nasal cavity via the oral route. For example, RetroNose uses a breath-actuated pressurised metered-dose inhaler (pMDI) to administer drugs through the buccal cavity during the nasal expiratory phase. Such methods allow the drug particles to enter the nasal cavities through the pharynx.

10 Preferably, the antibodies of the invention are administered intranasally.

With intranasal administration, a drug is provided through the nostrils to the upper respiratory tract as part of a prophylactic and/or therapeutic treatment as disclosed herein. Preferably, the administration provides for drug in the nasal cavity. Nasal
15 administration can either be a form of topical administration or systemic administration, as the drugs thus locally delivered can go on to have either local or systemic effects. In the present case, with antibodies as disclosed herein, nasal administration is preferably a form of topical administration.

20 Intranasal administration as disclosed herein may be done using a medicament in liquid form, preferably in the form of drops or nasal spray. The aqueous liquid may comprise adjuvants. These adjuvants may for example be salts, oils, cytokines, emulsifiers, buffering agents, carbohydrates and combinations thereof. Intranasal administration may also be done using a medicament in solid form, such as powders.

25

Oral inhalation

The term 'oral inhalation', as used herein, may also be referred to as 'mouth inhalation', and includes reference to a route of administration in which a drug is provided through the mouth to the upper and/or lower respiratory tract such as lungs, as part of a
30 prophylactic and/or therapeutic treatment of the invention. Oral inhalation may for example be applied for drugs in their powdered form and drugs in the form of liquid droplets or aerosols.

Preferably, the antibodies of the invention are administered by oral inhalation.

With oral inhalation, a drug is provided through the mouth to the respiratory tract, preferably lower respiratory tract such as lungs, as part of a prophylactic and/or therapeutic treatment of the invention. As described further herein, oral inhalation also includes nasal drug delivery (also referred to as nasal drug delivery via the oral route).

Oral inhalation may for example be applied for drugs in their powdered form and drugs in the form of liquid droplets or aerosols. Oral inhalation may include the use of an inhaler. The inhaler may be involved in the achievement of the dose that was determined. The drug that is administered by oral inhalation may reach the lung but may also partially be cleared out by exhalation.

Administration by oral inhalation as disclosed herein may be done using a medicament comprising aerosols in powdered (solid) or liquid form. Powdered aerosols comprising particles smaller than 3 μm in diameter will primarily reach the respiratory region of the lung, and will therefore be absorbed better than larger particles. The medicament may comprise adjuvants. These adjuvants may for example be salts, oils, cytokines, emulsifiers, buffering agents, carbohydrates and combinations thereof.

Oropharyngeal administration

The term 'oropharyngeal administration', as used herein, may also be referred to as delivery to the part of the pharynx that lies between the soft palate and the hyoid bone and includes reference to a route of administration in which a drug is provided via either the mouth or nasal passages as part of a prophylactic and/or therapeutic treatment. Oropharyngeal administration may, for example, be used for drugs in their powdered form and drugs in the form of liquid droplets or aerosols.

Preferably, the antibodies of the invention are administered by oropharyngeal administration.

Prior to

The term 'prior to', as used herein, includes reference to the administration of an antibody before an individual has been exposed to, or is infected with, a coronavirus.

Preferably, the antibody as disclosed is administered to an individual up to 24 hours prior to coronavirus exposure, for example between zero and 24 hours before the individual has been exposed to said coronavirus.

Preferably, the antibody as disclosed is administered to an individual up to 48 hours prior to coronavirus exposure, for example between zero and 48 hours before the individual has been exposed to said coronavirus.

In a preferred embodiment, the antibody is administered 2 days or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 3 days or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 4 days, or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 5 days or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 6 days or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 7 days or more prior to coronavirus exposure.

20

Dosage

The term 'dosage' as used herein, refers to the amount of antibody to be given at a particular time (e.g., over the course of a 24-hour, 12-hour, 30-minute period, etc.). A dose refers to a single dosing episode, whether the dose is a unit dosage form or multiple unit dosage forms taken together (e.g., ingestion of two or more pills, receiving two or more nasal administrations). A dosage includes reference to a pharmaceutical dosage form wherein the medicament is packaged for administration as, e.g., a single-unit dose or multiple-unit dose. A dosage may also be administered as, e.g., one or more drops of an antibody-comprising composition (e.g., nasal drops) or one or more sprays of an antibody-comprising composition (e.g., nasal sprays).

Preferably, a suitable dosage of an antibody as disclosed herein contains a dose of between 0.01 mg and 20 mg, preferably 0.1 mg and 15 mg, more preferably around 0.5 mg and 10

mg or even around 1 mg, *e.g.* when the dosage is for intranasal administration. Such dosages are also referred to as “flat dosages” or “nominal dosages” in contrast to dosages based on the weight of the patient. Flat dosages have the advantage that the medicament can be packaged in a single-unit dose, for example. A single dose of an antibody according to the present invention can provide protection from coronavirus infection for several days and may be provided “on demand” or “as needed”. For example, an individual may administer antibody before leaving the house or before coming into contact with other individuals.

In order to provide long-lasting protection, the antibody may be administered on a regular basis. For example, the antibody is administered once, or at least once per month. In a preferred embodiment, the antibody is administered once, or at least once per week, *e.g.*, twice weekly. In a preferred embodiment, the antibody is administered once, or at least once per day. As is clear to a skilled person, less antibody may be administered when the antibody is administered more frequently (*e.g.*, daily). In a preferred embodiment, between 0.01 mg to 20 mg of antibody is administered per week (*e.g.*, once or twice weekly or daily). In an exemplary embodiment, between 0.1 mg and 25 mg is administered daily (*i.e.* between 0.7 mg and 175 mg per week). In an exemplary embodiment, 0.5 mg to 3.5 mg is administered daily (*i.e.* between 3.5 mg and 24.5 mg per week).

20

The invention also provides a composition formulated for intranasal administration and/or oral inhalation comprising an antibody as disclosed herein, preferably in a single dose unit between 0.1 mg to 20 mg, preferably 0.5 mg to 15 mg or preferably 1 mg to 12.5 mg.

25

Use in a method for treatment

The present invention relates *inter alia* to an antibody as disclosed herein, for use in a method for treatment of coronavirus infection in an individual, more specifically the antibody can be used in a method for the prophylactic and/or therapeutic treatment of coronavirus infection in an individual.

30

Complementarity-determining regions (CDRs)

Preferably, the CDR regions are identified according to Kabat *et al.* (1991) as described in Sequences of Proteins of Immunological Interest.

In a preferred embodiment, the binding interaction of the binding molecules, preferably the antibody, and the stem helix is mediated exclusively by light and heavy chain variable sequences.

5

The antibody as disclosed herein may be capable of specifically binding to a coronavirus that is in attenuated or inactivated form or that is viable, and/or in an infective form.

The antibody as disclosed herein is also capable of specifically binding to one or more
10 fragments of the coronavirus.

An antibody as disclosed herein comprises a preferred heavy chain CDR1 sequence comprising any one of the following SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069. A CDR comprising the amino acid sequence SEQ ID NO:
15 046 is especially preferred.

An antibody as disclosed herein comprises a preferred heavy chain CDR2 sequence comprising any one of the following SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196. A CDR comprising the amino acid sequence SEQ ID NO:
20 114 is especially preferred.

An antibody as disclosed herein comprises a preferred heavy chain CDR3 sequence comprising any one of the following SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296. A CDR comprising the amino acid sequence SEQ ID NO:
25 254 is especially preferred.

An antibody as disclosed herein comprises a preferred light chain CDR1 sequence comprising any one of the following SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405. A CDR comprising the amino acid sequence SEQ ID NO:
30 367 is especially preferred.

An antibody as disclosed herein comprises a preferred light chain CDR2 sequence comprising any one of the following SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463

to 468, 479 to 484, 502 to 507. A CDR comprising the amino acid sequence SEQ ID NO: 430 is especially preferred.

5 An antibody as disclosed herein comprises a preferred light chain CDR3 sequence comprising any one of the following SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622. A CDR comprising the amino acid sequence SEQ ID NO: 545 is especially preferred.

10 An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a heavy chain framework region FR1 of SEQ ID NO: 631.

An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a heavy chain framework region FR2 of SEQ ID NO: 632.

15 An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a heavy chain framework region FR3 of SEQ ID NO: 633.

An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a heavy chain framework region FR4 of SEQ ID NO: 634.

20

In a preferred embodiment, the heavy chain variable domain of said antibody comprises - a heavy chain framework region FR1 of SEQ ID NO: 631, a heavy chain framework region FR2 of SEQ ID NO: 632, a heavy chain framework region FR3 of SEQ ID NO: 633, and/or a heavy chain framework region FR4 of SEQ ID NO: 634, preferably all said heavy chain
25 heavy chain framework regions FR1 to FR4.

An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a light chain framework region FR1 of SEQ ID NO: 635.

30 An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a light chain framework region FR2 of SEQ ID NO: 636.

An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a light chain framework region FR3 of SEQ ID NO: 637.

5 An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a light chain framework region FR4 of SEQ ID NO: 638.

In a preferred embodiment, the light chain variable domain of said antibody comprises - a light chain framework region FR1 of SEQ ID NO: 635, a light chain framework region FR2 of SEQ ID NO: 636, a light chain framework region FR3 of SEQ ID NO: 637, and/or
10 a light chain framework region FR4 of SEQ ID NO: 638, preferably all said light chain framework regions are FR1 to FR4.

Most preferably, an antibody as disclosed herein comprises a heavy chain variable domain having the sequence of SEQ ID NO: 629 and/or a light chain variable domain having the
15 sequence of SEQ ID NO: 630.

In treatment methods of the invention, the heavy chain variable domain (VH) of the antibody is preferably indicated as SEQ ID NO:629. In treatment methods or compositions of the invention, the light chain variable domain (VL) of the antibody is preferably
20 indicated as SEQ ID NO:630. In treatment methods or compositions of the invention, the antibody can be an antibody as disclosed herein, or a binding molecule comprising an antigen-binding domain such as a variable domain (V) thereof.

Preferably, an antibody as disclosed herein comprises a heavy chain variable domain
25 having the sequence of SEQ ID NO:629 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, more preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions.

Preferably, an antibody as disclosed herein comprises a light chain variable domain
30 having the sequence of SEQ ID NO:630 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, more preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions.

Preferably, said amino acid insertions, deletions, substitutions in respect of either the heavy chain variable domain and/or the light chain variable domain are not in the CDRs.

SEQUENCES

CDRs and framework regions defined herein are based on the Kabat numbering scheme as described in Sequences of Proteins of Immunological Interest (Kabat *et al.*, 1991).

5 **Heavy chain CDR1 region (SEQ ID NO:001 to SEQ ID NO:076)**

	SEQ ID NO.: 001	DTFS
	SEQ ID NO.: 002	DTFSS
	SEQ ID NO.: 003	DTFSSH
10	SEQ ID NO.: 004	DTFSSHY
	SEQ ID NO.: 005	DTFSSHYM
	SEQ ID NO.: 006	DTFSSHYMH
	SEQ ID NO.: 007	DTFSSHYMHW
	SEQ ID NO.: 008	DTFSSHYMHWV
15	SEQ ID NO.: 009	DTFSSHYMHWVR
	SEQ ID NO.: 010	DTFSSHYMHWVRQ
	SEQ ID NO.: 011	DTFSSHYMHWVRQA
	SEQ ID NO.: 012	FSSH
	SEQ ID NO.: 013	FSSHY
20	SEQ ID NO.: 014	FSSHYM
	SEQ ID NO.: 015	FSSHYMH
	SEQ ID NO.: 016	FSSHYMHW
	SEQ ID NO.: 017	FSSHYMHWV
	SEQ ID NO.: 018	FSSHYMHWVR
25	SEQ ID NO.: 019	FSSHYMHWVRQ
	SEQ ID NO.: 020	FSSHYMHWVRQA
	SEQ ID NO.: 021	GDTFS
	SEQ ID NO.: 022	GDTFSS
	SEQ ID NO.: 023	GDTFSSH
30	SEQ ID NO.: 024	GDTFSSHY
	SEQ ID NO.: 025	GDTFSSHYM

	SEQ ID NO.: 026	GDTFSSHVMH
	SEQ ID NO.: 027	GDTFSSHVMHW
	SEQ ID NO.: 028	GDTFSSHVMHWV
	SEQ ID NO.: 029	GDTFSSHVMHWVR
5	SEQ ID NO.: 030	GDTFSSHVMHWVRQ
	SEQ ID NO.: 031	GDTFSSHVMHWVRQA
	SEQ ID NO.: 032	HWVR
	SEQ ID NO.: 033	HWVRQ
	SEQ ID NO.: 034	HWVRQA
10	SEQ ID NO.: 035	HVMH
	SEQ ID NO.: 036	HVMHW
	SEQ ID NO.: 037	HVMHWV
	SEQ ID NO.: 038	HVMHWVR
	SEQ ID NO.: 039	HVMHWVRQ
15	SEQ ID NO.: 040	HVMHWVRQA
	SEQ ID NO.: 041	MHWV
	SEQ ID NO.: 042	MHWVR
	SEQ ID NO.: 043	MHWVRQ
	SEQ ID NO.: 044	MHWVRQA
20	SEQ ID NO.: 045	SHVM
	SEQ ID NO.: 046	SHVMH
	SEQ ID NO.: 047	SHVMHW
	SEQ ID NO.: 048	SHVMHWV
	SEQ ID NO.: 049	SHVMHWVR
25	SEQ ID NO.: 050	SHVMHWVRQ
	SEQ ID NO.: 051	SHVMHWVRQA
	SEQ ID NO.: 052	SSHV
	SEQ ID NO.: 053	SSHVM
	SEQ ID NO.: 054	SSHVMH
30	SEQ ID NO.: 055	SSHVMHW

	SEQ ID NO.: 056	SSHYMHWV
	SEQ ID NO.: 057	SSHYMHWVR
	SEQ ID NO.: 058	SSHYMHWVRQ
	SEQ ID NO.: 059	SSHYMHWVRQA
5	SEQ ID NO.: 060	TFSS
	SEQ ID NO.: 061	TFSSH
	SEQ ID NO.: 062	TFSSHY
	SEQ ID NO.: 063	TFSSHYM
	SEQ ID NO.: 064	TFSSHYMH
10	SEQ ID NO.: 065	TFSSHYMHW
	SEQ ID NO.: 066	TFSSHYMHWV
	SEQ ID NO.: 067	TFSSHYMHWVR
	SEQ ID NO.: 068	TFSSHYMHWVRQ
	SEQ ID NO.: 069	TFSSHYMHWVRQA
15	SEQ ID NO.: 070	WVRQ
	SEQ ID NO.: 071	WVRQA
	SEQ ID NO.: 072	YMHV
	SEQ ID NO.: 073	YMHV
	SEQ ID NO.: 074	YMHVVR
20	SEQ ID NO.: 075	YMHVVRQ
	SEQ ID NO.: 076	YMHVVRQA

Heavy chain CDR2 region (SEQ ID NO:077 to SEQ ID NO:196)

25	SEQ ID NO.: 077	EWMGIINPSGSGTAYG
	SEQ ID NO.: 078	EWMGIINPSGSGTAYGQ
	SEQ ID NO.: 079	EWMGIINPSGSGTAYGQK
	SEQ ID NO.: 080	EWMGIINPSGSGTAYGQKF
	SEQ ID NO.: 081	EWMGIINPSGSGTAYGQKFQ
30	SEQ ID NO.: 082	EWMGIINPSGSGTAYGQKFQG
	SEQ ID NO.: 083	EWMGIINPSGSGTAYGQKFQGR

	SEQ ID NO.: 084	EWMGIINPSGSGTAYGQKFQGRL
	SEQ ID NO.: 085	EWMGIINPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 086	EWMGIINPSGSGTAYGQKFQGRLTM
	SEQ ID NO.: 087	EWMGIINPSGSGTAYGQKFQGRLTMT
5	SEQ ID NO.: 088	GIINPSGSGTAYG
	SEQ ID NO.: 089	GIINPSGSGTAYGQ
	SEQ ID NO.: 090	GIINPSGSGTAYGQK
	SEQ ID NO.: 091	GIINPSGSGTAYGQKF
	SEQ ID NO.: 092	GIINPSGSGTAYGQKFQ
10	SEQ ID NO.: 093	GIINPSGSGTAYGQKFQG
	SEQ ID NO.: 094	GIINPSGSGTAYGQKFQGR
	SEQ ID NO.: 095	GIINPSGSGTAYGQKFQGRL
	SEQ ID NO.: 096	GIINPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 097	GIINPSGSGTAYGQKFQGRLTM
15	SEQ ID NO.: 098	GIINPSGSGTAYGQKFQGRLTMT
	SEQ ID NO.: 099	GSGTAYGQ
	SEQ ID NO.: 100	GSGTAYGQK
	SEQ ID NO.: 101	GSGTAYGQKF
	SEQ ID NO.: 102	GSGTAYGQKFQ
20	SEQ ID NO.: 103	GSGTAYGQKFQG
	SEQ ID NO.: 104	GSGTAYGQKFQGR
	SEQ ID NO.: 105	GSGTAYGQKFQGRL
	SEQ ID NO.: 106	GSGTAYGQKFQGRLT
	SEQ ID NO.: 107	GSGTAYGQKFQGRLTM
25	SEQ ID NO.: 108	GSGTAYGQKFQGRLTMT
	SEQ ID NO.: 109	IINPSGSGTAYG
	SEQ ID NO.: 110	IINPSGSGTAYGQ
	SEQ ID NO.: 111	IINPSGSGTAYGQK
	SEQ ID NO.: 112	IINPSGSGTAYGQKF
30	SEQ ID NO.: 113	IINPSGSGTAYGQKFQ

	SEQ ID NO.: 114	IINPSGSGTAYGQKFQG
	SEQ ID NO.: 115	IINPSGSGTAYGQKFQGR
	SEQ ID NO.: 116	IINPSGSGTAYGQKFQGRL
	SEQ ID NO.: 117	IINPSGSGTAYGQKFQGRLT
5	SEQ ID NO.: 118	IINPSGSGTAYGQKFQGRLTM
	SEQ ID NO.: 119	IINPSGSGTAYGQKFQGRLTMT
	SEQ ID NO.: 120	INPSGSGTAYG
	SEQ ID NO.: 121	INPSGSGTAYGQ
	SEQ ID NO.: 122	INPSGSGTAYGQK
10	SEQ ID NO.: 123	INPSGSGTAYGQKF
	SEQ ID NO.: 124	INPSGSGTAYGQKFQ
	SEQ ID NO.: 125	INPSGSGTAYGQKFQG
	SEQ ID NO.: 126	INPSGSGTAYGQKFQGR
	SEQ ID NO.: 127	INPSGSGTAYGQKFQGRL
15	SEQ ID NO.: 128	INPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 129	INPSGSGTAYGQKFQGRLTM
	SEQ ID NO.: 130	INPSGSGTAYGQKFQGRLTMT
	SEQ ID NO.: 131	MGIINPSGSGTAYG
	SEQ ID NO.: 132	MGIINPSGSGTAYGQ
20	SEQ ID NO.: 133	MGIINPSGSGTAYGQK
	SEQ ID NO.: 134	MGIINPSGSGTAYGQKF
	SEQ ID NO.: 135	MGIINPSGSGTAYGQKFQ
	SEQ ID NO.: 136	MGIINPSGSGTAYGQKFQG
	SEQ ID NO.: 137	MGIINPSGSGTAYGQKFQGR
25	SEQ ID NO.: 138	MGIINPSGSGTAYGQKFQGRL
	SEQ ID NO.: 139	MGIINPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 140	MGIINPSGSGTAYGQKFQGRLTM
	SEQ ID NO.: 141	MGIINPSGSGTAYGQKFQGRLTMT
	SEQ ID NO.: 142	NPSGSGTAYG
30	SEQ ID NO.: 143	NPSGSGTAYGQ

	SEQ ID NO.: 144	NPSGSGTAYGQK
	SEQ ID NO.: 145	NPSGSGTAYGQKF
	SEQ ID NO.: 146	NPSGSGTAYGQKFQ
	SEQ ID NO.: 147	NPSGSGTAYGQKFQG
5	SEQ ID NO.: 148	NPSGSGTAYGQKFQGR
	SEQ ID NO.: 149	NPSGSGTAYGQKFQGRL
	SEQ ID NO.: 150	NPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 151	NPSGSGTAYGQKFQGRLTM
	SEQ ID NO.: 152	NPSGSGTAYGQKFQGRLTMT
10	SEQ ID NO.: 153	PEWMGIINPSGSGTAYG
	SEQ ID NO.: 154	PEWMGIINPSGSGTAYGQ
	SEQ ID NO.: 155	PEWMGIINPSGSGTAYGQK
	SEQ ID NO.: 156	PEWMGIINPSGSGTAYGQKF
	SEQ ID NO.: 157	PEWMGIINPSGSGTAYGQKFQ
15	SEQ ID NO.: 158	PEWMGIINPSGSGTAYGQKFQG
	SEQ ID NO.: 159	PEWMGIINPSGSGTAYGQKFQGR
	SEQ ID NO.: 160	PEWMGIINPSGSGTAYGQKFQGRL
	SEQ ID NO.: 161	PEWMGIINPSGSGTAYGQKFQGRLT
	SEQ ID NO.: 162	PEWMGIINPSGSGTAYGQKFQGRLTM
20	SEQ ID NO.: 163	PEWMGIINPSGSGTAYGQKFQGRLTMT
	SEQ ID NO.: 164	PSGSGTAYG
	SEQ ID NO.: 165	PSGSGTAYGQ
	SEQ ID NO.: 166	PSGSGTAYGQK
	SEQ ID NO.: 167	PSGSGTAYGQKF
25	SEQ ID NO.: 168	PSGSGTAYGQKFQ
	SEQ ID NO.: 169	PSGSGTAYGQKFQG
	SEQ ID NO.: 170	PSGSGTAYGQKFQGR
	SEQ ID NO.: 171	PSGSGTAYGQKFQGRL
	SEQ ID NO.: 172	PSGSGTAYGQKFQGRLT
30	SEQ ID NO.: 173	PSGSGTAYGQKFQGRLTM

SEQ ID NO.: 174 PSGSGTAYGQKFQGRLTMT
SEQ ID NO.: 175 SGSGTAYG
SEQ ID NO.: 176 SGSGTAYGQ
SEQ ID NO.: 177 SGSGTAYGQK
5 SEQ ID NO.: 178 SGSGTAYGQKF
SEQ ID NO.: 179 SGSGTAYGQKFQ
SEQ ID NO.: 180 SGSGTAYGQKFQG
SEQ ID NO.: 181 SGSGTAYGQKFQGR
SEQ ID NO.: 182 SGSGTAYGQKFQGRL
10 SEQ ID NO.: 183 SGSGTAYGQKFQGRLT
SEQ ID NO.: 184 SGSGTAYGQKFQGRLTM
SEQ ID NO.: 185 SGSGTAYGQKFQGRLTMT
SEQ ID NO.: 186 WMGIINPSGSGTAYG
SEQ ID NO.: 187 WMGIINPSGSGTAYGQ
15 SEQ ID NO.: 188 WMGIINPSGSGTAYGQK
SEQ ID NO.: 189 WMGIINPSGSGTAYGQKF
SEQ ID NO.: 190 WMGIINPSGSGTAYGQKFQ
SEQ ID NO.: 191 WMGIINPSGSGTAYGQKFQG
SEQ ID NO.: 192 WMGIINPSGSGTAYGQKFQGR
20 SEQ ID NO.: 193 WMGIINPSGSGTAYGQKFQGRL
SEQ ID NO.: 194 WMGIINPSGSGTAYGQKFQGRLT
SEQ ID NO.: 195 WMGIINPSGSGTAYGQKFQGRLTM
SEQ ID NO.: 196 WMGIINPSGSGTAYGQKFQGRLTMT

25 **Heavy chain CDR3 region (SEQ ID NO:197 to SEQ ID NO:296)**

SEQ ID NO.: 197 CGGGSG
SEQ ID NO.: 198 CGGGSGG
SEQ ID NO.: 199 CGGGSGGL
30 SEQ ID NO.: 200 CGGGSGGLF
SEQ ID NO.: 201 CGGGSGGLFA

	SEQ ID NO.: 202	CGGGSGGLFAY
	SEQ ID NO.: 203	CGGGSGGLFAYW
	SEQ ID NO.: 204	CGGGSGGLFAYWG
	SEQ ID NO.: 205	CGGGSGGLFAYWGQ
5	SEQ ID NO.: 206	CGGGSGGLFAYWGQG
	SEQ ID NO.: 207	CGGGSGGLFAYWGQGT
	SEQ ID NO.: 208	FAYW
	SEQ ID NO.: 209	FAYWG
	SEQ ID NO.: 210	FAYWGQ
10	SEQ ID NO.: 211	FAYWGQG
	SEQ ID NO.: 212	FAYWGQGT
	SEQ ID NO.: 213	GGGSG
	SEQ ID NO.: 214	GGGSGG
	SEQ ID NO.: 215	GGGSGGL
15	SEQ ID NO.: 216	GGGSGGLF
	SEQ ID NO.: 217	GGGSGGLFA
	SEQ ID NO.: 218	GGGSGGLFAY
	SEQ ID NO.: 219	GGGSGGLFAYW
	SEQ ID NO.: 220	GGGSGGLFAYWG
20	SEQ ID NO.: 221	GGGSGGLFAYWGQ
	SEQ ID NO.: 222	GGGSGGLFAYWGQG
	SEQ ID NO.: 223	GGGSGGLFAYWGQGT
	SEQ ID NO.: 224	GGLF
	SEQ ID NO.: 225	GGLFA
25	SEQ ID NO.: 226	GGLFAY
	SEQ ID NO.: 227	GGLFAYW
	SEQ ID NO.: 228	GGLFAYWG
	SEQ ID NO.: 229	GGLFAYWGQ
	SEQ ID NO.: 230	GGLFAYWGQG
30	SEQ ID NO.: 231	GGLFAYWGQGT

	SEQ ID NO.: 232	GGSG
	SEQ ID NO.: 233	GGSGG
	SEQ ID NO.: 234	GGSGGL
	SEQ ID NO.: 235	GGSGGLF
5	SEQ ID NO.: 236	GGSGGLFA
	SEQ ID NO.: 237	GGSGGLFAY
	SEQ ID NO.: 238	GGSGGLFAYW
	SEQ ID NO.: 239	GGSGGLFAYWG
	SEQ ID NO.: 240	GGSGGLFAYWGQ
10	SEQ ID NO.: 241	GGSGGLFAYWGQG
	SEQ ID NO.: 242	GGSGGLFAYWGQGT
	SEQ ID NO.: 243	GLFA
	SEQ ID NO.: 244	GLFAY
	SEQ ID NO.: 245	GLFAYW
15	SEQ ID NO.: 246	GLFAYWG
	SEQ ID NO.: 247	GLFAYWGQ
	SEQ ID NO.: 248	GLFAYWGQG
	SEQ ID NO.: 249	GLFAYWGQGT
	SEQ ID NO.: 250	GSGG
20	SEQ ID NO.: 251	GSGGL
	SEQ ID NO.: 252	GSGGLF
	SEQ ID NO.: 253	GSGGLFA
	SEQ ID NO.: 254	GSGGLFAY
	SEQ ID NO.: 255	GSGGLFAYW
25	SEQ ID NO.: 256	GSGGLFAYWG
	SEQ ID NO.: 257	GSGGLFAYWGQ
	SEQ ID NO.: 258	GSGGLFAYWGQG
	SEQ ID NO.: 259	GSGGLFAYWGQGT
	SEQ ID NO.: 260	LFAY
30	SEQ ID NO.: 261	LFAYW

	SEQ ID NO.: 262	LFAYWG
	SEQ ID NO.: 263	LFAYWGQ
	SEQ ID NO.: 264	LFAYWGQG
	SEQ ID NO.: 265	LFAYWGQGT
5	SEQ ID NO.: 266	SGGL
	SEQ ID NO.: 267	SGGLF
	SEQ ID NO.: 268	SGGLFA
	SEQ ID NO.: 269	SGGLFAY
	SEQ ID NO.: 270	SGGLFAYW
10	SEQ ID NO.: 271	SGGLFAYWG
	SEQ ID NO.: 272	SGGLFAYWGQ
	SEQ ID NO.: 273	SGGLFAYWGQG
	SEQ ID NO.: 274	SGGLFAYWGQGT
	SEQ ID NO.: 275	YCGGSG
15	SEQ ID NO.: 276	YCGGSGG
	SEQ ID NO.: 277	YCGGSGGL
	SEQ ID NO.: 278	YCGGSGGLF
	SEQ ID NO.: 279	YCGGSGGLFA
	SEQ ID NO.: 280	YCGGSGGLFAY
20	SEQ ID NO.: 281	YCGGSGGLFAYW
	SEQ ID NO.: 282	YCGGSGGLFAYWG
	SEQ ID NO.: 283	YCGGSGGLFAYWGQ
	SEQ ID NO.: 284	YCGGSGGLFAYWGQG
	SEQ ID NO.: 285	YCGGSGGLFAYWGQGT
25	SEQ ID NO.: 286	YYCGGSG
	SEQ ID NO.: 287	YYCGGSGG
	SEQ ID NO.: 288	YYCGGSGGL
	SEQ ID NO.: 289	YYCGGSGGLF
	SEQ ID NO.: 290	YYCGGSGGLFA
30	SEQ ID NO.: 291	YYCGGSGGLFAY

SEQ ID NO.: 292 YYCGGGSGGLFAYW
SEQ ID NO.: 293 YYCGGGSGGLFAYWG
SEQ ID NO.: 294 YYCGGGSGGLFAYWGQ
SEQ ID NO.: 295 YYCGGGSGGLFAYWGQG
5 SEQ ID NO.: 296 YYCGGGSGGLFAYWGQGT

Light chain CDR1 region (SEQ ID NO:297 to SEQ ID NO:414)

SEQ ID NO.: 297 ASQIVR
10 SEQ ID NO.: 298 ASQIVRS
SEQ ID NO.: 299 ASQIVRSN
SEQ ID NO.: 300 ASQIVRSNY
SEQ ID NO.: 301 ASQIVRSNYL
SEQ ID NO.: 302 ASQIVRSNYLA
15 SEQ ID NO.: 303 ASQIVRSNYLAW
SEQ ID NO.: 304 ASQIVRSNYLAWY
SEQ ID NO.: 305 ASQIVRSNYLAWYQ
SEQ ID NO.: 306 ASQIVRSNYLAWYQQ
SEQ ID NO.: 307 ASQIVRSNYLAWYQQK
20 SEQ ID NO.: 308 ATLSCRASQIVR
SEQ ID NO.: 309 ATLSCRASQIVRS
SEQ ID NO.: 310 ATLSCRASQIVRSN
SEQ ID NO.: 311 ATLSCRASQIVRSNY
SEQ ID NO.: 312 ATLSCRASQIVRSNYL
25 SEQ ID NO.: 313 ATLSCRASQIVRSNYLA
SEQ ID NO.: 314 ATLSCRASQIVRSNYLAW
SEQ ID NO.: 315 ATLSCRASQIVRSNYLAWY
SEQ ID NO.: 316 ATLSCRASQIVRSNYLAWYQ
SEQ ID NO.: 317 ATLSCRASQIVRSNYLAWYQQ
30 SEQ ID NO.: 318 ATLSCRASQIVRSNYLAWYQQK
SEQ ID NO.: 319 CRASQIVR

	SEQ ID NO.: 320	CRASQIVRS
	SEQ ID NO.: 321	CRASQIVRSN
	SEQ ID NO.: 322	CRASQIVRSNY
	SEQ ID NO.: 323	CRASQIVRSNYL
5	SEQ ID NO.: 324	CRASQIVRSNYLA
	SEQ ID NO.: 325	CRASQIVRSNYLAW
	SEQ ID NO.: 326	CRASQIVRSNYLAWY
	SEQ ID NO.: 327	CRASQIVRSNYLAWYQ
	SEQ ID NO.: 328	CRASQIVRSNYLAWYQQ
10	SEQ ID NO.: 329	CRASQIVRSNYLAWYQQK
	SEQ ID NO.: 330	IVRS
	SEQ ID NO.: 331	IVRSN
	SEQ ID NO.: 332	IVRSNY
	SEQ ID NO.: 333	IVRSNYL
15	SEQ ID NO.: 334	IVRSNYLA
	SEQ ID NO.: 335	IVRSNYLAW
	SEQ ID NO.: 336	IVRSNYLAWY
	SEQ ID NO.: 337	IVRSNYLAWYQ
	SEQ ID NO.: 338	IVRSNYLAWYQQ
20	SEQ ID NO.: 339	IVRSNYLAWYQQK
	SEQ ID NO.: 340	LSCRASQIVR
	SEQ ID NO.: 341	LSCRASQIVRS
	SEQ ID NO.: 342	LSCRASQIVRSN
	SEQ ID NO.: 343	LSCRASQIVRSNY
25	SEQ ID NO.: 344	LSCRASQIVRSNYL
	SEQ ID NO.: 345	LSCRASQIVRSNYLA
	SEQ ID NO.: 346	LSCRASQIVRSNYLAW
	SEQ ID NO.: 347	LSCRASQIVRSNYLAWY
	SEQ ID NO.: 348	LSCRASQIVRSNYLAWYQ
30	SEQ ID NO.: 349	LSCRASQIVRSNYLAWYQQ

	SEQ ID NO.: 350	LSCRASQIVRSNYLAWYQQK
	SEQ ID NO.: 351	QIVR
	SEQ ID NO.: 352	QIVRS
	SEQ ID NO.: 353	QIVRSN
5	SEQ ID NO.: 354	QIVRSNY
	SEQ ID NO.: 355	QIVRSNYL
	SEQ ID NO.: 356	QIVRSNYLA
	SEQ ID NO.: 357	QIVRSNYLAW
	SEQ ID NO.: 358	QIVRSNYLAWY
10	SEQ ID NO.: 359	QIVRSNYLAWYQ
	SEQ ID NO.: 360	QIVRSNYLAWYQQ
	SEQ ID NO.: 361	QIVRSNYLAWYQQK
	SEQ ID NO.: 362	RASQIVR
	SEQ ID NO.: 363	RASQIVRS
15	SEQ ID NO.: 364	RASQIVRSN
	SEQ ID NO.: 365	RASQIVRSNY
	SEQ ID NO.: 366	RASQIVRSNYL
	SEQ ID NO.: 367	RASQIVRSNYLA
	SEQ ID NO.: 368	RASQIVRSNYLAW
20	SEQ ID NO.: 369	RASQIVRSNYLAWY
	SEQ ID NO.: 370	RASQIVRSNYLAWYQ
	SEQ ID NO.: 371	RASQIVRSNYLAWYQQ
	SEQ ID NO.: 372	RASQIVRSNYLAWYQQK
	SEQ ID NO.: 373	SCRASQIVR
25	SEQ ID NO.: 374	SCRASQIVRS
	SEQ ID NO.: 375	SCRASQIVRSN
	SEQ ID NO.: 376	SCRASQIVRSNY
	SEQ ID NO.: 377	SCRASQIVRSNYL
	SEQ ID NO.: 378	SCRASQIVRSNYLA
30	SEQ ID NO.: 379	SCRASQIVRSNYLAW

	SEQ ID NO.: 380	SCRASQIVRSNYLAWY
	SEQ ID NO.: 381	SCRASQIVRSNYLAWYQ
	SEQ ID NO.: 382	SCRASQIVRSNYLAWYQQ
	SEQ ID NO.: 383	SCRASQIVRSNYLAWYQQK
5	SEQ ID NO.: 384	SQIVR
	SEQ ID NO.: 385	SQIVRS
	SEQ ID NO.: 386	SQIVRSN
	SEQ ID NO.: 387	SQIVRSNY
	SEQ ID NO.: 388	SQIVRSNYL
10	SEQ ID NO.: 389	SQIVRSNYLA
	SEQ ID NO.: 390	SQIVRSNYLAW
	SEQ ID NO.: 391	SQIVRSNYLAWY
	SEQ ID NO.: 392	SQIVRSNYLAWYQ
	SEQ ID NO.: 393	SQIVRSNYLAWYQQ
15	SEQ ID NO.: 394	SQIVRSNYLAWYQQK
	SEQ ID NO.: 395	TLSCRASQIVR
	SEQ ID NO.: 396	TLSCRASQIVRS
	SEQ ID NO.: 397	TLSCRASQIVRSN
	SEQ ID NO.: 398	TLSCRASQIVRSNY
20	SEQ ID NO.: 399	TLSCRASQIVRSNYL
	SEQ ID NO.: 400	TLSCRASQIVRSNYLA
	SEQ ID NO.: 401	TLSCRASQIVRSNYLAW
	SEQ ID NO.: 402	TLSCRASQIVRSNYLAWY
	SEQ ID NO.: 403	TLSCRASQIVRSNYLAWYQ
25	SEQ ID NO.: 404	TLSCRASQIVRSNYLAWYQQ
	SEQ ID NO.: 405	TLSCRASQIVRSNYLAWYQQK
	SEQ ID NO.: 406	VRSN
	SEQ ID NO.: 407	VRSNY
	SEQ ID NO.: 408	VRSNYL
30	SEQ ID NO.: 409	VRSNYLA

SEQ ID NO.: 410 VRSNYLAW
SEQ ID NO.: 411 VRSNYLAWY
SEQ ID NO.: 412 VRSNYLAWYQ
SEQ ID NO.: 413 VRSNYLAWYQQ
5 SEQ ID NO.: 414 VRSNYLAWYQQK

Light chain CDR2 region (SEQ ID NO:415 to SEQ ID NO:507)

SEQ ID NO.: 415 ASSR
10 SEQ ID NO.: 416 ASSRA
SEQ ID NO.: 417 ASSRAT
SEQ ID NO.: 418 ASSRATG
SEQ ID NO.: 419 ASSRATGT
SEQ ID NO.: 420 ASSRATGTP
15 SEQ ID NO.: 421 ASSRATGTPD
SEQ ID NO.: 422 ASSRATGTPDR
SEQ ID NO.: 423 ATGT
SEQ ID NO.: 424 ATGTP
SEQ ID NO.: 425 ATGTPD
20 SEQ ID NO.: 426 ATGTPDR
SEQ ID NO.: 427 GASS
SEQ ID NO.: 428 GASSR
SEQ ID NO.: 429 GASSRA
SEQ ID NO.: 430 GASSRAT
25 SEQ ID NO.: 431 GASSRATG
SEQ ID NO.: 432 GASSRATGT
SEQ ID NO.: 433 GASSRATGTP
SEQ ID NO.: 434 GASSRATGTPD
SEQ ID NO.: 435 GASSRATGTPDR
30 SEQ ID NO.: 436 IYGA
SEQ ID NO.: 437 IYGAS

SEQ ID NO.: 438 IYGASS
SEQ ID NO.: 439 IYGASSR
SEQ ID NO.: 440 IYGASSRA
SEQ ID NO.: 441 IYGASSRAT
5 SEQ ID NO.: 442 IYGASSRATG
SEQ ID NO.: 443 IYGASSRATGT
SEQ ID NO.: 444 IYGASSRATGTP
SEQ ID NO.: 445 IYGASSRATGTPD
SEQ ID NO.: 446 IYGASSRATGTPDR
10 SEQ ID NO.: 447 LIYGA
SEQ ID NO.: 448 LIYGAS
SEQ ID NO.: 449 LIYGASS
SEQ ID NO.: 450 LIYGASSR
SEQ ID NO.: 451 LIYGASSRA
15 SEQ ID NO.: 452 LIYGASSRAT
SEQ ID NO.: 453 LIYGASSRATG
SEQ ID NO.: 454 LIYGASSRATGT
SEQ ID NO.: 455 LIYGASSRATGTP
SEQ ID NO.: 456 LIYGASSRATGTPD
20 SEQ ID NO.: 457 LIYGASSRATGTPDR
SEQ ID NO.: 458 LLIYGA
SEQ ID NO.: 459 LLIYGAS
SEQ ID NO.: 460 LLIYGASS
SEQ ID NO.: 461 LLIYGASSR
25 SEQ ID NO.: 462 LLIYGASSRA
SEQ ID NO.: 463 LLIYGASSRAT
SEQ ID NO.: 464 LLIYGASSRATG
SEQ ID NO.: 465 LLIYGASSRATGT
SEQ ID NO.: 466 LLIYGASSRATGTP
30 SEQ ID NO.: 467 LLIYGASSRATGTPD

	SEQ ID NO.: 468	LLIYGASSRATGTPDR
	SEQ ID NO.: 469	RATG
	SEQ ID NO.: 470	RATGT
	SEQ ID NO.: 471	RATGTP
5	SEQ ID NO.: 472	RATGTPD
	SEQ ID NO.: 473	RATGTPDR
	SEQ ID NO.: 474	RLLIYGA
	SEQ ID NO.: 475	RLLIYGAS
	SEQ ID NO.: 476	RLLIYGASS
10	SEQ ID NO.: 477	RLLIYGASSR
	SEQ ID NO.: 478	RLLIYGASSRA
	SEQ ID NO.: 479	RLLIYGASSRAT
	SEQ ID NO.: 480	RLLIYGASSRATG
	SEQ ID NO.: 481	RLLIYGASSRATGT
15	SEQ ID NO.: 482	RLLIYGASSRATGTP
	SEQ ID NO.: 483	RLLIYGASSRATGTPD
	SEQ ID NO.: 484	RLLIYGASSRATGTPDR
	SEQ ID NO.: 485	SRAT
	SEQ ID NO.: 486	SRATG
20	SEQ ID NO.: 487	SRATGT
	SEQ ID NO.: 488	SRATGTP
	SEQ ID NO.: 489	SRATGTPD
	SEQ ID NO.: 490	SRATGTPDR
	SEQ ID NO.: 491	SSRA
25	SEQ ID NO.: 492	SSRAT
	SEQ ID NO.: 493	SSRATG
	SEQ ID NO.: 494	SSRATGT
	SEQ ID NO.: 495	SSRATGTP
	SEQ ID NO.: 496	SSRATGTPD
30	SEQ ID NO.: 497	SSRATGTPDR

	SEQ ID NO.: 498	YGAS
	SEQ ID NO.: 499	YGASS
	SEQ ID NO.: 500	YGASSR
	SEQ ID NO.: 501	YGASSRA
5	SEQ ID NO.: 502	YGASSRAT
	SEQ ID NO.: 503	YGASSRATG
	SEQ ID NO.: 504	YGASSRATGT
	SEQ ID NO.: 505	YGASSRATGTP
	SEQ ID NO.: 506	YGASSRATGTPD
10	SEQ ID NO.: 507	YGASSRATGTPDR

Light chain CDR3 region (SEQ ID NO:508 to SEQ ID NO:622)

	SEQ ID NO.: 508	AVYYCLQYDSS
15	SEQ ID NO.: 509	AVYYCLQYDSSP
	SEQ ID NO.: 510	AVYYCLQYDSSPP
	SEQ ID NO.: 511	AVYYCLQYDSSPPT
	SEQ ID NO.: 512	AVYYCLQYDSSPPTY
	SEQ ID NO.: 513	AVYYCLQYDSSPPTYI
20	SEQ ID NO.: 514	AVYYCLQYDSSPPTYIF
	SEQ ID NO.: 515	AVYYCLQYDSSPPTYIFG
	SEQ ID NO.: 516	AVYYCLQYDSSPPTYIFGQ
	SEQ ID NO.: 517	AVYYCLQYDSSPPTYIFGQG
	SEQ ID NO.: 518	AVYYCLQYDSSPPTYIFGQGT
25	SEQ ID NO.: 519	CLQYDSS
	SEQ ID NO.: 520	CLQYDSSP
	SEQ ID NO.: 521	CLQYDSSPP
	SEQ ID NO.: 522	CLQYDSSPPT
	SEQ ID NO.: 523	CLQYDSSPPTY
30	SEQ ID NO.: 524	CLQYDSSPPTYI
	SEQ ID NO.: 525	CLQYDSSPPTYIF

	SEQ ID NO.: 526	CLQYDSSPPTYIFG
	SEQ ID NO.: 527	CLQYDSSPPTYIFGQ
	SEQ ID NO.: 528	CLQYDSSPPTYIFGQG
	SEQ ID NO.: 529	CLQYDSSPPTYIFGQGT
5	SEQ ID NO.: 530	DSSP
	SEQ ID NO.: 531	DSSPP
	SEQ ID NO.: 532	DSSPPT
	SEQ ID NO.: 533	DSSPPTY
	SEQ ID NO.: 534	DSSPPTYI
10	SEQ ID NO.: 535	DSSPPTYIF
	SEQ ID NO.: 536	DSSPPTYIFG
	SEQ ID NO.: 537	DSSPPTYIFGQ
	SEQ ID NO.: 538	DSSPPTYIFGQG
	SEQ ID NO.: 539	DSSPPTYIFGQGT
15	SEQ ID NO.: 540	LQYDSS
	SEQ ID NO.: 541	LQYDSSP
	SEQ ID NO.: 542	LQYDSSPP
	SEQ ID NO.: 543	LQYDSSPPT
	SEQ ID NO.: 544	LQYDSSPPTY
20	SEQ ID NO.: 545	LQYDSSPPTYI
	SEQ ID NO.: 546	LQYDSSPPTYIF
	SEQ ID NO.: 547	LQYDSSPPTYIFG
	SEQ ID NO.: 548	LQYDSSPPTYIFGQ
	SEQ ID NO.: 549	LQYDSSPPTYIFGQG
25	SEQ ID NO.: 550	LQYDSSPPTYIFGQGT
	SEQ ID NO.: 551	QYDSS
	SEQ ID NO.: 552	QYDSSP
	SEQ ID NO.: 553	QYDSSPP
	SEQ ID NO.: 554	QYDSSPPT
30	SEQ ID NO.: 555	QYDSSPPTY

	SEQ ID NO.: 556	QYDSSPPTYI
	SEQ ID NO.: 557	QYDSSPPTYIF
	SEQ ID NO.: 558	QYDSSPPTYIFG
	SEQ ID NO.: 559	QYDSSPPTYIFGQ
5	SEQ ID NO.: 560	QYDSSPPTYIFGQG
	SEQ ID NO.: 561	QYDSSPPTYIFGQGT
	SEQ ID NO.: 562	SPPT
	SEQ ID NO.: 563	SPPTY
	SEQ ID NO.: 564	SPPTYI
10	SEQ ID NO.: 565	SPPTYIF
	SEQ ID NO.: 566	SPPTYIFG
	SEQ ID NO.: 567	SPPTYIFGQ
	SEQ ID NO.: 568	SPPTYIFGQG
	SEQ ID NO.: 569	SPPTYIFGQGT
15	SEQ ID NO.: 570	SSPP
	SEQ ID NO.: 571	SSPPT
	SEQ ID NO.: 572	SSPPTY
	SEQ ID NO.: 573	SSPPTYI
	SEQ ID NO.: 574	SSPPTYIF
20	SEQ ID NO.: 575	SSPPTYIFG
	SEQ ID NO.: 576	SSPPTYIFGQ
	SEQ ID NO.: 577	SSPPTYIFGQG
	SEQ ID NO.: 578	SSPPTYIFGQGT
	SEQ ID NO.: 579	VYYCLQYDSS
25	SEQ ID NO.: 580	VYYCLQYDSSP
	SEQ ID NO.: 581	VYYCLQYDSSPP
	SEQ ID NO.: 582	VYYCLQYDSSPPT
	SEQ ID NO.: 583	VYYCLQYDSSPPTY
	SEQ ID NO.: 584	VYYCLQYDSSPPTYI
30	SEQ ID NO.: 585	VYYCLQYDSSPPTYIF

	SEQ ID NO.: 586	VYYCLQYDSSPPTYIFG
	SEQ ID NO.: 587	VYYCLQYDSSPPTYIFGQ
	SEQ ID NO.: 588	VYYCLQYDSSPPTYIFGQG
	SEQ ID NO.: 589	VYYCLQYDSSPPTYIFGQGT
5	SEQ ID NO.: 590	YCLQYDSS
	SEQ ID NO.: 591	YCLQYDSSP
	SEQ ID NO.: 592	YCLQYDSSPP
	SEQ ID NO.: 593	YCLQYDSSPPT
	SEQ ID NO.: 594	YCLQYDSSPPTY
10	SEQ ID NO.: 595	YCLQYDSSPPTYI
	SEQ ID NO.: 596	YCLQYDSSPPTYIF
	SEQ ID NO.: 597	YCLQYDSSPPTYIFG
	SEQ ID NO.: 598	YCLQYDSSPPTYIFGQ
	SEQ ID NO.: 599	YCLQYDSSPPTYIFGQG
15	SEQ ID NO.: 600	YCLQYDSSPPTYIFGQGT
	SEQ ID NO.: 601	YDSS
	SEQ ID NO.: 602	YDSSP
	SEQ ID NO.: 603	YDSSPP
	SEQ ID NO.: 604	YDSSPPT
20	SEQ ID NO.: 605	YDSSPPTY
	SEQ ID NO.: 606	YDSSPPTYI
	SEQ ID NO.: 607	YDSSPPTYIF
	SEQ ID NO.: 608	YDSSPPTYIFG
	SEQ ID NO.: 609	YDSSPPTYIFGQ
25	SEQ ID NO.: 610	YDSSPPTYIFGQG
	SEQ ID NO.: 611	YDSSPPTYIFGQGT
	SEQ ID NO.: 612	YYCLQYDSS
	SEQ ID NO.: 613	YYCLQYDSSP
	SEQ ID NO.: 614	YYCLQYDSSPP
30	SEQ ID NO.: 615	YYCLQYDSSPPT

SEQ ID NO.: 616 YYCLQYDSSPPTY
SEQ ID NO.: 617 YYCLQYDSSPPTYI
SEQ ID NO.: 618 YYCLQYDSSPPTYIF
SEQ ID NO.: 619 YYCLQYDSSPPTYIFG
5 SEQ ID NO.: 620 YYCLQYDSSPPTYIFGQ
SEQ ID NO.: 621 YYCLQYDSSPPTYIFGQG
SEQ ID NO.: 622 YYCLQYDSSPPTYIFGQGT

Heavy chain variable domain (SEQ ID NO: 629)

10 QVQLVQSGAEVKKPAASVKVCKASGDTFSSHYMHVVRQAPGQGPEWMGIINPSGS
GTAYGQKFQGRLLTMTRDTSTSTVYMESSLTSDDTAVYYCGGGSGGLFAYWGQGT
LTVSS

Light chain variable domain (SEQ ID NO: 630)

15 EIVLTQSPGTLSPGERATLSCRASQIVRSNYLAWYQQKPGQAPRLLIYGASSRATGT
PDRFSGGGSGTDFTLTINRLEPEDFAVYYCLQYDSSPPTYIFGQGTKLEIK

Heavy chain FR1 region (SEQ ID NO:631)

20 SEQ ID NO:631 QVQLVQSGAEVKKPAASVKVCKASGDTFS

Heavy chain FR2 region (SEQ ID NO:632)

SEQ ID NO:632 WVRQAPGQGPEWMG

Heavy chain FR3 region (SEQ ID NO:633)

25 SEQ ID NO:633 RLTMTRDTSTSTVYMESSLTSDDTAVYYCGG

Heavy chain FR4 region (SEQ ID NO:634)

SEQ ID NO:634 WGQGTLLTVSS

30

Light chain FR1 region (SEQ ID NO:635)

SEQ ID NO:635 EIVLTQSPGTLSPGERATLSC

Light chain FR2 region (SEQ ID NO:636)

SEQ ID NO:636 WYQQKPGQAPRLLIY

5

Light chain FR3 region (SEQ ID NO:637)

SEQ ID NO:637 GTPDRFSGGGSGTDFTLTINRLEPEDFAVYYC

Light chain FR4 region (SEQ ID NO:638)

10 SEQ ID NO:638 FGQGTKLEIK

Heavy chain CDR1 region (SEQ ID NO:639)

SEQ ID NO.: 639 DYRIH

Heavy chain CDR2 region (SEQ ID NO: 640)

15

SEQ ID NO.: 640 RMNPKSGDTNFAQKFQG

Heavy chain CDR3 region (SEQ ID NO: 641)

SEQ ID NO.: 641 LLIVGGFDPLDDFEV

20

Light chain CDR1 region (SEQ ID NO: 642)

SEQ ID NO.: 642 SGTSSDVGGYNFVS

Light chain CDR2 region (SEQ ID NO: 643)

25

SEQ ID NO.: 643 EVTKRPS

Light chain CDR3 region (SEQ ID NO: 644)

SEQ ID NO.: 644 SSYGGTNNLL

Heavy chain CDR1 region (SEQ ID NO: 645)

30

SEQ ID NO.: 645 GYAMH

Heavy chain CDR2 region (SEQ ID NO: 646)

SEQ ID NO.: 646 VISRDARNKYYADSVKG

5 **Heavy chain CDR3 region (SEQ ID NO: 647)**

SEQ ID NO.: 647 LIIPGITEPGSPDALDI

Light chain CDR1 region (SEQ ID NO: 648)

SEQ ID NO.: 648 RASQDISKWLA

10

Light chain CDR2 region (SEQ ID NO: 649)

SEQ ID NO.: 649 AASSLQS

Light chain CDR3 region (SEQ ID NO: 650)

15 SEQ ID NO.: 650 QQASSFPWSIT

Heavy chain CDR1 region (SEQ ID NO: 651)

SEQ ID NO.: 651 YFYLH

20 **Heavy chain CDR2 region (SEQ ID NO: 652)**

SEQ ID NO.: 652 IINPRGDGTRYAQKFQG

Heavy chain CDR3 region (SEQ ID NO: 653)

SEQ ID NO.: 653 GADHGAFDI

25

Light chain CDR1 region (SEQ ID NO: 654)

SEQ ID NO.: 654 RASQSVRRNYFA

Light chain CDR2 region (SEQ ID NO: 655)

30 SEQ ID NO.: 655 DASTRAT

Light chain CDR3 region (SEQ ID NO: 656)

SEQ ID NO.: 656 QQYDSSPPMYI

Heavy chain CDR1 region (SEQ ID NO: 657)

5 SEQ ID NO.: 657 SYVMH

Heavy chain CDR2 region (SEQ ID NO: 658)

SEQ ID NO.: 658 LITPSGDDTYAQRFG

Heavy chain CDR3 region (SEQ ID NO: 659)

10 SEQ ID NO.: 659 MSRAGGFDV

Light chain CDR1 region (SEQ ID NO: 660)

SEQ ID NO.: 660 RASQSITGRYLA

15

Light chain CDR2 region (SEQ ID NO: 661)

SEQ ID NO.: 661 GESSRVT

Light chain CDR3 region (SEQ ID NO: 662)

20 SEQ ID NO.: 662 QHFASSPPTYT

Heavy chain variable domain (SEQ ID NO: 663)QMQLMQSGAEVKKPGASVTVSCKASGDTFSYRIHWVRQAPGQGLEWMGRMNPKS
GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
25 VWGQGTMTVISS**Light chain variable domain (SEQ ID NO: 664)**QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNFVSWYQHHPGKAPKILYEVTKRPS
GVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVL

30

Heavy chain variable domain (SEQ ID NO: 665)

QVQLVESGGGVVQPGRSLRLSCAASGLTFSGYAMHWVRQAPGKGLEWVAVISR
DARNKYYADSVKGRFTISRDNKKTIVYLEMNSLRVEDTAVYYCAILIPGITEPGSPD
ALDIWGQGTMTVSVSS

5 **Light chain variable domain (SEQ ID NO: 666)**

DIQMTQSPSSMSASVGDRVITITCRASQDISKWLAHYQQRP
GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS
SLQPEDFATYYCQQASSFPWSITFGQGT
RLEIR

EXAMPLES

The monoclonal antibody CV3-25 has shown *in vitro* protection against the original Wuhan strain of SARS-CoV-2 binding specifically to the stem helix of SARS-CoV-2, a binding region shared with antibodies of the present invention. When administered
5 mucosally at lower dosages, CV3-25 affords a lower level of protection when compared to its systemic administration. In contrast, however, when antibodies of the present invention are administered mucosally, they afford a greater level of protection as demonstrated by the *in vivo* studies presented below.

10 **Example 1: CV3-25**

The aim of this study was to assess the pre-exposure efficacy of the monoclonal antibody CV3-25 following systemic intraperitoneal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

15 Animals (n=10 per group) were treated with an intraperitoneal dose range of the test CV3-25 (15 to 0.2 mg/kg) or PBS control as vehicle at study day -1. At study day 0, animals were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

20 The monoclonal antibody CV3-25 was dissolved and diluted with phosphate-buffered saline (PBS), thereby preparing a CV3-25 dilution.

The CV3-25 dilution was made up at various concentrations so that 200 μ L administrations to the mean weight of the dosing group resulted in CV3-25 doses ranging
25 from 15 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

The antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and the temperature of the storage unit was monitored.

30 The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2), which has been passed three times through Vero-hSLAM cells.

Animals

The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg (B6.Cg-Tg(K18-ACE2)2PrImn/JArc; Jax™ Stock No.: 034860) mouse model, at a weight of c. 17-26 g on day -9. 60 mice were used at the age of 11-13 weeks on the day of test article administration and were 83.3% female. Ten animals were randomly allocated to 6 treatment groups based on day -9 weights to create groups with comparable mean weight, with 20% males per group, except 15 mg/kg which was exclusively female. All mice were housed in individually ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days. Food and water were inspected daily and topped up as needed.

Study design

The dose level of CV3-25 applied in the current example was based on a dose range proven to have prophylactic activity. A total number of 60 mice, 11-13 weeks of age were transported to the animal facility and allocated to 6 experimental groups according to Table 1 (see below). Mice were given a period of >3 days for acclimatization.

Table 1: Intraperitoneal experimental detail

Test group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
15	CV3-25	I.P.	15	-1	10
5	CV3-25	I.P.	5	-1	10
1.7	CV3-25	I.P.	1.7	-1	10
0.5	CV3-25	I.P.	0.5	-1	10
0.2	CV3-25	I.P.	0.2	-1	10
Vehicle	---	I.P.	0	-1	10

SARS-CoV-2 Delta K18 hACE2 mice (20% males per group, except 15 mg/kg which was exclusively female) were treated via the Intraperitoneal route of administration with the antibody at a dose between 15 mg/kg and 0.2 mg/kg based upon the average group weight

at day -9 adjusted with a 4% average weight gain (based on a subset of the animals weighted at day -1). On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for weight loss and mortality until the end of the study at day 11.

5

Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table1), was formulated according to average group weight at day -9 adjusted with a 4% average weight gain (based on a subset of the animals weighted at day -1)

10

Prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle, allowed briefly to warm to room temperature and then administered to each mouse. Mice receive the indicated dose by intraperitoneal administration of 200 μL of antibody solution into the intraperitoneal cavity, mice were scruffed and held inverted at a -45 deg angle for administration (200 μL per mouse).

15

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration. Once defrosted, the material was diluted in sterile PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 μL . As required, the animals were anesthetized by isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50 μL (25 μL in each nare) of virus corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation. Unused material was frozen at -20°C to -80°C for back titration.

20

Laboratory analysis

Inoculum was back titrated and the dose of the virus administered was verified by titrating replicate samples on Vero cells.

25

Clinical monitoring

30

General health observations were performed on each animal from the day of arrival until the end of the study at least once daily (during normal servicing procedures). Each animal was weighed daily, beginning at the day of infection (day 0).

Terminal investigations

At the end of the study, on day 11, mice were euthanized by cervical dislocation. Gross necropsy was not performed.

5

Data analysis and statistical methods

Survival proportions at day 11, survival times and change in bodyweight (Area Under the Curve) were compared to the control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS solution) control group. P-values were adjusted according to Bonferroni (for two comparisons to vehicle) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

10

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.

15

Survival

Prophylactic treatment with ≥ 0.5 mg/kg test antibody provided a statistically significant increase in survival compared to the control group (See Figure 1). The animals that were treated with ≥ 0.5 mg/kg test antibody had a 80% survival rate, animals treated with ≥ 1.7 mg/kg had a survival rate of 100%, whereas the survival proportion at day 11 in the control group was 20%. The median survival time of the control group was 6.5 days.

20

Prophylactic treatment with ≥ 0.5 mg/kg test antibody resulted in a significant improvement in survival time compared to the control group.

25

Body weight

Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at day 0 was used as baseline and weight change was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic treatment with ≥ 0.5 mg/kg test antibody resulted in a significant reduction in weight loss compared to the control group.

30

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of ≥ 0.5 mg/kg test antibody provides a statistically significant improvement in survival and a reduction in weight loss compared to control, whereas eight out of ten animals in the control group did not survive.

Example 2: CV3-25

The aim of this study was to assess the pre-exposure efficacy of the monoclonal antibody CV3-25 following intranasal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

Animals (n=10 per group) were treated with an intranasal dose range of the test CV3-25 (15 to 0.2 mg/kg) or PBS control as vehicle on study day -1. At study day 0, animals were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

The monoclonal antibody CV3-25 was dissolved and diluted with phosphate-buffered saline (PBS), thereby preparing a CV3-25 dilution.

20

The CV3-25-dilution was made up at various concentrations so that 50 μ L administrations to the mean weight of the dosing group resulted in CV3-25 doses ranging from 15 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

The formulations were stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and the temperature of the storage unit was monitored.

The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2), which had been passed three times through Vero-hSLAM cells.

30

Animals

The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg (B6.Cg-Tg(K18-ACE2)2PrImn/JArc; Jax™ Stock No.: 034860) mouse model, at a weight of c. 17-26 g on day -9. 60 mice were used at the age of 11-13 weeks on the day of test article administration and were 83.3% female. Ten animals were randomly allocated to 6 treatment groups, based on day -9 weights to create groups with comparable mean weight, with 20% males per group, except 15 mg/kg which was exclusively female. All mice were housed in individually ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days. Food and water were inspected daily and topped up as needed.

Study design

The dose level of CV3-25 applied in the current example was extrapolated from a dose range proven to have prophylactic activity intravenously. A total number of 60 mice, 11-13 weeks of age at the time of arrival, were transported to the animal facility and allocated to 6 experimental groups according to Table 2 (see below). Mice were given a period of >3 days for acclimatization.

Table 2: Intranasal experimental detail

Test Group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
15	CV3-25	I.N.	15	-1	10
5	CV3-25	I.N.	5	-1	10
1.7	CV3-25	I.N.	1.7	-1	10
0.5	CV3-25	I.N.	0.5	-1	10
0.2	CV3-25	I.N.	0.2	-1	10
Vehicle	---	I.N.	0	-1	10

Female SARS-CoV-2 Delta K18 hACE2 mice (20% males per group, except 15 mg/kg which was exclusively female) were treated via the intranasal route of administration with the antibody at a dose between 15 mg/kg and 0.2 mg/kg based upon the average weight at day -9 adjusted with a 4% average weight gain (based on a subset of the animals

weighted at day -1). On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for weight loss and mortality until the end of the study at day 11.

5 Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table 2), was formulated according to average group weight at day -9 adjusted with a 4% average weight gain (based on a subset of animals weighted at day -1).

10

Just prior to dosing, the material was drawn into a syringe, allowed briefly to warm to room temperature and then administered to each mouse. Mice were anaesthetized with isoflurane (4% v/v with 2 L/min O₂) for two minutes. The mice were then scruffed and held at a +45 deg angle. 50 µL of compound or vehicle control was then slowly administered to the nares of each mouse (25 µL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

15

Virus administration

20 The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration. Once defrosted, the material was diluted in cold PBS corresponding to approximately $10^{3.5}$ TCID₅₀/50 µL. As required, the animals were anesthetized with isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50µL (25 µL each nare) of virus corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation using a pipette tip. Unused material was frozen at -20°C to -80°C for back titration.

25

Laboratory analysis

Inoculum was returned to the lab and the dose of the virus administered was verified by titrating replicate samples on Vero cells.

30

Clinical monitoring

General health observations were performed on each animal from the day of arrival until the end of the study at least once daily (during normal servicing procedures). Each animal was weighed daily beginning one day prior to infection (day -1).

5

Terminal investigations

At the end of the study, on day 11, mice were euthanized by cervical dislocation. Gross necropsy was not performed

Data analysis and statistical methods

Two animals in the 15 mg/kg CV3-25 were misdosed (sneezed out part of the antibody volume). These two animals were excluded from the statistical analysis.

Survival proportions at day 11, survival times and change in bodyweight (Area Under the Curve) were compared to the control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS solution) control group. P-values were adjusted according to Bonferroni (for two comparisons to vehicle) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

20

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.

Survival

Prophylactic treatment with ≥ 1.7 mg/kg test antibody provided statistically significant increase in survival compared to the control group (See Figure 2). The median survival time of the control group was 6.0 days.

25

Prophylactic treatment with ≥ 1.7 mg/kg test antibody resulted in a significant improvement in survival time compared to the control group.

30

Body weight

Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at day 0 was used as baseline and weight change was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic treatment with ≥ 0.2 mg/kg test antibody resulted in a significant reduction in weight loss compared to the control group.

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal administration of ≥ 1.7 mg/kg test antibody provides a statistically significant improvement in survival and a reduction in weight loss compared to control. In contrast, the control group showed 10% survival with a median survival time of 6 days.

Example 3: Antibody according to the invention

The aim of this study was to assess the pre-exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545, following systemic intraperitoneal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

Animals (n=10 per group) were treated with an intraperitoneal dose range of the test antibody described above (10 to 0.2 mg/kg) or PBS control as vehicle at study day -1. At study day 0, animals were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

The monoclonal test antibody described above, was buffered in phosphate-buffered saline PBS was diluted to the final concentrations for administration (10 to 0.2mg/kg in 200 μ L). thereby preparing the test antibody dilution.

The test antibody dilution was made up at various concentrations so that 200 µL administrations to the mean weight per cage of the dosing group resulted in test antibody doses ranging from 10 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

- 5 The antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and the temperature of the storage unit was monitored.

The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2), which had been passed three times through Vero-hSLAM cells.

10

Animals

The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg (B6.Cg-Tg(K18-ACE2)2PrImn/JArc; Jax™ Stock No.: 034860) mouse model. 60 mice were used and ten animals were allocated to 6 treatment groups. All mice were housed in individually
15 ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days. Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at the day of infection
20 (Day 0).

Study design

The dose level of test antibody applied in the current example was based on the maximal dosing possible for the material stock concentration (4 mg/mL) and based on literature
25 and previous experience with an anti-S2 antibody (CV3-25) showing protection IP at doses ≥ 0.5 mg/kg. A total number of 60 mice were allocated to 6 experimental groups according to Table 3 (see below). Mice were given a period of > 3 days for acclimatization.

Table 3: Intraperitoneal experimental detail

Test Group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	As disclosed above.	I.P.	10	-1	10
5		I.P.	5	-1	10
1.7		I.P.	1.7	-1	10
0.5		I.P.	0.5	-1	10
0.2		I.P.	0.2	-1	10
Vehicle	---	I.N.	0	-1	10

Female SARS-CoV-2 Delta K18 hACE2 mice were treated via the intraperitoneal route of administration with the antibody at a dose between 10 mg/kg and 0.2 mg/kg based upon average group weight. On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for weight loss and mortality until the end of the study at day 14.

Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table 3), was formulated using the average weight per cage and group on day -5.

Prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle and then administered to each mouse. Mice in the treatment group received the indicated dose by intraperitoneal administration of 200 μL of antibody solution into the intraperitoneal cavity, mice were scruffed and held inverted at a -45° angle for administration (200 μL per mouse). Mice in the vehicle group that received PBS were anaesthetized with isoflurane (4% v/v with 2 L/min O₂) for two minutes. The mice were then scruffed and held at a $+45^{\circ}$ angle. 50 μL of compound or vehicle control was then slowly administered to the nares of each mouse (25 μL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration, at a titer of $10^{6.3}$ TCID₅₀/mL. Once defrosted, the material was diluted in sterile PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 μL). As required, the animals were
5 anesthetized by isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50 μL (25 μL in each nare) of virus corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation. Unused material was frozen at -20°C to -80°C for back titration.

10 Laboratory analysis

Inoculum was back titrated and the actual dose of the virus administered was verified by titrating replicate samples on Vero cells.

Terminal investigations

15 At the end of the study, on day 14, mice were euthanized by cervical dislocation. Gross necropsy was not performed.

Data analysis and statistical methods

Survival proportions at day 14, survival times and change in bodyweight (Area Under the
20 Curve) were compared to the control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS solution) control group. P-values were adjusted according to Bonferroni (for two comparisons to vehicle) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

25

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.

Survival - Intraperitoneal

Prophylactic treatment with test antibody provides statistically significant increase in
30 survival compared to the control group.

Prophylactic treatment test antibody resulted in a significant improvement in survival time compared to the control group.

Body weight

5 Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at day 0 was used as baseline and weight change was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic
10 treatment with test antibody resulted in a significant reduction in weight loss compared to the control group.

Conclusion

15 In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of test antibody provides significant improvement in survival compared to vehicle and a reduction in weight loss whereas animals in the control group died.

Example 4. Antibody according to the invention IP

20 The aim of this study was to assess the pre-exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545, following systemic intraperitoneal administration in a SARS-CoV-2 Delta
25 K18 hACE2 Tg mouse model.

Animals (n=10 per group) were treated with an intraperitoneal dose range of the test antibody described above (10 to 0.2 mg/kg) or PBS control as vehicle control at study Day -1. At study Day 0, animals were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta
30 variant.

Materials and Methods

The monoclonal test antibody described above, was buffered in phosphate-buffered saline PBS was diluted to the final concentrations for administration (10 to 0.2 mg/kg in 200 µL), thereby preparing the test antibody dilution.

- 5 The test antibody dilution was made up at various concentrations so that 200 µL administrations to the mean weight per cage resulted in test antibody doses ranging from 10 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

The antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and
10 the temperature of the storage unit was monitored.

The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2), which had been passed three times through Vero-hSLAM cells.

15 Animals

The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg (B6.Cg-Tg(K18-ACE2)2PrImn/JArc; Jax™ Stock No.: 034860) mouse model, at a weight of 17.1g-23.4 g at day of viral challenge. 60 mice were used at the age of 12-13 weeks of age and were exclusively female. Ten animals were allocated to 6 treatment groups. All mice were
20 housed in individually ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days. Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at
25 the day of infection (Day 0).

Study design

The dose level of test antibody applied in the current example was based on the maximal dosing possible for the material stock concentration (4 mg/mL) and based on literature
30 and previous experience with an anti-S2 antibody (CV3-25) showing protection IP at doses ≥ 0.5 mg/kg. A total number of 60 mice were allocated to 6 experimental groups according to Table 4 (see below). Mice were given a period of > 3 days for acclimatization.

Table 4: Intraperitoneal experimental detail

Test group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	As disclosed above.	I.P.	10	-1	10
5		I.P.	5	-1	10
1.7		I.P.	1.7	-1	10
0.5		I.P.	0.5	-1	10
0.2		I.P.	0.2	-1	10
Vehicle control	---	I.N.	0	-1	10

Female SARS-CoV-2 Delta K18 hACE2 mice were treated via the intraperitoneal route of administration with the antibody at a dose between 10 mg/kg and 0.2 mg/kg based upon average group weight. On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for weight loss and mortality until the end of the study at Day 14.

Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table 4), was formulated using the average weight per cage.

Prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle and then administered to each mouse. Mice in the treatment group received the indicated dose by intraperitoneal administration of 200 μL of antibody solution into the intraperitoneal cavity, mice were scruffed and held inverted at a -45° angle for administration (200 μL per mouse). Mice in the vehicle control group that received PBS were anaesthetized with isoflurane (4% v/v with 2 L/min O₂) for two minutes. The mice were then scruffed and held at a $+45^{\circ}$ angle. 50 μL of compound or vehicle control was then slowly administered to the nares of each mouse (25 μL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration, at a titer of $10^{6.3}$ TCID₅₀/mL. Once defrosted, the material was diluted in sterile PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 μL). As required, the animals were anesthetized by isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50 μL (25 μL in each nare) of virus corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation. Unused material was frozen at -20°C to -80°C for back titration.

Laboratory analysis

Inoculum was back titrated and the actual dose of the virus administered was verified by titrating replicate samples on Vero cells.

Terminal investigations

At the end of the study, on Day 14, mice were euthanized by cervical dislocation. Gross necropsy was not performed.

Data analysis and statistical methods

Survival proportions at Day 14, survival times and change in bodyweight (Area Under the Curve) were compared to the control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS solution) control group. P-values were adjusted according to Bonferroni (for two comparisons to vehicle control) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.

Survival - Intraperitoneal

Prophylactic treatment with ≥ 0.5 mg/kg test antibody provides statistically significant increase in survival compared to vehicle control (See Figure 5A). The survival proportion at Day 6 in the control group was 0%. The median survival time of the control group was 6 days.

Survival times of the test antibody treated groups were compared to the control group using a log-rank test. Prophylactic treatment with ≥ 0.2 mg/kg test antibody resulted in a significant improvement in survival time.

5

Body weight

Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at Day 0 was used as baseline and weight change
10 was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic treatment with ≥ 0.5 mg/kg of the test antibody resulted in a significant reduction in weight loss compared to the control group (Figure 5B).

15

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of ≥ 0.5 mg/kg test antibody provides significant improvement in survival compared to a vehicle control group and reduction in weight loss whereas all the animals in the control group did not survive (Figure 5).

20

Example 5: Antibody according to the invention

The aim of this study was to assess the pre-exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as
25 SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545, following intranasal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

Animals (n=10 per group) were treated with an intranasal dose range of the test antibody described above (10 to 0.2 mg/kg) or PBS control at study day -1. At study day 0, animals
30 were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

The monoclonal antibody according to the invention was buffered in phosphate-buffered saline PBS was diluted to the final concentrations for administration (10 to 0.2 mg/kg in 50 µL)

- 5 The monoclonal dilution was made up at various concentrations so that 50 µL administrations to the mean weight per cage of the dosing group at day -5 resulted in test antibody doses ranging from 10 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

- 10 The antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and the temperature of the storage unit was monitored.

The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2)., which had been passed three times through Vero-hSLAM cells.

15 Animals

- The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg mouse model. 60 mice were used and ten animals were allocated to 6 treatment groups. All mice were housed in individually ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal
20 nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days. Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at the day of infection (Day 0).

25 Study design

- The dose level of the monoclonal antibody applied in the current example was based on the maximal dosing possible for the material stock concentration (4 mg/mL) and based on literature and previous experience with an anti-S2 antibody (CV3-25) showing protection IN at doses ≥ 1.7 mg/kg. A total number of 60 mice were transported to the animal facility
30 and allocated to 6 experimental groups according to Table 5 (see below). Mice were given a period of >3 days for acclimatization.

Table 5: Intranasal experimental detail

Test group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	As disclosed above.	I.N.	10	-1	10
5		I.N.	5	-1	10
1.7		I.N.	1.7	-1	10
0.5		I.N.	0.5	-1	10
0.2		I.N.	0.2	-1	10
Vehicle	---	I.N.	0	-1	10

Female SARS-CoV-2 Delta K18 hACE2 mice were treated via the intranasal route of administration with the antibody at a dose between 10 mg/kg and 0.2 mg/kg based upon group average mouse weight per cage. On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for survival and weight loss until the end of the study at day 14.

Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table 5), was formulated using the average weight per cage and group on day -5.

Just prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle, and then administered to each mouse. Mice were anaesthetized with isoflurane (4% v/v with 2 L/min O₂) for two minutes. The mice were then scruffed and held at a +45 deg angle. 50 µL of compound or vehicle control was then slowly administered to the nares of each mouse (25 µL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration. Once defrosted, the material was diluted in cold PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 µL. As required, the animals were anesthetized by isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50 µL (25 µL each nare) of virus

corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation. Unused material was frozen at -20°C to -80°C for back titration.

Laboratory analysis

5 Inoculum was back titrated and the dose of the virus administered was verified by titrating replicate samples on Vero cells.

Terminal investigations

At the end of the study, on day 14, mice were euthanized by cervical dislocation. Gross
10 necropsy was not performed.

Data analysis and statistical methods

Survival proportions at day 14, survival times and change in bodyweight (Area Under the Curve) were compared to the corresponding control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS
15 solution) control group. P-values were adjusted according to Bonferroni (for two comparisons to vehicle) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

20

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.

Survival - Intranasal

Prophylactic treatment with test antibody provides statistically significant protection
25 compared to vehicle.

Survival times of the test antibody treated groups were compared to the control group using a log-rank test. Prophylactic treatment with test antibody resulted in a significant improvement in survival time.

30

Body weight

Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at day 0 was used as baseline and weight change
5 was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic treatment with test antibody resulted in a significant reduction in weight loss compared to the control group.

Conclusion

10 In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal administration of test antibody provides significant improvement in survival and a reduction in weight loss compared to vehicle, whereas animals in the control group died by day 6.

Example 6: Antibody according to the invention

The aim of this study was to assess the pre-exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as
20 SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545, following intranasal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

Animals (n=10 per group) were treated with an intranasal dose range of the test antibody described above (10 to 0.2 mg/kg) or PBS control at study Day -1. At study Day 0, animals
25 were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

The monoclonal antibody according to the invention was buffered in phosphate-buffered
30 saline PBS was diluted to the final concentrations for administration (10 to 0.2 mg/kg in 50 µL)

The monoclonal dilution was made up at various concentrations so that 50 µL administrations to the mean weight per cage resulted in test antibody doses ranging from 10 mg/kg, 5 mg/kg, 1.7 mg/kg, 0.5 mg/kg to 0.2 mg/kg.

- 5 The antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and the temperature of the storage unit was monitored.

The virus strain tested was SARS-CoV-2 Delta variant (Aus/VIC/18440/2021 (B.1.617.2)., which had been passed three times through Vero-hSLAM cells.

10

Animals

- The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg mouse model, at a weight of 17.1g- 23.4 g on the day of test article administration. 60 mice were used at the age of 12-13 weeks and were exclusively female. Ten animals were allocated to 6 treatment groups based on creating groups with similar mean weight and weight variability. All mice were housed in individually ventilated cages (IVCs), with corn cob bedding, tissues or shredded paper as nesting material, a wooden chew block, accessible food pellets and acidic water for animal nourishment and red plastic tunnels. Each cage system holds 3 to 5 mice per cage. All mice were transferred to fresh cages every 14 days.
- 15 Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at the day of infection (Day 0).
- 20

Study design

- The dose level of the monoclonal antibody applied in the current example was based on the maximal dosing possible for the material stock concentration (4 mg/mL) and based on literature and previous experience with an anti-S2 antibody (CV3-25) showing protection IN at doses ≥ 1.7 mg/kg. A total number of 60 mice, 12-13 weeks of age were transported to the animal facility and allocated to 6 experimental groups according to Table 6 (see below). Mice were given a period of >3 days for acclimatization.
- 25

30

Table 6: Intranasal experimental detail

Test group	Antibody	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	As disclosed above.	I.N.	10	-1	10
5		I.N.	5	-1	10
1.7		I.N.	1.7	-1	10
0.5		I.N.	0.5	-1	10
0.2		I.N.	0.2	-1	10
Vehicle	---	I.N.	0	-1	10

Female SARS-CoV-2 Delta K18 hACE2 mice were treated via the intranasal route of administration with the antibody at a dose between 10 mg/kg and 0.2 mg/kg based upon group average mouse weight per cage. On Day 0, all mice were challenged with a lethal dose ($10^{3.5}$ TCID₅₀) of the SARS-CoV-2 Delta variant and observed for survival and weight loss until the end of the study at Day 14.

Antibody administration

The test antibody was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ upon arrival. The appropriate dose, according to the treatment schedule (Table 6), was formulated using the average weight per cage.

Just prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle, and then administered to each mouse. Mice were anaesthetized with isoflurane (4% v/v with 2 L/min O₂) for two minutes. The mice were then scruffed and held at a +45 deg angle. 50 μL of compound or vehicle control was then slowly administered to the nares of each mouse (25 μL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration. Once defrosted, the material was diluted in cold PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 μL . As required, the animals were anesthetized by isoflurane (4% v/v with 2 L/min O₂) and each animal received approximately 50 μL (25 μL each nare) of virus
5 corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation. Unused material was frozen at -20°C to -80°C for back titration.

Laboratory analysis

Inoculum was back titrated and the dose of the virus administered was verified by
10 titrating replicate samples on Vero cells.

Terminal investigations

At the end of the study, on Day 14, mice were euthanized by cervical dislocation. Gross necropsy was not performed.
15

Data analysis and statistical methods

Survival proportions at Day 14, survival times and change in bodyweight (Area Under the Curve) were compared to the control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups were compared to the vehicle (PBS solution) control group.
20 P-values were adjusted according to Bonferroni (for two comparisons to vehicle) followed by a stepwise approach (starting with the highest antibody dose conditionally testing a lower dose if the previous step was statistically significant).

Statistical analysis was performed using R and statistical significance was set at $\alpha = 0.05$.
25

Survival - Intranasal

Prophylactic treatment with ≥ 0.5 mg/kg test antibody provides statistically significant increase in survival compared to vehicle (See Figure 6A). The survival proportion at Day 7 in the control group was 0%. The median survival time of the control group was 6 days.
30

Prophylactic treatment with ≥ 0.2 mg/kg test antibody resulted in a significant improvement in survival time.

Body weight

Change in bodyweight was analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight was carried forward if a mouse died / was euthanized during the study. The weight per mouse at Day 0 was used as baseline and weight change was determined relative to baseline and the net AUC was defined as the summation of the area above and below the baseline using the percentage change per day. Prophylactic treatment with ≥ 0.2 mg/kg of the test antibody resulted in a significant reduction in weight loss compared to the control group (Figure 6B).

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal administration of ≥ 0.5 mg/kg test antibody provides significant improvement in survival and a dose of ≥ 0.2 mg/kg resulted in a reduction in weight loss compared to vehicle, whereas animals in the control group had not survived by Day 6 (see Figure 6).

Example 7: Antibody according to the invention

The aim of this study is to assess the pre- and post- exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545, following intranasal administration in a NHP model in which each subject is pre-screened for the absence of serum antibodies against SARS-CoV-2 viruses.

NHP subjects are treated with an intranasal dose of the composition comprising the antibody described above. The flat dose, or nominal dose, of the antibody administered to each NHP subject is between 0.01 mg and 10 mg (e.g. between 0.01 to 2.0 mg ("Low Dose") or between 2.0 to 10 mg ("High Dose")) or Control (e.g. vehicle only) at study day -1.

Materials and Methods

The monoclonal antibody according to the invention is provided in a sodium acetate buffer (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5) and is diluted

to the final concentration for administration ranging from 0.01 mg to 2.0 mg or 2.0 to 10 mg nominal dose, administered as 50 µL to 500 µL per nare.

5 The NHP subjects allocated to the Control Group (Sodium acetate buffer) are administered with vehicle (e.g. 20 mM Sodium Acetate, 75 mM Sodium Chloride, 5% sucrose, pH 5.5), administered as 50 µL to 500 µL per nare.

All NHPs receive intranasal challenge with SARS-CoV-2 at day 0.

10 Samples are taken during the study, sample types include nasal sampling (e.g. nasal swabs, wash or scrapes), serum and / or bronchoalveolar lavage (BAL) samples. Sampling period includes study duration, in a time frame between day -1 to the end of the study (e.g. 7 to 21 days follow-up period).

15 Samples are analyzed as required for viral quantification (by quantitative or RT PCR and/or TCID₅₀) and / or antibody titers are analyzed by ELISA, HPLC or similar method.

Animals

20 The NHP subjects are used at a weight of between 3 to 12 kg (e.g. 5 kg per animal) on commencement of the study. Between 5 and 12 animals are allocated to each treatment group.

Study design

25 The dose level of the monoclonal antibody applied in the current example is based on the maximal dosing and a lower dose based upon allometric calculations obtained from murine studies.

Table7: Intranasal experimental detail per antibody

Test group	Antibody	Admin. route	Dose (mg)	Day of admin.	No. of Animals
High dose	As disclosed above.	I.N.	2.0 – 10	-1	5 – 12
Low dose		I.N.	0.01 – 2.0	-1	5 – 12
Vehicle	---	I.N.	0	-1	5 – 12

The NHP subjects receive intranasal administrations with compositions comprising the antibody at a dose between 0.01 mg to 2.0 mg or 2.0 mg to 10 mg (Nominal Dose). On Day 0, all NHP subjects are challenged with a dose of the SARS-CoV-2 and observed for clinical manifestations (e.g. weight loss and / or temperature) and virology measurements until the end of the study (e.g. Day 7 to 21).

Antibody administration

The test antibody or vehicle only is administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 7), using volumes of between 50 µL to 500 µL per nare.

Virus administration

The virus material is defrosted prior to administration. Once defrosted, the material is diluted and each animal receives between 50 µL to 500 µL of virus solution per nare. The NHP subjects are infected with between 10^2 and 10^8 TCID₅₀ of SARS-CoV-2 (e.g. 10^5 TCID₅₀ of SARS-CoV-2).

Data analysis and statistical methods

Clinical manifestations (e.g. body weight loss and temperature) and virological measurements are used for comparisons between treatment and Control Group.

Results – Clinical Manifestations

Prophylactic treatment with the Low Dose and High Dose antibody administration provides reduction in clinical manifestation measurements, compared to the Control Group.

Results – Virological Measurements

Prophylactic treatment with the Low Dose and High Dose antibody administration provides reduction in virological measurements, compared to the Control Group. All Control Group NHPs show viral loads in samples after SARS-CoV-2 challenge.

Conclusion

In this SARS-CoV-2 NHP model, the prophylactic intranasal administration of 2.0 to 10 mg (High Dose) and 0.01 to 2.0 mg (Low Dose) of the test antibody according to the invention provides a reduction in virological measurements and / or a reduction in clinical manifestations as compared with Control Group NHPs.

Example 8: Composition comprising an antibody according to the invention

The aim of this study is to assess the pre- and post- exposure efficacy of a composition comprising a first monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 046, heavy chain CDR2 as SEQ ID NO: 114, heavy chain CDR3 as SEQ ID NO: 254, a light chain CDR1 as SEQ ID NO: 367, a light chain CDR2 as SEQ ID NO: 430, and a light chain CDR3 as SEQ ID NO: 545 ("First Antibody"), and a second monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 639, heavy chain CDR2 as SEQ ID NO: 640, heavy chain CDR3 as SEQ ID NO: 641, a light chain CDR1 as SEQ ID NO: 642, a light chain CDR2 as SEQ ID NO: 643, and a light chain CDR3 as SEQ ID NO: 644 ("Second Antibody"), following intranasal administration in a NHP model in which each subject is pre-screened for the absence of serum antibodies against SARS-CoV-2 viruses.

NHP subjects are treated with an intranasal dose of the composition comprising the antibodies described above (single antibodies or combinations of both antibodies). The flat dose, or nominal dose, of the antibodies administered to each NHP subject is between 0.003 mg and 5 mg or Control (e.g. vehicle only) at study day -1.

Materials and Methods

The monoclonal antibody according to the invention is provided in a sodium acetate buffer (e.g. 20 mM Sodium Acetate, 75 mM Sodium Chloride, 5% sucrose, pH 5.5) and is diluted to the final concentration for administration ranging from 0.003 mg and 5mg nominal
5 dose, administered as 50 µL to 500 µL per nare.

The NHP subjects allocated to the Control Group (Sodium acetate buffer) are administered with vehicle (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5), administered as 50 µL to 500 µL per nare.
10

All NHPs receive intranasal challenge with SARS-CoV-2 at day 0.

Samples are taken during the study, sample types include nasal sampling (e.g. nasal swabs, wash or scrapes), serum and / or bronchoalveolar lavage (BAL) samples. Sampling
15 period includes study duration, in a time frame between day -1 to the end of the study (e.g. 7 to 21 days follow-up period).

Samples are analyzed as required for viral quantification (by quantitative or RT-PCR and / or TCID₅₀) and/ or antibody titers by ELISA or similar methods.
20

Animals

The NHP subjects are used at a weight of between 3 to 12 kg (e.g. 5 kg per animal) on commencement of the study. Between 4 and 12 animals are allocated to each treatment group.
25

Study design

The dose level of the monoclonal antibody and the combination applied in the current example is based on the maximal dosing and based upon allometric calculations obtained from murine studies.
30

Table 8: Intranasal experimental detail

Treatment group	Antibody	Dose (mg)	Day of admin.	No. of Animals
1	First Antibody only	0.003 – 5.0	-1	4 – 12
2	Second Antibody only	0.003 – 5.0	-1	4 – 12
3	First and Second Antibody	0.003 – 5.0	-1	4 – 12
Vehicle	---	0	-1	4 – 12

The NHP subjects receive intranasal administrations with compositions comprising either single antibody nominal doses of between 0.003 - 5 mg (Treatment Groups 1 or 2).

5 Different NHP subjects receive intranasal administrations with compositions comprising the First and Second Antibody at nominal doses between 0.003 - 5 mg (Treatment Group 3). On Day 0, all NHP subjects are challenged with a dose of the SARS-CoV-2 and observed for clinical manifestations (e.g. weight loss and / or temperature) and virology measurements until the end of the study (e.g. Day 7 to 21).

10

Antibody administration

The antibody compositions (Treatment Groups 1 to 3) or vehicle only are administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 8), using volumes of between 50 µL to 500 µL per nare.

15

Virus administration

The virus material is defrosted prior to administration. Once defrosted, the material is diluted and each animal receives between 50 µL to 500 µL of virus solution per nare. The NHP subjects are infected with between 10^2 and 10^8 TCID₅₀ of SARS-CoV-2 (e.g. 10^5 TCID₅₀ of SARS-CoV-2).

20

Data analysis and statistical methods

Clinical manifestations (e.g. body weight loss and temperature) and virological measurements are used for comparisons between treatments (e.g. Treatment Groups 1 to 3) and Control Group and/or comparison within treatment groups (e.g. Treatment Group 1 against Treatment Group 3).

25

Results – Clinical Manifestations

Prophylactic treatment with treatments (as indicated in Table 8) provides reduction in clinical manifestation measurements, compared to the Control Group or compared within
5 treatment groups.

Results – Virological Measurements

Prophylactic treatment with treatments (as indicated in Table 8) provides reduction in virological measurements, compared to the Control Group or compared within treatment
10 groups.

Conclusion

In this SARS-CoV-2 NHP model, the prophylactic intranasal administration of treatments (as indicated in Table 8) according to the invention provides a reduction in
15 clinical manifestations and / or a reduction in virological measurements, as compared with control group NHPs and within treatments.

Example 9: Bi-specific antibody according to the invention

20 The aim of this intranasal murine study is to assess the pre- and post- exposure efficacy of a bispecific monoclonal antibody in comparison with the parental antibodies, according to the invention, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2. The first parental antibody ("Parental mAb 1") has the following CDRs as described in SEQ ID
25 Numbers: 046, 114, 254, 367, 430 and 545. The second parental antibody ("Parental mAb 2") has the following CDRs as described in SEQ ID Numbers: 645, 646, 647, 648, 649 and 650. The bi-specific antibody according to the invention has a first Fab that comprises a sequence comprising any one or more of SEQ ID Numbers: 046, 114, 254, 367, 430 or 545; the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers:
30 645, 646, 647, 648, 649 to 650.

Animals are treated with an intranasal nominal dose (0.001 mg/kg to 15 mg/kg) of comprising either Parental mAb 1, or Parental mAb 2, or the bispecific antibody described above, or vehicle control at study day -1.

5 Materials and Methods

The monoclonal parental and bispecific antibodies according to the invention is provided in a sodium acetate buffer (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5) and is diluted to the final concentration for administration ranging from 0.001 mg/kg to 15 mg/kg, administered as 25 µL to 50 µL per nare.

10

The mice allocated to the control group (Sodium acetate buffer) are administered with vehicle (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5), administered as 25 µL to 50 µL per nare.

15 All mice receive intranasal challenge with SARS-CoV-2 Delta at day 0.

Animals

The SARS-CoV-2 Delta K18 hACE2 Tg mice are used at a weight of c. 15g to 22g (e.g. 20 g per animal) on commencement of the study. Between 6 and 10 animals are allocated to each treatment group.

20

Study design

The dose level of the monoclonal and bispecific antibodies applied in the current example is based on the maximal dosing and based upon previous results from efficacy studies in mice with the parental antibodies alone. From the maximal dose of ≤15 mg/kg, a 3- or 4-fold dilution curve for each the parental or bispecific antibody is applied.

25

Table 9: Intranasal experimental detail per antibody

Test group	Antibody	Dose (mg/kg)	Day of admin.	No. of Animals
1	Parental mAb 1 (dose 1)	0.001-15 (e.g. 0.0027, 0.063)	-1	6 – 10
2	Parental mAb 1 (dose 2)	0.001-15 (e.g. 0.106, 0.189)	-1	6 – 10
3	Parental mAb 1 (dose 3)	0.001-15 (e.g. 0.425, 0.567)	-1	6 – 10
4	Parental mAb 1 (dose 4)	0.001-15 (e.g. 1.7)	-1	6 – 10
5	Parental mAb 2 (dose 1)	0.001-15 (e.g. 0.0027, 0.063)	-1	6 – 10
6	Parental mAb 2 (dose 2)	0.001-15 (e.g. 0.106, 0.189)	-1	6 – 10
7	Parental mAb 2 (dose 3)	0.001-15 (e.g. 0.425, 0.567)	-1	6 – 10
8	Parental mAb 2 (dose 4)	0.001-15 (e.g. 1.7)	-1	6 – 10
9	Bispecific mAb (dose 1)	0.001-15 (e.g. 0.007, 0.005)	-1	6 – 10
10	Bispecific mAb (dose 2)	0.001-15 (e.g. 0.027, 0.020)	-1	6 – 10
11	Bispecific mAb (dose 3)	0.001-15 (e.g. 0.106, 0.080)	-1	6 – 10
12	Bispecific mAb (dose 4)	0.001-15 (e.g. 0.425, 0.310)	-1	6 – 10
13	Bispecific mAb (dose 5)	0.001-15 (e.g. 1.7, 1.25)	-1	6 – 10
14	Bispecific mAb (dose 6)	0.001-15 (e.g. 5.0)	-1	6 – 10
Vehicle	---	0	-1	6 – 10

The mice are treated via the intranasal route of administration with compositions comprising either parental antibodies or the bispecific antibody at dose ranges between 0.001 and 15 mg/kg. On Day 0, all mice are challenged with a dose of the SARS-CoV-2 and observed for survival and body weight until the end of the study (e.g. Day 10-15).

Antibody administration

The parental monoclonal antibodies or bispecific antibody or vehicle only is administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 9), using volumes of between 25 µL to 50 µL per nare.

5

Virus administration

The virus material is defrosted prior to administration. Once defrosted, the material is diluted and each animal received between 25 µL to 50 µL of virus per nare. The mice are infected with between 10^2 and 10^8 TCID₅₀ of SARS-CoV-2 (e.g. $10^{3.5}$ TCID₅₀ of SARS-CoV-2).

10

Laboratory analysis

Inoculum is returned to the lab and the dose of the virus administered is verified by titrating replicate samples on Vero cells.

15

Clinical monitoring

General health observations are performed on each animal from the day of arrival until the end of the study at least once daily (during normal servicing procedures). Each animal is weighed daily beginning one day prior to infection (day -1).

20

Data analysis and statistical methods

Survival proportions and survival times and change in bodyweight (Area Under the Curve) are compared to the corresponding control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups are compared to the vehicle control group. P values are adjusted according to Bonferroni (for three comparisons to vehicle) followed by a stepwise approach within antibody (starting with the highest dose and conditionally testing a lower dose if the previous step was statistically significant).

25

Combination index

Survival dose response curves are fitted for each of the treatments (Parental mAb 1, Parental mAb 2 and Bispecific) and the ED₅₀ is estimated. The efficacy of the bispecific antibody is then compared to the parental antibodies by calculation of the combination index.

30

Survival

Prophylactic treatment with Parental mAb 1, Parental mAb 2 or bispecific antibody (as indicated in Table 9) compared to the control group provides statistically significant protection against mortality and a significant improvement in survival time compared to the control group.

Body weight

Change in bodyweight is analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight is carried forward if a mouse died/ is euthanized during the study. The weight per mouse at day 0 is used as baseline and weight change is determined relative to baseline with the net AUC defined as the summation of the area above and below the baseline using the percentage change per day.

Prophylactic treatment with the parental or bispecific antibodies (as indicated in Table 9) provides a statistically significant reduction in weight loss, compared to the control group.

Conclusion

In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of a bispecific antibody (as indicated in Table 9) according to the invention provides significant improvement in survival and a reduction in body weight loss compared with Control Group. The outcome of the combination index is suggestive of at least a comparable, an additive or potentially synergistic effect for the bispecific compared to the parental antibodies.

25

Example 10: Composition comprising antibody combination according to the invention

The aim of this intranasal murine study is to assess the pre- and post- exposure efficacy of a composition comprising a first antibody according to the invention capable of binding to the stem helix of SARS-CoV-2, and second antibody capable of binding to the fusion peptide of SARS-CoV-2. The first antibody ("First mAb") has the following CDRs as described in SEQ ID Numbers: 046, 114, 254, 367, 430 or 545. The second antibody

("Second mAb") has the following CDRs as described in SEQ ID Numbers: 639, 640, 641, 642, 643 and SEQ ID NO.: 644.

5 Animals are treated with an intranasal nominal dose (0.001 mg/kg to 15 mg/kg) comprising either First mAb, or Second mAb, or the composition comprising the first and second antibody described above, or vehicle control at study day -1.

Materials and Methods

10 The First mAb and Second mAb are provided in a sodium acetate buffer (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5) and is diluted to the final concentration for administration ranging from 0.001 mg/kg to 15 mg/kg, administered as 25 µL to 50 µL per nare.

15 The mice allocated to the control group (Sodium acetate buffer) are administered with vehicle (e.g. 20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5), administered as 25 µL to 50 µL per nare.

All mice receive intranasal challenge with SARS-CoV-2 Delta at day 0.

20 Animals

The SARS-CoV-2 Delta K18 hACE2 Tg mice are used at a weight of c. 15g to 22g (e.g. 20 g per animal) on commencement of the study. Between 6 and 10 animals are allocated to each treatment group.

25 Study design

The dose level of the First mAb, or Second mAb, or the composition comprising the first and second antibody described above in the current example is based on the maximal dosing and based upon previous results from efficacy studies in mice with the parental antibodies alone. From the maximal dose of ≤15 mg/kg, a 3- or 4-fold dilution curve for
30 each the parental or bispecific antibody is applied.

Table 10: Intranasal experimental detail per antibody

Test group	Antibody	Dose (mg/kg)	Day of admin.	No. of Animals
1	First mAb 1 (dose 1)	0.001-15 (e.g. 0.0027, 0.063)	-1	6 – 10
2	First mAb 1 (dose 2)	0.001-15 (e.g. 0.106, 0.189)	-1	6 – 10
3	First mAb 1 (dose 3)	0.001-15 (e.g. 0.425, 0.567)	-1	6 – 10
4	First mAb 1 (dose 4)	0.001-15 (e.g. 1.7)	-1	6 – 10
5	Second mAb 2 (dose 1)	0.001-15 (e.g. 0.0027, 0.063)	-1	6 – 10
6	Second mAb 2 (dose 2)	0.001-15 (e.g. 0.106, 0.189)	-1	6 – 10
7	Second mAb 2 (dose 3)	0.001-15 (e.g. 0.425, 0.567)	-1	6 – 10
8	Second mAb 2 (dose 4)	0.001-15 (e.g. 1.7)	-1	6 – 10
9	Combination mAb (dose 1)	0.001-15 (e.g. 0.007, 0.005)	-1	6 – 10
10	Combination mAb (dose 2)	0.001-15 (e.g. 0.027, 0.020)	-1	6 – 10
11	Combination mAb (dose 3)	0.001-15 (e.g. 0.106, 0.080)	-1	6 – 10
12	Combination mAb (dose 4)	0.001-15 (e.g. 0.425, 0.310)	-1	6 – 10
13	Combination mAb (dose 5)	0.001-15 (e.g. 1.7, 1.25)	-1	6 – 10
14	Combination mAb (dose 6)	0.001-15 (e.g. 5.0)	-1	6 – 10
Vehicle	---	0	-1	6 – 10

The mice are treated via the intranasal route of administration with compositions comprising either First or Second antibodies or the composition comprising the combination at dose ranges between 0.001 and 15 mg/kg. On Day 0, all mice are challenged with a dose of the SARS-CoV-2 and observed for survival and body weight until the end of the study (e.g. Day 10-15).

Antibody administration

The First or Second antibodies or the composition comprising the combination or vehicle only is administered to each nare (e.g. pipette or spray) according to the treatment
5 schedule (Table 10), using volumes of between 25 µL to 50 µL per nare.

Virus administration

The virus material is defrosted prior to administration. Once defrosted, the material is diluted and each animal received between 25 µL to 50 µL of virus per nare. The mice are
10 infected with between 10^2 and 10^8 TCID₅₀ of SARS-CoV-2 (e.g. $10^{3.5}$ TCID₅₀ of SARS-CoV-2).

Laboratory analysis

Inoculum is returned to the lab and the dose of the virus administered is verified by
15 titrating replicate samples on Vero cells.

Clinical monitoring

General health observations are performed on each animal from the day of arrival until the end of the study at least once daily (during normal servicing procedures). Each animal
20 is weighed daily beginning one day prior to infection (day -1).

Data analysis and statistical methods

Survival proportions and survival times and change in bodyweight (Area Under the Curve) are compared to the corresponding control group using Fisher's exact test, log-rank and Welch's t-test, respectively. All groups are compared to the vehicle control group.
25 P values are adjusted according to Bonferroni (for three comparisons to vehicle) followed by a stepwise approach within antibody (starting with the highest dose and conditionally testing a lower dose if the previous step was statistically significant).

Combination index

Survival dose response curves are fitted for each of the treatments (First or Second antibodies or the composition comprising the combination) and the ED₅₀ is estimated. The
30

efficacy of the combination is then compared to the First and Second antibodies by calculation of the combination index.

Survival

5 Prophylactic treatment with the First or Second antibodies or the composition comprising the combination (as indicated in Table 10) compared to the control group provides statistically significant protection against mortality and a significant improvement in survival time compared to the control group.

Body weight

10 Change in bodyweight is analyzed using an Area Under the Curve (AUC) analysis in which the last observed body weight is carried forward if a mouse died/ is euthanized during the study. The weight per mouse at day 0 is used as baseline and weight change is determined relative to baseline with the net AUC defined as the summation of the area
15 above and below the baseline using the percentage change per day.

Prophylactic treatment with the composition comprising the combination (as indicated in Table 10) provides a statistically significant reduction in weight loss, compared to the control group.

Conclusion

20 In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of the composition comprising the combination (as indicated in Table 10) according to the invention provides significant improvement in survival and a reduction in body weight
25 loss compared with Control Group. The outcome of the combination index is suggestive of at least a comparable, an additive or potentially synergistic effect for the combination compared to the First or Second antibodies administered alone.

Example 11: ELISA binding assessment of an antibody according to the invention

30 The objective of this study was to assess the binding of the antibody against different Corona Spike antigens, a variety of alpha and beta coronaviruses.

Binding was tested in an enzyme-linked immunosorbent assay (ELISA). Briefly, a Spike antigen was used to coat the surface of a microwell of an ELISA plate. The antibody was then added in decreasing concentration to the coated and pre-blocked microwell surface in duplicates, attaching to the coated antigen. A detection antibody was added, labeled with horse radish peroxide (HRP), that then generates a colorimetric signal upon addition of the substrate. The readout was optical density and reflects binding. The antibody was assayed in duplicate against a number of alpha and beta coronavirus spike antigens, including but not limited to SARS-CoV-2 Delta, Omicron XBB.1.5 and human coronavirus NL63. The antibody was tested in comparison to other anti-S1 antibodies in the range of 10.0 - 0.000002 nM. Half maximal effective concentration (EC₅₀) was calculated for each antibody on each antigen as an estimate of binding affinity.

Table 12: ELISA EC₅₀ values (nM) for the antibody according to invention. N/D = no EC₅₀ value was determined, due to lack of binding.

	CoV-2 Delta	CoV-2 XBB.1.5	NL63
Parental mAb 1	0.0015	0.00056	N/D
Anti-S1 antibody DZIF-10c	6.9	N/D	N/D
Anti-S1 mAb ImdevimAb	0.010	N/D	N/D
Isotype control	N/D	N/D	N/D

The ELISA binding assay (Table 12) shows that the antibody according to invention was able to effectively bind all tested Spike antigens from beta coronaviruses, including SARS-CoV-2 Delta and Omicron XBB.1.5. Alpha coronavirus NL63 was not bound by the antibody. The anti-S1 antibodies tested only bound the SARS-CoV-2 Delta, as expected from literature and did not show breadth amongst alpha coronavirus NL63. The isotype control antibody did not show any binding to the coronavirus antigens.

Example 12: Affinity binding by Meso Scale Discovery (MSD)

The objective of this study was to assess relative binding affinity against Spike antigens in a multiplexed way, with very high specificity and low sample input. Therefore, an

antibody was tested in a multiplexed assay, Meso Scale Discovery (MSD), which uses electrochemiluminescent labels that were conjugated to detection antibodies. In this assay, up to ten trimeric viral antigens are separately printed onto a spot each well of the plate, allowing for a multiplexed assay readout. The antibody according to the invention

5 bind the viral antigens through Fab-mediated recognition, then an anti-human IgG Sulfo-Tag detection antibody is added, recognizing human IgG Fab. Upon addition of read buffer containing substrate, and running a current through the plate electrodes, an electro-(current) chemi- (buffer substrate) luminescent (light) cascade is initiated which results in light emission. The intensity of emitted light is measured per spot, revealing bound

10 levels of analyte. The antibody was assayed in duplicate against Spike antigens of SARS-CoV-2, SARS-CoV-1, MERS, hCoV NL63, hCoV HKU, hCoV OC43 and hCoV 229E (V-Plex COVID-19 Coronavirus Panel 3 (IgG) Kit cat# K15399U-2) (Table 13), as well as a set of Omicron variants (V-Plex SARS-CoV-2 Panel 34 (IgG) Kit cat# K15690U-2) in a separate assay (Table 14). The antibody was tested in a dilution range starting from 555

15 ng/ml for the Panel 3 and 10 ng/ml in the Omicron Panel 24 kit. Light emission from the MSD sulfo-tag antibody was quantified with MSD Discovery workbench, calibration curves were used to calculate antibody concentrations, by fitting the raw electrochemiluminescent units (eCLU) from the calibrators to a logistic regression for curve fitting (Sigmoidal, 4PL, $X = \text{conc}$), and the model asymptotes were constrained to

20 the lower limit of detection (LLOQ) and the upper limit of detection (ULOQ). The concentration (ng/ml) corresponding to the midpoint of the dynamic range (ie the range between the lower and upper limit of quantification, LLOQ and ULOQ) was reported.

Table 13: Antibody concentrations corresponding to the midpoint of the dynamic range (LOQ+ULOQ)/2 (ng/ml) for the antibody according to the invention against different alpha and beta coronaviruses is shown. N/D = antibody concentration could not be determined.

25

	SARS-CoV-2	SARS-CoV-1	MERS-CoV	hCoV-OC43	hCoV-HKU1	hCoV-NL63	hCoV-229E	SARS-CoV-2 S1 RBD
Parental mAb 1	0.40	0.19	0.14	0.90	6.73	N/D	N/D	N/D
Anti-S1 mAb DZIF-10c	0.16	N/D	N/D	N/D	N/D	N/D	N/D	0.09

isotype control	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D
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The MSD binding array (see Table 13) showed that the antibody was able to effectively bind all Spike antigens from beta coronaviruses, including SARS-CoV-2, MERS, HKU1 and OC43. Alpha coronaviruses including 229E and NL63 and SARS-CoV-2 receptor binding domain (RBD) on the S1 part of the Spike were not bound by the antibody. The anti-S1 antibody tested here bound the RBD domain and the wildtype SARS-CoV-2 very well, as expected from literature and did not show breadth amongst other coronaviruses. While the antibody according to the invention bound all tested beta coronavirus Spike antigens, the anti-RBD antibody only bound SARS-CoV-2 Spike and RBD antigens. The isotype control antibody did not show any binding to the coronavirus antigens.

Table 14: Antibody concentrations corresponding to the midpoint of the dynamic range $(LOQ+ULOQ)/2$ (pg/ml) for the antibody according to the invention against different SARS-CoV-2 Omicron viruses is shown. N/D = antibody concentration could not be determined.

	SAR S- CoV- 2	SAR S- CoV- 2 BA.1	SARS- CoV-2 BA.2.7 5	SAR S- CoV- 2 BA.5	SAR S- CoV- 2 BF.7	SAR S- CoV- 2 BN.1	SAR S- CoV- 2 BQ.1	SAR S- CoV- 2 BQ.1. 1	SAR S- CoV- 2 XBB. 1	SARS- CoV-2 XBB.1. 5
Parental mAb 1	427	75	104	117	101	76	129	113	118	119
Anti-S1 mAb DZIF-10c	117	93	81	630	1362 5	1155 8	N/D	N/D	N/D	N/D
isotype control	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D

The MSD binding array showed that the antibody according to invention can effectively bind all Omicron variants tested in this assay (Table 14). While the anti-S1 control

antibody bound SARS-CoV-2 Spike at lower concentrations than the antibody according to invention, the earlier Omicron mutants were only bound at very high concentrations and the later Omicron mutants such as BQ and XBB were not bound. This suggests that the antibody according to the invention showed more breadth across the tested Omicron variants than the anti-RBD antibody. The isotype control antibody did not show any binding to the coronavirus antigens.

Example 13: Live virus neutralization

The objective of this study was to assess the ability of an antibody to neutralize live corona viruses. The antibody was tested for functional activity in a live virus microneutralization assay against MERS, SARS-CoV-1 and SARS-CoV-2 Wuhan. Briefly, dilution series of an antibody were pre-incubated with the corresponding virus and then added to the respective cell line (Vero: MERS and SARS-CoV-1, SARS-CoV-2: Vero E6 cells) in quadruplicates. After incubation, cells were fixed, stained with an anti-nucleocapsid antibody, and an enzymatically tagged detection antibody was added. Colored precipitate signaling nucleocapsid presence was read out via an Immunospot analyzer and 50% inhibitory concentration (IC₅₀), was reported via the Zielinska method (REF: <https://doi.org/10.1186/1743-422X-2-84>). The antibody was tested for neutralizing activity in the range of 0.025 to 500 µg/ml.

Table 15: Live virus neutralization assay. IC₅₀ values in ug/ml are displayed for against three different beta coronaviruses. A pooled convalescent serum from SARS-CoV-2 patients was used as a comparator and SARS-CoV-2 positive control, MN₅₀ titers are shown. N/D = IC₅₀ could not be determined

Live virus neutralization	SARS-CoV-2 Wuhan	SARS-CoV-1	MERS-CoV
Parental mAb 1	9.49	6.65	1.11
SARS-CoV-2 pooled convalescent serum	142.00	N/D	N/D

Overall, the antibody was able to neutralize the tested viruses SARS-CoV-1, SARS-CoV-2 and MERS at varying concentrations (see Table 5), with the lowest IC₅₀ concentrations for MERS-CoV, suggesting that the binding efficacy observed in the binding assays also

lead to neutralizing activity for the antibody according to the invention. The positive serum control for SARS-CoV-2 requires a high MN₅₀ titer.

Example 14: Pseudovirion neutralization

5 The objective of this study was to assess the ability of an antibody to neutralize different pseudotyped virus particles. The advantage over a live virus assay was that pseudotyped viruses can be used at a lower biosafety level laboratory and new variants of concern can be produced and tested more rapidly, allowing for broader testing across variants of concern or interest. Briefly, pseudovirions were produced by co-transfecting virus
10 expression plasmids with the pHIV-1NL43 ΔEnv-NanoLuc reporter virus plasmid in HEK293T cells. Then, dilution series of the antibody were pre-incubated with the corresponding pseudovirus and then added to HEK 293T cells expressing ACE2, the entry receptor for SARS-CoV-2, SARS-CoV-1 and NL63. For hCoV 229E, the diluted antibody mixed with virus was added to Huh7 cells which express the aminopeptidase N (APN
15 receptor which facilitates entry of hCoV 229E into host cells. After incubation, cells were washed and lysed to measure the luciferase activity in cell lysates using the Nano-Glo Luciferase Assay System and GloMax system, with a readout of relative light units (RLUs). The 50% inhibitory concentrations (IC₅₀) were determined as the antibody concentration at which infectivity was inhibited by 50% using a four Parameter Logistic
20 Regression (4PL) curve fit. The bispecific antibody was tested for neutralizing activity in the range of 0.0042 to 250 µg/ml against SARS-CoV-1, SARS-CoV-2 Wuhan, Delta, Omicron BA4, Omicron BQ.1.1, Omicron XBB.1, hCoV NL63 and hCoV 229E

Table 16: Pseudovirion neutralization assay. IC₅₀ values in ug/ml were displayed for the
25 anti-stem helix antibody against different alpha and beta coronaviruses. For multiple runs, the geometric mean with the 95% normal range is shown.

	SARS-CoV-1	SARS-CoV-2 Wuhan	SARS-CoV-2 Delta	SARS-CoV-2 BA4	SARS-CoV-2 XBB.1	SARS-CoV-2 BQ.1.1	CoV 229E	CoV NL63
Parental mAb 1	4.113 (3.980-4.250)	0.167 (0.046-0.612)	4.840 (2.067-11.334)	6.202 (5.526-6.961)	7.112 (4.312-11.730)	6.755 (4.528-10.079)	>250	>250

Overall, the antibody was able to neutralize the tested beta viruses SARS-CoV-1, SARS-CoV-2 including variants of concern at varying concentrations (see Table 16), with an overall trend of higher IC₅₀ concentrations for the Omicron variants and lowest IC₅₀ values for SARS-CoV-2 Wuhan. The antibody did not neutralize alpha coronaviruses hCoV NL63 and 229E, as expected based on the lack of binding in the ELISA and MSD assay.

Example 15: Epitope mapping

The goal of this study was to precisely determine the amino acid sequence that the antibody binds to in the Spike protein across different alpha and beta coronaviruses. The method includes mapping of linear epitopes using libraries of overlapping synthetic peptides from the spike protein. Briefly, linear epitopes of the sequence of interest were synthesized directly on a solid chip, generating a library of linear mimics, aiding identification of the correct amino acid sequence of the target antibody. The library of peptides consists of overlapping 15-amino acid fragments, with an overlap of 14 amino acids. Binding of the antibody to each of the synthesized peptide chips was tested in an enzyme-linked immunosorbent assay (ELISA) assay via incubation of the peptide arrays with antibody solutions. After washing, peptide arrays were incubated with an antibody peroxidase conjugate and substrate was added, and the reaction was then stopped using hydrogen peroxide. Colour development was measured and intensity was reported.

The antibody bound the peptide array of alpha and beta coronaviruses in a specific epitope of a 10- 20 amino acids (see Figure 7). The method allowed for a high confidence in the epitope definition, with certain variance in the outer areas of the epitope, indicated by asterisk for the respective strain.

CLAIMS

1. A method for the treatment of a coronavirus infection in an individual, the method comprising administering to an individual in need thereof an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising
5 any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a
10 light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the
15 antibody is administered to the mucosa.
2. A mucosal composition comprising an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy
20 chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119, 136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372,
25 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622.
- 30 3. An antibody for use in a method of prevention or treatment of a coronavirus infection in an individual, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 015 to 020, 026 to 031, 046 to 051, 054 to 059, 064 to 069, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 114 to 119,

136 to 141, 158 to 163, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 218 to 223, 237 to 242, 254 to 259, 280 to 285, 291 to 296, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 313 to 318, 324 to 329, 345 to 350, 367 to 372, 378 to 383, 400 to 405, a light chain CDR2 region comprising any one of SEQ ID NO: 430 to 435, 441 to 446, 452 to 457, 463 to 468, 479 to 484, 502 to 507, and a light chain CDR3 region comprising any one of SEQ ID NO: 513 to 518, 524 to 529, 545 to 550, 584 to 589, 595 to 600, 617 to 622, wherein the antibody is administered to mucosa.

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4. A method, composition or antibody according to any preceding claim, wherein the antibody comprises a heavy chain variable domain that comprises a heavy chain CDR1 region comprising SEQ ID NO: 046, a heavy chain CDR2 region comprising SEQ ID NO: 114, and a heavy chain CDR3 region comprising SEQ ID NO: 254, a light chain variable domain that comprises a light chain CDR1 region comprising SEQ ID NO: 367, a light chain CDR2 region comprising SEQ ID NO: 430, and a light chain CDR3 region comprising SEQ ID NO: 545.

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5. A method, composition or antibody according to any preceding claim, wherein the method for treatment of coronavirus virus infection is a method for prophylactic and/or therapeutic treatment of a coronavirus, preferably wherein the method for treatment is for the prophylactic treatment of a SARS-COV-2 infection.

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6. A method, composition or antibody according to any preceding claim, wherein the antibody comprises a heavy chain variable domain having the sequence of SEQ ID NO:629 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid insertions, deletions, substitutions which are not in the heavy chain CDRs.

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7. A method, composition or antibody according to any preceding claim, wherein the antibody comprises a light chain variable domain having the sequence of SEQ ID NO:630 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid insertions, deletions, substitutions which are not in the light chain CDRs.

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8. A method, composition or antibody according to any preceding claim, wherein the antibody is an IgG antibody, preferably an IgG1 antibody.
9. A method, composition or antibody according to any preceding claim, wherein the antibody is provided to the individual prophylactically.
10. A method, composition or antibody according to any preceding claim, wherein the administration route comprises at least one of oral inhalation, nasal administration, ocular administration and oropharyngeal administration.
11. A method, composition or antibody according to any preceding claim, wherein the antibody is administered at least once or at least twice monthly.
12. A method, composition or antibody according to any preceding claim, wherein the antibody is administered to the individual at a dosage of between 0.01 mg and 20 mg.
13. A composition according to any preceding claim, comprising an antibody in a single dose unit of between 0.01 mg and 20 mg, preferably between 0.1 mg and 15 mg or preferably 0.5 mg and 10 mg, wherein the antibody is as defined in any one of claims 1 to 12.
14. A composition according to any preceding claim, wherein the composition is self-administered.
15. A medicament delivery device comprising a composition according to any preceding claim.