

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 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, six other coronaviruses 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) and the alphacoronaviruses. Spillover events, where humans get infected with coronaviruses that circulate in animal reservoirs, are common. Recently, three betacoronaviruses crossed 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) present on these spike proteins.

10

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 and an S2 subunit involved in fusion of the viral and cell
15 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 human 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 the 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 fusion peptide

20 The fusion peptide is a domain located on the Spike protein of coronaviruses that is involved in membrane fusion between the viral envelope and host cell upon infection.

Some parts of the S2 subunit are called cryptic epitopes, which are hidden antigenic sites

25 because of their presence on the surface that become buried and are only accessible after conformational changes. Unlike the stem helix, which is always available for binding, antigenic sites such as the fusion peptide are considered cryptic, meaning they are hidden until receptor (ACE2) engagement. The latest Omicron variants may protect cryptic epitopes by closely packing the RBDs in the down state and possibly stabilizing the S2-

30 closed state.

Treatments and prevention

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
5 wearing. These methods are non-specific, and efficacy largely depends on compliance. 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).

10 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. Betacoronaviruses, including SARS-CoV-2, and alphacoronaviruses also infect a range of
15 species known 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.

There is therefore an urgent need to develop therapeutic mAbs that broadly target β -
20 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 coronaviruses. We have surprisingly developed a novel array of broadly protective
25 antibodies which are disclosed herein.

SUMMARY OF THE INVENTION

The inventors have discovered that an antibody having complementarity-determining regions (CDR) as disclosed herein can advantageously be used in the treatment of a
30 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

prophylactic route of administration method compared with intraperitoneal administration.

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

10 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.

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

15

Complementarity-determining regions (CDRs)

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

20 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of
25 SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 379, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of
30 SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

In a preferred embodiment, the invention provides an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ

ID NO: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 379, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 379, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401

to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

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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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068,
10 a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to
15 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, wherein the antibody is administered to mucosal epithelium.

20 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: 027, a heavy chain CDR2 region comprising SEQ ID NO: 180, and a heavy chain CDR3 region comprising SEQ ID NO: 275, a light chain variable domain that comprises a light chain
25 CDR1 region comprising SEQ ID NO: 379, a light chain CDR2 region comprising SEQ ID NO: 432, and a light chain CDR3 region comprising SEQ ID NO: 573.

In a preferred embodiment, the invention provides an antibody, or a method or composition comprising the antibody, wherein the antibody comprises a heavy chain
30 variable domain that comprises a heavy chain CDR1 region consisting of SEQ ID NO: 027, a heavy chain CDR2 region consisting of SEQ ID NO: 180, and a heavy chain CDR3 region consisting of SEQ ID NO: 275, a light chain variable domain that comprises a light chain CDR1 region consisting of SEQ ID NO: 379, a light chain CDR2 region consisting of SEQ ID NO: 432, and a light chain CDR3 region consisting of SEQ ID NO: 573.

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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, 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 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, 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 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, and wherein between 0.1 mg and 20 mg of the antibody is administered by oral inhalation.

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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, 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.

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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313.

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: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising
5 any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

Preferably, in a method for treatment of the invention, the antibody comprises a heavy
10 chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313.

15 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: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467,
20 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

In an alternative preferred embodiment, the invention provides an antibody that comprises a heavy chain variable domain that comprises a heavy chain CDR1 region
25 comprising any one of SEQ ID NO: 009 to 014, 020 to 025, 028 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 181 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 276 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1
30 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 380 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 433 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 574 to 578, 603 to 608, 614 to 619, 625 to 630.

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: 092 to 097, 114
5 to 119, 136 to 141, 169 to 174, 180 to 185, 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
10 is administered by mucosal 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 intravenous administration.
15

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
20 administration.

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.
25 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 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.

30 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain
5 CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light
10 chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

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

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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.

20 **Clauses**

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

Clause 1:

25 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141,
30 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467,

473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, wherein the antibody is administered to the mucosa.

5 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to
10 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478,
15 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630.

Clause 3:

An antibody for use in a method of prevention or treatment of a coronavirus infection in
20 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202
25 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, a light chain CDR2 region comprising any one of SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, and a light chain CDR3 region comprising any one of SEQ ID NO:
30 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630, wherein the antibody is administered to mucosa.

Clause 4:

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: 027, a heavy chain CDR2 region comprising SEQ ID NO: 180, and a heavy chain CDR3 region comprising SEQ ID NO: 275, a light chain variable domain that comprises a light chain CDR1 region comprising SEQ ID NO: 379, a light chain CDR2 region comprising SEQ ID NO: 432, and a light chain CDR3 region comprising SEQ ID NO: 573.

Clause 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.

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:631 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.

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:632 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.

Clause 8:

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

Clause 9:

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

5 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.

10 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.

Clause 12:

15 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:

20 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:

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

Clause 15:

30 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,
5 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,
10 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
15 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.

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,
20 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.

25 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
30 preferably between 0.100 mg and 10.5 mg.

The flat dose, or nominal dose, of the antibody to be delivered to a human subject is
preferably between 0.1 µg and 10 µg, preferably between 0.2 µg and 9 µg, preferably
between 0.3 µg and 8 µg, preferably between 0.4 µg and 7 µg, preferably between 0.5 µg

and 6 µg, preferably between 0.6 µg and 5 µg, preferably between 0.7 µg and 4 µg, preferably between 0.8 µg and 3 µg, preferably between 0.9 µg and 2 µg or preferably around 1 µg.

- 5 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
10 between 10 mg and 20 mg.

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
15 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 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
20 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.

25

In a preferred embodiment, the disclosure further provides a composition formulated for 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.

30

In a preferred embodiment, the disclosure further provides a composition formulated for 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 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.

5

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.

10

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, 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.

20

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 preferably between 0.100 mg and 0.5 mg.

25

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.

30

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, 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 5 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 10 SEQ ID NO: 631 and/or a light chain variable domain having the sequence of SEQ ID NO: 632.

Preferably, the heavy chain variable domain of said antibody further comprises a heavy chain framework region FR1 of SEQ ID NO: 633, a heavy chain framework region FR2 of 15 SEQ ID NO: 634, a heavy chain framework region FR3 of SEQ ID NO: 635, and/or a heavy chain framework region FR4 of SEQ ID NO: 636.

Preferably, said light chain variable domain further comprises a light chain framework region FR1 of SEQ ID NO: 637, a light chain framework region FR2 of SEQ ID NO: 638, 20 a light chain framework region FR3 of SEQ ID NO: 639, and/or a light chain framework region FR4 of SEQ ID NO: 640.

Combination compositions

In a preferred embodiment, we disclose a composition comprising a First binding fragment 25 as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, 432 to 437, 451 to 456, 462 to 30 467, 473 to 478, 484 to 489, 516 to 521, 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 027, 180, 275, 379, 432 or 573. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 641, 642, 643, 644, 645 or SEQ ID NO.: 646. 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 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, 330 to 335, 10 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630. More preferably wherein the First fragment comprises any one or more of SEQ ID NO: 027, 180, 275, 379, 432 or 573. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 647, 648, 649, 650, 651 or SEQ ID NO.: 652. 15 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.

20 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, 330 to 335, 25 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 027, 180, 275, 379, 432 or 573. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 653, 654, 655, 30 656, 657 or SEQ ID NO.: 658. 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: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068, 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196, 202 to 207, 213 to 218, 246 to 251, 275 to 280, 297 to 302, 308 to 313, 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428, 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521, 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 027, 180, 275, 379, 432 and 573. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 659, 660, 661, 662, 663 or SEQ ID NO.: 664. 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

Bispecific antibodies

In a preferred embodiment, we disclose a bispecific antibody, wherein the bispecific antibody is capable of binding to the fusion-peptide of the spike protein of a coronavirus. In a preferred embodiment, we disclose a bispecific antibody, wherein the bispecific antibody is capable of binding to the fusion peptide of the spike protein 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 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.

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: 647, 648, 649, 650, 651 to 652; alternatively wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 653, 654, 655, 656,

657 or 658; or alternatively wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 659, 660, 661, 662, 663 to 664, and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 641, 642, 643, 644, 645 to 646; or alternatively wherein the second Fab
5 comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 or 573.

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
10 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: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 641, 642, 643, 644, 645 to 646. Preferably, the fragment is selected from anyone of the group comprising a
15 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 an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix
20 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: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 647, 648, 649, 650, 651 to 652. Preferably, the fragment is selected from anyone of the group comprising a
25 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 an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix
30 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: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises

a sequence comprising any one or more of preferred SEQ ID Numbers: 653, 654, 655, 656, 657 to 658. 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, 5 tetrabodies and epitope binding fragments thereof.

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 10 SEQ ID Numbers: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 659, 660, 661, 662, 663 to 664. 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 15 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 bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in 20 preferred SEQ ID Numbers: 027, 180 or 275, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 644, 645, or 646.

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 25 preferred SEQ ID Numbers: 641, 642, or 643, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 379, 432 or 573.

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 30 preferred SEQ ID Numbers: 027, 180 or 275, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 650, 651, or 652.

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: 027, 180 or 275, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 656, 657, or 658.

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: 027, 180 or 275, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 662, 663, or 664.

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: 647, 648, or 649, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 379, 432 or 573.

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: 653, 654 or 655, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 379, 432 or 573.

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: 659, 660, or 661, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 379, 432 or 573.

25 The present invention also provides construction, expression, purification methods for a bispecific antibody having a function of binding to the fusion peptide of the Spike protein 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

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

5 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 fusion peptide 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
10 sequence comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 641, 642, 643, 644, 645 to 646.

15 Clause 27:

A bispecific antibody or an antigen binding fragment thereof according to Clause 26, comprising a first Fab capable of binding to the fusion peptide 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: 027, 180, 275, 379, 432 and/or 573 and wherein
20 the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 641, 642, 643, 644, 645 and/or 646.

25 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 fusion peptide 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: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 and a light chain variable region
30 comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and

- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 641, a Heavy Chain CDR2 region of SEQ ID NO: 642 and a Heavy Chain CDR3 region of SEQ ID NO: 643 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 644, a Light Chain CDR2 region of SEQ ID NO: 645 and a Light Chain CDR3 region of SEQ ID NO: 646.

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 fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, 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: 641, a Heavy Chain CDR2 region of SEQ ID NO: 642 and a Heavy Chain CDR3 region of SEQ ID NO: 643 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: 644, a Light Chain CDR2 region of SEQ ID NO: 645 and a Light Chain CDR3 region of SEQ ID NO: 646.

5

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 fusion peptide 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.

15

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 fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and

25

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: 641, a Heavy Chain CDR2 region of SEQ ID NO: 642 and a Heavy Chain CDR3 region of SEQ ID NO: 643 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: 644, a Light Chain CDR2 region of SEQ ID NO: 645 and a Light Chain CDR3 region of SEQ ID NO: 646.

30

Clause 33:

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

- 5 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 fusion peptide of a coronavirus, preferably SARS-CoV-2; and
- 10 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.

Clause 34:

15 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, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 631.

20

Clause 35:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 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, 25 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.

Clause 36:

30 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, 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: 632.

Clause 37:

5 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
10 sequences set forth in SEQ ID NO: 666.

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
15 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.

20 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
25 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
30 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, 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. 027, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 027,
- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 180, 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. 180,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 275, or a third nucleic acid sequence encoding the amino acid sequence having at most 1, 2 or 3 amino acids different from SEQ ID NO. 275,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 379, 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. 379,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 432, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 432,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 573, 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. 573,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 641, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 641,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 642, or an eighth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 642,

- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 643, 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. 643,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 644, 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. 644,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 645, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 645, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 646, 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. 646.

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.

Clause 43:

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

Clause 44:

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

Clause 45:

- 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.

Clause 47:

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

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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 excipient or carrier.

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Clause 49:

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

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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 26 to 38, wherein the bispecific antibody or an antigen binding fragment thereof is bivalent.

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Clause 52:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 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.

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Clauses

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

5 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 fusion peptide of a coronavirus, preferably SARS-CoV-2 and a second Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence
10 comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 647, 648, 649, 650, 651 to 652.

Clause 54:

15 A bispecific antibody or an antigen binding fragment thereof according to Clause 53, comprising a first Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, and a second Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 and/or 573 and wherein
20 the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 647, 648, 649, 650, 651 and/or 652.

Clause 55:

A bispecific antibody or an antigen binding fragment thereof according to Clauses 53 or
25 54, comprising a first Fab specifically binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, and a second Fab specifically binding to the stem helix 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: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180
30 and a Heavy Chain CDR3 region of SEQ ID NO: 275 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and

- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a Heavy Chain CDR3 region of SEQ ID NO: 649 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.

Clause 56:

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 or an antigen binding fragment thereof, capable of binding to the fusion peptide 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 to the stem helix 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 fusion peptide of a coronavirus, preferably SARS-CoV-2, are replaced by each other.

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 fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and

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: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a Heavy Chain CDR3 region of SEQ ID NO: 649 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: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.

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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 fusion peptide 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 stem helix 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.

15

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 fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and

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wherein the VH domain of the antibody 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: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a Heavy Chain CDR3 region of SEQ ID NO: 649 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: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.

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Clause 60:

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 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; 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 stem helix of a coronavirus,
10 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.

Clause 61:

- 15 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, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid
20 sequences set forth in SEQ ID NO: 631.

Clause 62:

- A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 53 to 60, wherein the second Fab comprises a heavy chain variable region having an amino
25 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: 667.

Clause 63:

- 30 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,

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: 632.

5 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: 668.

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.

20

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.

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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

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antigen binding fragment thereof according to any of Claims 53 to 65, preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.

Claim 68:

- 5 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 Claims 53 to 65 and Claim 67, wherein the nucleic acid sequence comprises at least any one of:
- 10 (i) a first nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 027, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 027,
- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 180, or a second nucleic acid sequence encoding the amino acid sequence having
- 15 at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 180,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 275, or a third nucleic acid sequence encoding the amino acid sequence having at most 1, 2 or 3 amino acids different from SEQ ID NO. 275,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ
- 20 ID NO. 379, 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. 379,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 432, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 432,
- 25 (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 573, 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. 573,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 647, or a seventh nucleic acid sequence encoding the amino acid sequence having
- 30 at most 1 or 2 amino acids different from SEQ ID NO. 647,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 648, or an eighth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 648,

- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 649, 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. 649,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 650, 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. 650,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 651, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 651, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 652, 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. 652.

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.

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:

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

Clause 72:

- 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.

Clause 74:

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

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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 excipient or carrier.

10

Clause 76:

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

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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 53 to 65, wherein the bispecific antibody or an antigen binding fragment thereof is bivalent.

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Clause 79:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 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.

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DESCRIPTION OF THE DRAWINGS

Figure 1. Survival after lethal challenge - Antibody according to the invention.

5 Kaplan-Meier survival curves of the intraperitoneal prophylactic treatment group. Animals (n=10 per group), treated with a dose titration with the antibody having heavy chain CDR1 as SEQ ID NO: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, at day -1. At day 0, animals
10 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 – Antibody according to the invention.

15 Kaplan-Meier survival curves of the intranasal prophylactic treatment group. Animals (n=10 per group, except 10 mg/kg where n=9), treated with a dose titration with the antibody having heavy chain CDR1 as SEQ ID NO: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, at
20 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 - Antibody according to the invention.

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 antibody having heavy chain CDR1 as SEQ ID NO: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, at day -1
30 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 - Antibody according to the invention.

Bodyweight change (%) relative to day 0, for the intranasal prophylactic treatment group. Animals (n=10 per group, except 10 mg/kg where n=9) were treated with a dose titration of the antibody having heavy chain CDR1 as SEQ ID NO: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, 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: Linear epitope mapping against Spike fusion peptide 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. Epitope footprints (A) and paratope hotspots (B) for the antibody against the FP domain of SARS-CoV-2. The CRDs of the heavy and light chains are indicated.

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.

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'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.

15 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.

20

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 (yet) infected with coronavirus.

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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 infection involves the entry of the body by the virus, 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 disease, but may also be latent, in other words may reside in the body without causing symptoms or disease.

5 **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 fusion-peptide of a coronavirus, in particular SARS-CoV-2.

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

15 Preferably, the antibody as disclosed herein is capable of neutralizing a coronavirus, in 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
20 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
25 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 phrase "is capable of" as used here, encompasses but not limited to the phrase "specifically binding" or "specifically bind to".

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Coronavirus infection

The term '**coronavirus infection**', as used herein, includes reference to the pathological 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
5 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
10 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

15 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

20 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
25 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 respiratory disease such as asthma, COPD, chronic bronchitis and lung emphysema, (ii)
30 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.

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).

- 5 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
10 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

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
20 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
25 infection, and an elevated risk of dying from coronavirus infection.

Antibody

The term '**antibody**', as used herein, includes reference to an intact immunoglobulin, including monoclonal antibodies, such as chimeric, humanized or human monoclonal
30 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 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 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 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), 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 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 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 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 particular the fusion peptide of the spike protein. The antibody as disclosed herein binds to a conserved epitope in the fusion peptide 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.

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.

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, 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 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, 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.

5

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 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.

15

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

Framework regions

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 (or region) which may also be referred to as an antigen-binding region or domain.

25

Antibodies may be neutralizing, which includes reference to inhibition of a virus as 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 neutralization. Preferably, the antibody is cross-neutralizing, which includes reference to

30

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.

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

10 The phrase “antigen-binding fragments”, “antigen binding fragments”, “antigen fragment”, “a fragment of an antibody” or “antigen-binding molecule” as used herein, 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
15 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.

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

IgG antibody

25 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.

30 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
5 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.

10

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
15 antibodies are of type λ or κ .

Preferably, the antibody is an IgM antibody.

Anti-Coronavirus antibody

20 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.

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

A composition

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
30 the sole active ingredient.

In a preferred embodiment, the active ingredients comprise an antibody disclosed herein, 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.

- 5 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
10 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 around 5.5. Preferably the pH is around 7.4.

15 **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 mucosal flushing or removal action.

- 20 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 and/or therapeutic treatment as disclosed herein.

25 **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 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
30 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 abrasive particles and bodily fluids, as well as invasive pathogens.

Preferably, the antibodies of the invention are administered mucosally.

Intranasally

5 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
10 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 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)
15 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.

Preferably, the antibodies of the invention are administered intranasally.

20 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 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
25 present case, with antibodies as disclosed herein, nasal administration is preferably a form of topical administration.

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
30 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.

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 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.

10

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).

15

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.

20

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.

25

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.

30

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
5 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.

10

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.

15 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.
25 In a preferred embodiment, the antibody is administered 7 days or more prior to coronavirus exposure.

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
30

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).

5

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.

15

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

25

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.

30

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.

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.

10

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

15 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 fragments of the coronavirus.

20

An antibody as disclosed herein comprises a preferred heavy chain CDR1 sequence comprising any one of the following SEQ ID NO: 009 to 014, 020 to 025, 027 to 032, 041 to 046, 053 to 058, 063 to 068. A CDR comprising the amino acid sequence SEQ ID NO: 027 is especially preferred.

25

An antibody as disclosed herein comprises a preferred heavy chain CDR2 sequence comprising any one of the following SEQ ID NO: 092 to 097, 114 to 119, 136 to 141, 169 to 174, 180 to 185, 191 to 196. A CDR comprising the amino acid sequence SEQ ID NO: 180 is especially preferred.

30

An antibody as disclosed herein comprises a preferred heavy chain CDR3 sequence comprising any one of the following SEQ ID NO: 202 to 207, 213 to 218, 246 to 251, 275

to 280, 297 to 302, 308 to 313. A CDR comprising the amino acid sequence SEQ ID NO: 275 is especially preferred.

5 An antibody as disclosed herein comprises a preferred light chain CDR1 sequence comprising any one of the following SEQ ID NO: 330 to 335, 358 to 363, 379 to 384, 401 to 406, 412 to 417, 423 to 428. A CDR comprising the amino acid sequence SEQ ID NO: 379 is especially preferred.

10 An antibody as disclosed herein comprises a preferred light chain CDR2 sequence comprising any one of the following SEQ ID NO: 432 to 437, 451 to 456, 462 to 467, 473 to 478, 484 to 489, 516 to 521. A CDR comprising the amino acid sequence SEQ ID NO: 432 is especially preferred.

15 An antibody as disclosed herein comprises a preferred light chain CDR3 sequence comprising any one of the following SEQ ID NO: 538 to 543, 549 to 554, 573 to 578, 603 to 608, 614 to 619, 625 to 630. A CDR comprising the amino acid sequence SEQ ID NO: 573 is especially preferred.

20 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: 633.

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: 634.

25 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: 635.

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: 636.

30

In a preferred embodiment, the heavy chain variable domain of said antibody comprises - a heavy chain framework region FR1 of SEQ ID NO: 633, a heavy chain framework region FR2 of SEQ ID NO: 634, a heavy chain framework region FR3 of SEQ ID NO: 635, and/or

a heavy chain framework region FR4 of SEQ ID NO: 636, preferably all said heavy chain heavy chain framework regions FR1 to FR4.

5 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: 637.

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: 638.

10 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: 639.

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: 640.

15

In a preferred embodiment, the light chain variable domain of said antibody comprises - a heavy chain framework region FR1 of SEQ ID NO: 637, a light chain framework region FR2 of SEQ ID NO: 638, a light chain framework region FR3 of SEQ ID NO: 639, and/or a light chain framework region FR4 of SEQ ID NO: 640, preferably all said light chain
20 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: 631 and/or a light chain variable domain having the sequence of SEQ ID NO: 632.

25

In treatment methods of the invention, the heavy chain variable domain (VH) of the antibody is preferably indicated as SEQ ID NO:631. In treatment methods or compositions of the invention, the light chain variable domain (VL) of the antibody is preferably indicated as SEQ ID NO:632. In treatment methods or compositions of the invention, the
30 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 having the sequence of SEQ ID NO:631 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.

5

Preferably, an antibody as disclosed herein comprises a light chain variable domain having the sequence of SEQ ID NO:632 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.

10

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	AMHW
	SEQ ID NO.: 002	AMHWV
	SEQ ID NO.: 003	AMHWVR
10	SEQ ID NO.: 004	AMHWVRQ
	SEQ ID NO.: 005	AMHWVRQA
	SEQ ID NO.: 006	FSGY
	SEQ ID NO.: 007	FSGYA
	SEQ ID NO.: 008	FSGYAM
15	SEQ ID NO.: 009	FSGYAMH
	SEQ ID NO.: 010	FSGYAMHW
	SEQ ID NO.: 011	FSGYAMHWV
	SEQ ID NO.: 012	FSGYAMHWVR
	SEQ ID NO.: 013	FSGYAMHWVRQ
20	SEQ ID NO.: 014	FSGYAMHWVRQA
	SEQ ID NO.: 015	GLTFS
	SEQ ID NO.: 016	GLTFSG
	SEQ ID NO.: 017	GLTFSGY
	SEQ ID NO.: 018	GLTFSGYA
25	SEQ ID NO.: 019	GLTFSGYAM
	SEQ ID NO.: 020	GLTFSGYAMH
	SEQ ID NO.: 021	GLTFSGYAMHW
	SEQ ID NO.: 022	GLTFSGYAMHWV
	SEQ ID NO.: 023	GLTFSGYAMHWVR
30	SEQ ID NO.: 024	GLTFSGYAMHWVRQ
	SEQ ID NO.: 025	GLTFSGYAMHWVRQA

	SEQ ID NO.: 026	GYAM
	SEQ ID NO.: 027	GYAMH
	SEQ ID NO.: 028	GYAMHW
	SEQ ID NO.: 029	GYAMHWV
5	SEQ ID NO.: 030	GYAMHWVR
	SEQ ID NO.: 031	GYAMHWVRQ
	SEQ ID NO.: 032	GYAMHWVRQA
	SEQ ID NO.: 033	HWVR
	SEQ ID NO.: 034	HWVRQ
10	SEQ ID NO.: 035	HWVRQA
	SEQ ID NO.: 036	LTFS
	SEQ ID NO.: 037	LTFSG
	SEQ ID NO.: 038	LTFSGY
	SEQ ID NO.: 039	LTFSGYA
15	SEQ ID NO.: 040	LTFSGYAM
	SEQ ID NO.: 041	LTFSGYAMH
	SEQ ID NO.: 042	LTFSGYAMHW
	SEQ ID NO.: 043	LTFSGYAMHWV
	SEQ ID NO.: 044	LTFSGYAMHWVR
20	SEQ ID NO.: 045	LTFSGYAMHWVRQ
	SEQ ID NO.: 046	LTFSGYAMHWVRQA
	SEQ ID NO.: 047	MHWV
	SEQ ID NO.: 048	MHWVR
	SEQ ID NO.: 049	MHWVRQ
25	SEQ ID NO.: 050	MHWVRQA
	SEQ ID NO.: 051	SGYA
	SEQ ID NO.: 052	SGYAM
	SEQ ID NO.: 053	SGYAMH
	SEQ ID NO.: 054	SGYAMHW
30	SEQ ID NO.: 055	SGYAMHWV

	SEQ ID NO.: 056	SGYAMHWVR
	SEQ ID NO.: 057	SGYAMHWVRQ
	SEQ ID NO.: 058	SGYAMHWVRQA
	SEQ ID NO.: 059	TFSG
5	SEQ ID NO.: 060	TFSGY
	SEQ ID NO.: 061	TFSGYA
	SEQ ID NO.: 062	TFSGYAM
	SEQ ID NO.: 063	TFSGYAMH
	SEQ ID NO.: 064	TFSGYAMHW
10	SEQ ID NO.: 065	TFSGYAMHWV
	SEQ ID NO.: 066	TFSGYAMHWVR
	SEQ ID NO.: 067	TFSGYAMHWVRQ
	SEQ ID NO.: 068	TFSGYAMHWVRQA
	SEQ ID NO.: 069	WVRQ
15	SEQ ID NO.: 070	WVRQA
	SEQ ID NO.: 071	YAMH
	SEQ ID NO.: 072	YAMHW
	SEQ ID NO.: 073	YAMHWV
	SEQ ID NO.: 074	YAMHWVR
20	SEQ ID NO.: 075	YAMHWVRQ
	SEQ ID NO.: 076	YAMHWVRQA

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

25	SEQ ID NO.: 077	ARNKYYAD
	SEQ ID NO.: 078	ARNKYYADS
	SEQ ID NO.: 079	ARNKYYADSV
	SEQ ID NO.: 080	ARNKYYADSVK
	SEQ ID NO.: 081	ARNKYYADSVKG
30	SEQ ID NO.: 082	ARNKYYADSVKGR
	SEQ ID NO.: 083	ARNKYYADSVKGRF

	SEQ ID NO.: 084	ARNKYYADSVKGRFT
	SEQ ID NO.: 085	ARNKYYADSVKGRFTI
	SEQ ID NO.: 086	ARNKYYADSVKGRFTIS
	SEQ ID NO.: 087	AVISRDARNKYYA
5	SEQ ID NO.: 088	AVISRDARNKYYAD
	SEQ ID NO.: 089	AVISRDARNKYYADS
	SEQ ID NO.: 090	AVISRDARNKYYADSV
	SEQ ID NO.: 091	AVISRDARNKYYADSVK
	SEQ ID NO.: 092	AVISRDARNKYYADSVKG
10	SEQ ID NO.: 093	AVISRDARNKYYADSVKGR
	SEQ ID NO.: 094	AVISRDARNKYYADSVKGRF
	SEQ ID NO.: 095	AVISRDARNKYYADSVKGRFT
	SEQ ID NO.: 096	AVISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 097	AVISRDARNKYYADSVKGRFTIS
15	SEQ ID NO.: 098	DARNKYYA
	SEQ ID NO.: 099	DARNKYYAD
	SEQ ID NO.: 100	DARNKYYADS
	SEQ ID NO.: 101	DARNKYYADSV
	SEQ ID NO.: 102	DARNKYYADSVK
20	SEQ ID NO.: 103	DARNKYYADSVKG
	SEQ ID NO.: 104	DARNKYYADSVKGR
	SEQ ID NO.: 105	DARNKYYADSVKGRF
	SEQ ID NO.: 106	DARNKYYADSVKGRFT
	SEQ ID NO.: 107	DARNKYYADSVKGRFTI
25	SEQ ID NO.: 108	DARNKYYADSVKGRFTIS
	SEQ ID NO.: 109	EWVAVISRDARNKYYA
	SEQ ID NO.: 110	EWVAVISRDARNKYYAD
	SEQ ID NO.: 111	EWVAVISRDARNKYYADS
	SEQ ID NO.: 112	EWVAVISRDARNKYYADSV
30	SEQ ID NO.: 113	EWVAVISRDARNKYYADSVK

	SEQ ID NO.: 114	EWVAVISRDARNKYYADSVKG
	SEQ ID NO.: 115	EWVAVISRDARNKYYADSVKGR
	SEQ ID NO.: 116	EWVAVISRDARNKYYADSVKGRF
	SEQ ID NO.: 117	EWVAVISRDARNKYYADSVKGRFT
5	SEQ ID NO.: 118	EWVAVISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 119	EWVAVISRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 120	ISRDARNKYYA
	SEQ ID NO.: 121	ISRDARNKYYAD
	SEQ ID NO.: 122	ISRDARNKYYADS
10	SEQ ID NO.: 123	ISRDARNKYYADSV
	SEQ ID NO.: 124	ISRDARNKYYADSVK
	SEQ ID NO.: 125	ISRDARNKYYADSVKG
	SEQ ID NO.: 126	ISRDARNKYYADSVKGR
	SEQ ID NO.: 127	ISRDARNKYYADSVKGRF
15	SEQ ID NO.: 128	ISRDARNKYYADSVKGRFT
	SEQ ID NO.: 129	ISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 130	ISRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 131	LEWVAVISRDARNKYYA
	SEQ ID NO.: 132	LEWVAVISRDARNKYYAD
20	SEQ ID NO.: 133	LEWVAVISRDARNKYYADS
	SEQ ID NO.: 134	LEWVAVISRDARNKYYADSV
	SEQ ID NO.: 135	LEWVAVISRDARNKYYADSVK
	SEQ ID NO.: 136	LEWVAVISRDARNKYYADSVKG
	SEQ ID NO.: 137	LEWVAVISRDARNKYYADSVKGR
25	SEQ ID NO.: 138	LEWVAVISRDARNKYYADSVKGRF
	SEQ ID NO.: 139	LEWVAVISRDARNKYYADSVKGRFT
	SEQ ID NO.: 140	LEWVAVISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 141	LEWVAVISRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 142	RDARNKYYA
30	SEQ ID NO.: 143	RDARNKYYAD

	SEQ ID NO.: 144	RDARNKYYADS
	SEQ ID NO.: 145	RDARNKYYADSV
	SEQ ID NO.: 146	RDARNKYYADSVK
	SEQ ID NO.: 147	RDARNKYYADSVKG
5	SEQ ID NO.: 148	RDARNKYYADSVKGR
	SEQ ID NO.: 149	RDARNKYYADSVKGRF
	SEQ ID NO.: 150	RDARNKYYADSVKGRFT
	SEQ ID NO.: 151	RDARNKYYADSVKGRFTI
	SEQ ID NO.: 152	RDARNKYYADSVKGRFTIS
10	SEQ ID NO.: 153	SRDARNKYYA
	SEQ ID NO.: 154	SRDARNKYYAD
	SEQ ID NO.: 155	SRDARNKYYADS
	SEQ ID NO.: 156	SRDARNKYYADSV
	SEQ ID NO.: 157	SRDARNKYYADSVK
15	SEQ ID NO.: 158	SRDARNKYYADSVKG
	SEQ ID NO.: 159	SRDARNKYYADSVKGR
	SEQ ID NO.: 160	SRDARNKYYADSVKGRF
	SEQ ID NO.: 161	SRDARNKYYADSVKGRFT
	SEQ ID NO.: 162	SRDARNKYYADSVKGRFTI
20	SEQ ID NO.: 163	SRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 164	VAVISRDARNKYYA
	SEQ ID NO.: 165	VAVISRDARNKYYAD
	SEQ ID NO.: 166	VAVISRDARNKYYADS
	SEQ ID NO.: 167	VAVISRDARNKYYADSV
25	SEQ ID NO.: 168	VAVISRDARNKYYADSVK
	SEQ ID NO.: 169	VAVISRDARNKYYADSVKG
	SEQ ID NO.: 170	VAVISRDARNKYYADSVKGR
	SEQ ID NO.: 171	VAVISRDARNKYYADSVKGRF
	SEQ ID NO.: 172	VAVISRDARNKYYADSVKGRFT
30	SEQ ID NO.: 173	VAVISRDARNKYYADSVKGRFTI

	SEQ ID NO.: 174	VAVISRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 175	VISRDARNKYYA
	SEQ ID NO.: 176	VISRDARNKYYAD
	SEQ ID NO.: 177	VISRDARNKYYADS
5	SEQ ID NO.: 178	VISRDARNKYYADSV
	SEQ ID NO.: 179	VISRDARNKYYADSVK
	SEQ ID NO.: 180	VISRDARNKYYADSVKG
	SEQ ID NO.: 181	VISRDARNKYYADSVKGR
	SEQ ID NO.: 182	VISRDARNKYYADSVKGRF
10	SEQ ID NO.: 183	VISRDARNKYYADSVKGRFT
	SEQ ID NO.: 184	VISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 185	VISRDARNKYYADSVKGRFTIS
	SEQ ID NO.: 186	WVAVISRDARNKYYA
	SEQ ID NO.: 187	WVAVISRDARNKYYAD
15	SEQ ID NO.: 188	WVAVISRDARNKYYADS
	SEQ ID NO.: 189	WVAVISRDARNKYYADSV
	SEQ ID NO.: 190	WVAVISRDARNKYYADSVK
	SEQ ID NO.: 191	WVAVISRDARNKYYADSVKG
	SEQ ID NO.: 192	WVAVISRDARNKYYADSVKGR
20	SEQ ID NO.: 193	WVAVISRDARNKYYADSVKGRF
	SEQ ID NO.: 194	WVAVISRDARNKYYADSVKGRFT
	SEQ ID NO.: 195	WVAVISRDARNKYYADSVKGRFTI
	SEQ ID NO.: 196	WVAVISRDARNKYYADSVKGRFTIS

25 **Heavy chain CDR3 region (SEQ ID NO:197 to SEQ ID NO:313)**

	SEQ ID NO.: 197	AILIIPGITEPGSP
	SEQ ID NO.: 198	AILIIPGITEPGSPD
	SEQ ID NO.: 199	AILIIPGITEPGSPDA
30	SEQ ID NO.: 200	AILIIPGITEPGSPDAL
	SEQ ID NO.: 201	AILIIPGITEPGSPDALD

	SEQ ID NO.: 202	AILIIPGITEPGSPDALDI
	SEQ ID NO.: 203	AILIIPGITEPGSPDALDIW
	SEQ ID NO.: 204	AILIIPGITEPGSPDALDIWG
	SEQ ID NO.: 205	AILIIPGITEPGSPDALDIWGQ
5	SEQ ID NO.: 206	AILIIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 207	AILIIPGITEPGSPDALDIWGQGT
	SEQ ID NO.: 208	CAILIIPGITEPGSP
	SEQ ID NO.: 209	CAILIIPGITEPGSPD
	SEQ ID NO.: 210	CAILIIPGITEPGSPDA
10	SEQ ID NO.: 211	CAILIIPGITEPGSPDAL
	SEQ ID NO.: 212	CAILIIPGITEPGSPDALD
	SEQ ID NO.: 213	CAILIIPGITEPGSPDALDI
	SEQ ID NO.: 214	CAILIIPGITEPGSPDALDIW
	SEQ ID NO.: 215	CAILIIPGITEPGSPDALDIWG
15	SEQ ID NO.: 216	CAILIIPGITEPGSPDALDIWGQ
	SEQ ID NO.: 217	CAILIIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 218	CAILIIPGITEPGSPDALDIWGQGT
	SEQ ID NO.: 219	GITEPGSP
	SEQ ID NO.: 220	GITEPGSPD
20	SEQ ID NO.: 221	GITEPGSPDA
	SEQ ID NO.: 222	GITEPGSPDAL
	SEQ ID NO.: 223	GITEPGSPDALD
	SEQ ID NO.: 224	GITEPGSPDALDI
	SEQ ID NO.: 225	GITEPGSPDALDIW
25	SEQ ID NO.: 226	GITEPGSPDALDIWG
	SEQ ID NO.: 227	GITEPGSPDALDIWGQ
	SEQ ID NO.: 228	GITEPGSPDALDIWGQG
	SEQ ID NO.: 229	GITEPGSPDALDIWGQGT
	SEQ ID NO.: 230	IIPGITEPGSP
30	SEQ ID NO.: 231	IIPGITEPGSPD

	SEQ ID NO.: 232	IIPGITEPGSPDA
	SEQ ID NO.: 233	IIPGITEPGSPDAL
	SEQ ID NO.: 234	IIPGITEPGSPDALD
	SEQ ID NO.: 235	IIPGITEPGSPDALDI
5	SEQ ID NO.: 236	IIPGITEPGSPDALDIW
	SEQ ID NO.: 237	IIPGITEPGSPDALDIWG
	SEQ ID NO.: 238	IIPGITEPGSPDALDIWGQ
	SEQ ID NO.: 239	IIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 240	IIPGITEPGSPDALDIWGQGT
10	SEQ ID NO.: 241	ILIIPGITEPGSP
	SEQ ID NO.: 242	ILIIPGITEPGSPD
	SEQ ID NO.: 243	ILIIPGITEPGSPDA
	SEQ ID NO.: 244	ILIIPGITEPGSPDAL
	SEQ ID NO.: 245	ILIIPGITEPGSPDALD
15	SEQ ID NO.: 246	ILIIPGITEPGSPDALDI
	SEQ ID NO.: 247	ILIIPGITEPGSPDALDIW
	SEQ ID NO.: 248	ILIIPGITEPGSPDALDIWG
	SEQ ID NO.: 249	ILIIPGITEPGSPDALDIWGQ
	SEQ ID NO.: 250	ILIIPGITEPGSPDALDIWGQG
20	SEQ ID NO.: 251	ILIIPGITEPGSPDALDIWGQGT
	SEQ ID NO.: 252	IPGITEPGSPD
	SEQ ID NO.: 253	IPGITEPGSPDA
	SEQ ID NO.: 254	IPGITEPGSPDALD
	SEQ ID NO.: 255	IPGITEPGSPDALDI
25	SEQ ID NO.: 256	IPGITEPGSPDALDIW
	SEQ ID NO.: 257	IPGITEPGSPDALDIWG
	SEQ ID NO.: 258	IPGITEPGSPDALDIWGQ
	SEQ ID NO.: 259	IPGITEPGSPDALDIWGQG
	SEQ ID NO.: 260	IPGITEPGSPDALDIWGQGT
30	SEQ ID NO.: 261	ITEPGSPD

	SEQ ID NO.: 262	ITEPGSPDA
	SEQ ID NO.: 263	ITEPGSPDALD
	SEQ ID NO.: 264	ITEPGSPDALDI
	SEQ ID NO.: 265	ITEPGSPDALDIW
5	SEQ ID NO.: 266	ITEPGSPDALDIWG
	SEQ ID NO.: 267	ITEPGSPDALDIWGQ
	SEQ ID NO.: 268	ITEPGSPDALDIWGQG
	SEQ ID NO.: 269	ITEPGSPDALDIWGQGT
	SEQ ID NO.: 270	LIIPGITEPGSP
10	SEQ ID NO.: 271	LIIPGITEPGSPD
	SEQ ID NO.: 272	LIIPGITEPGSPDA
	SEQ ID NO.: 273	LIIPGITEPGSPDAL
	SEQ ID NO.: 274	LIIPGITEPGSPDALD
	SEQ ID NO.: 275	LIIPGITEPGSPDALDI
15	SEQ ID NO.: 276	LIIPGITEPGSPDALDIW
	SEQ ID NO.: 277	LIIPGITEPGSPDALDIWG
	SEQ ID NO.: 278	LIIPGITEPGSPDALDIWGQ
	SEQ ID NO.: 279	LIIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 280	LIIPGITEPGSPDALDIWGQGT
20	SEQ ID NO.: 281	PGITEPGSP
	SEQ ID NO.: 282	PGITEPGSPD
	SEQ ID NO.: 283	PGITEPGSPDA
	SEQ ID NO.: 284	PGITEPGSPDAL
	SEQ ID NO.: 285	PGITEPGSPDALD
25	SEQ ID NO.: 286	PGITEPGSPDALDI
	SEQ ID NO.: 287	PGITEPGSPDALDIW
	SEQ ID NO.: 288	PGITEPGSPDALDIWG
	SEQ ID NO.: 289	PGITEPGSPDALDIWGQ
	SEQ ID NO.: 290	PGITEPGSPDALDIWGQG
30	SEQ ID NO.: 291	PGITEPGSPDALDIWGQGT

	SEQ ID NO.: 292	YCAILHIPGITEPGSP
	SEQ ID NO.: 293	YCAILHIPGITEPGSPD
	SEQ ID NO.: 294	YCAILHIPGITEPGSPDA
	SEQ ID NO.: 295	YCAILHIPGITEPGSPDAL
5	SEQ ID NO.: 296	YCAILHIPGITEPGSPDALD
	SEQ ID NO.: 297	YCAILHIPGITEPGSPDALDI
	SEQ ID NO.: 298	YCAILHIPGITEPGSPDALDIW
	SEQ ID NO.: 299	YCAILHIPGITEPGSPDALDIWG
	SEQ ID NO.: 300	YCAILHIPGITEPGSPDALDIWGQ
10	SEQ ID NO.: 301	YCAILHIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 302	YCAILHIPGITEPGSPDALDIWGQGT
	SEQ ID NO.: 303	YYCAILHIPGITEPGSP
	SEQ ID NO.: 304	YYCAILHIPGITEPGSPD
	SEQ ID NO.: 305	YYCAILHIPGITEPGSPDA
15	SEQ ID NO.: 306	YYCAILHIPGITEPGSPDAL
	SEQ ID NO.: 307	YYCAILHIPGITEPGSPDALD
	SEQ ID NO.: 308	YYCAILHIPGITEPGSPDALDI
	SEQ ID NO.: 309	YYCAILHIPGITEPGSPDALDIW
	SEQ ID NO.: 310	YYCAILHIPGITEPGSPDALDIWG
20	SEQ ID NO.: 311	YYCAILHIPGITEPGSPDALDIWGQ
	SEQ ID NO.: 312	YYCAILHIPGITEPGSPDALDIWGQG
	SEQ ID NO.: 313	YYCAILHIPGITEPGSPDALDIWGQGT

Light chain CDR1 region (SEQ ID NO:314 to SEQ ID NO:428)

25

	SEQ ID NO.: 314	ASQDI
	SEQ ID NO.: 315	ASQDIS
	SEQ ID NO.: 316	ASQDISK
	SEQ ID NO.: 317	ASQDISKW
30	SEQ ID NO.: 318	ASQDISKWL
	SEQ ID NO.: 319	ASQDISKWLA

	SEQ ID NO.: 320	ASQDISKWLA
	SEQ ID NO.: 321	ASQDISKWLA
	SEQ ID NO.: 322	ASQDISKWLA
	SEQ ID NO.: 323	ASQDISKWLA
5	SEQ ID NO.: 324	ASQDISKWLA
	SEQ ID NO.: 325	CRASQDI
	SEQ ID NO.: 326	CRASQDIS
	SEQ ID NO.: 327	CRASQDISK
	SEQ ID NO.: 328	CRASQDISKW
10	SEQ ID NO.: 329	CRASQDISKW
	SEQ ID NO.: 330	CRASQDISKLA
	SEQ ID NO.: 331	CRASQDISKWLA
	SEQ ID NO.: 332	CRASQDISKWLA
	SEQ ID NO.: 333	CRASQDISKWLA
15	SEQ ID NO.: 334	CRASQDISKWLA
	SEQ ID NO.: 335	CRASQDISKWLA
	SEQ ID NO.: 336	DISK
	SEQ ID NO.: 337	DISKW
	SEQ ID NO.: 338	DISKW
20	SEQ ID NO.: 339	DISKWLA
	SEQ ID NO.: 340	DISKWLA
	SEQ ID NO.: 341	DISKWLA
	SEQ ID NO.: 342	DISKWLA
	SEQ ID NO.: 343	DISKWLA
25	SEQ ID NO.: 344	DISKWLA
	SEQ ID NO.: 345	ISKW
	SEQ ID NO.: 346	ISKW
	SEQ ID NO.: 347	ISKWLA
	SEQ ID NO.: 348	ISKWLA
30	SEQ ID NO.: 349	ISKWLA

	SEQ ID NO.: 350	ISKWLAWYQ
	SEQ ID NO.: 351	ISKWLAWYQQ
	SEQ ID NO.: 352	ISKWLAWYQQR
	SEQ ID NO.: 353	ITCRASQDI
5	SEQ ID NO.: 354	ITCRASQDIS
	SEQ ID NO.: 355	ITCRASQDISK
	SEQ ID NO.: 356	ITCRASQDISKW
	SEQ ID NO.: 357	ITCRASQDISKWL
	SEQ ID NO.: 358	ITCRASQDISKWLA
10	SEQ ID NO.: 359	ITCRASQDISKWLA
	SEQ ID NO.: 360	ITCRASQDISKWLA
	SEQ ID NO.: 361	ITCRASQDISKWLA
	SEQ ID NO.: 362	ITCRASQDISKWLA
	SEQ ID NO.: 363	ITCRASQDISKWLA
15	SEQ ID NO.: 364	QDIS
	SEQ ID NO.: 365	QDISK
	SEQ ID NO.: 366	QDISKW
	SEQ ID NO.: 367	QDISKWL
	SEQ ID NO.: 368	QDISKWLA
20	SEQ ID NO.: 369	QDISKWLA
	SEQ ID NO.: 370	QDISKWLA
	SEQ ID NO.: 371	QDISKWLA
	SEQ ID NO.: 372	QDISKWLA
	SEQ ID NO.: 373	QDISKWLA
25	SEQ ID NO.: 374	RASQDI
	SEQ ID NO.: 375	RASQDIS
	SEQ ID NO.: 376	RASQDISK
	SEQ ID NO.: 377	RASQDISKW
	SEQ ID NO.: 378	RASQDISKWL
30	SEQ ID NO.: 379	RASQDISKWLA

	SEQ ID NO.: 380	RASQDISKWLaw
	SEQ ID NO.: 381	RASQDISKWLawY
	SEQ ID NO.: 382	RASQDISKWLawYQ
	SEQ ID NO.: 383	RASQDISKWLawYQQ
5	SEQ ID NO.: 384	RASQDISKWLawYQQR
	SEQ ID NO.: 385	SQDI
	SEQ ID NO.: 386	SQDIS
	SEQ ID NO.: 387	SQDISK
	SEQ ID NO.: 388	SQDISKW
10	SEQ ID NO.: 389	SQDISKWL
	SEQ ID NO.: 390	SQDISKWLA
	SEQ ID NO.: 391	SQDISKWLaw
	SEQ ID NO.: 392	SQDISKWLawY
	SEQ ID NO.: 393	SQDISKWLawYQ
15	SEQ ID NO.: 394	SQDISKWLawYQQ
	SEQ ID NO.: 395	SQDISKWLawYQQR
	SEQ ID NO.: 396	TCRASQDI
	SEQ ID NO.: 397	TCRASQDIS
	SEQ ID NO.: 398	TCRASQDISK
20	SEQ ID NO.: 399	TCRASQDISKW
	SEQ ID NO.: 400	TCRASQDISKWL
	SEQ ID NO.: 401	TCRASQDISKWLA
	SEQ ID NO.: 402	TCRASQDISKWLaw
	SEQ ID NO.: 403	TCRASQDISKWLawY
25	SEQ ID NO.: 404	TCRASQDISKWLawYQ
	SEQ ID NO.: 405	TCRASQDISKWLawYQQ
	SEQ ID NO.: 406	TCRASQDISKWLawYQQR
	SEQ ID NO.: 407	TITCRASQDI
	SEQ ID NO.: 408	TITCRASQDIS
30	SEQ ID NO.: 409	TITCRASQDISK

SEQ ID NO.: 410 TITCRASQDISKW
SEQ ID NO.: 411 TITCRASQDISKWL
SEQ ID NO.: 412 TITCRASQDISKWLA
SEQ ID NO.: 413 TITCRASQDISKWLAW
5 SEQ ID NO.: 414 TITCRASQDISKWLAWY
SEQ ID NO.: 415 TITCRASQDISKWLAWYQ
SEQ ID NO.: 416 TITCRASQDISKWLAWYQQ
SEQ ID NO.: 417 TITCRASQDISKWLAWYQQR
SEQ ID NO.: 418 VTITCRASQDI
10 SEQ ID NO.: 419 VTITCRASQDIS
SEQ ID NO.: 420 VTITCRASQDISK
SEQ ID NO.: 421 VTITCRASQDISKW
SEQ ID NO.: 422 VTITCRASQDISKWL
SEQ ID NO.: 423 VTITCRASQDISKWLA
15 SEQ ID NO.: 424 VTITCRASQDISKWLAW
SEQ ID NO.: 425 VTITCRASQDISKWLAWY
SEQ ID NO.: 426 VTITCRASQDISKWLAWYQ
SEQ ID NO.: 427 VTITCRASQDISKWLAWYQQ
SEQ ID NO.: 428 VTITCRASQDISKWLAWYQQR

20

Light chain CDR2 region (SEQ ID NO:429 to SEQ ID NO:521)

SEQ ID NO.: 429 AASS
SEQ ID NO.: 430 AASSL
25 SEQ ID NO.: 431 AASSLQ
SEQ ID NO.: 432 AASSLQS
SEQ ID NO.: 433 AASSLQSG
SEQ ID NO.: 434 AASSLQSGV
SEQ ID NO.: 435 AASSLQSGVP
30 SEQ ID NO.: 436 AASSLQSGVPS
SEQ ID NO.: 437 AASSLQSGVPSR

	SEQ ID NO.: 438	ASSL
	SEQ ID NO.: 439	ASSLQ
	SEQ ID NO.: 440	ASSLQS
	SEQ ID NO.: 441	ASSLQSG
5	SEQ ID NO.: 442	ASSLQSGV
	SEQ ID NO.: 443	ASSLQSGVP
	SEQ ID NO.: 444	ASSLQSGVPS
	SEQ ID NO.: 445	ASSLQSGVPSR
	SEQ ID NO.: 446	IYAA
10	SEQ ID NO.: 447	IYAAS
	SEQ ID NO.: 448	IYAASS
	SEQ ID NO.: 449	IYAASSL
	SEQ ID NO.: 450	IYAASSLQ
	SEQ ID NO.: 451	IYAASSLQS
15	SEQ ID NO.: 452	IYAASSLQSG
	SEQ ID NO.: 453	IYAASSLQSGV
	SEQ ID NO.: 454	IYAASSLQSGVP
	SEQ ID NO.: 455	IYAASSLQSGVPS
	SEQ ID NO.: 456	IYAASSLQSGVPSR
20	SEQ ID NO.: 457	KLLIYAA
	SEQ ID NO.: 458	KLLIYAAS
	SEQ ID NO.: 459	KLLIYAASS
	SEQ ID NO.: 460	KLLIYAASSL
	SEQ ID NO.: 461	KLLIYAASSLQ
25	SEQ ID NO.: 462	KLLIYAASSLQS
	SEQ ID NO.: 463	KLLIYAASSLQSG
	SEQ ID NO.: 464	KLLIYAASSLQSGV
	SEQ ID NO.: 465	KLLIYAASSLQSGVP
	SEQ ID NO.: 466	KLLIYAASSLQSGVPS
30	SEQ ID NO.: 467	KLLIYAASSLQSGVPSR

	SEQ ID NO.: 468	LIYAA
	SEQ ID NO.: 469	LIYAAS
	SEQ ID NO.: 470	LIYAASS
	SEQ ID NO.: 471	LIYAASSL
5	SEQ ID NO.: 472	LIYAASSLQ
	SEQ ID NO.: 473	LIYAASSLQS
	SEQ ID NO.: 474	LIYAASSLQSG
	SEQ ID NO.: 475	LIYAASSLQSGV
	SEQ ID NO.: 476	LIYAASSLQSGVP
10	SEQ ID NO.: 477	LIYAASSLQSGVPS
	SEQ ID NO.: 478	LIYAASSLQSGVPSR
	SEQ ID NO.: 479	LLIYAA
	SEQ ID NO.: 480	LLIYAAS
	SEQ ID NO.: 481	LLIYAASS
15	SEQ ID NO.: 482	LLIYAASSL
	SEQ ID NO.: 483	LLIYAASSLQ
	SEQ ID NO.: 484	LLIYAASSLQS
	SEQ ID NO.: 485	LLIYAASSLQSG
	SEQ ID NO.: 486	LLIYAASSLQSGV
20	SEQ ID NO.: 487	LLIYAASSLQSGVP
	SEQ ID NO.: 488	LLIYAASSLQSGVPS
	SEQ ID NO.: 489	LLIYAASSLQSGVPSR
	SEQ ID NO.: 490	LQSG
	SEQ ID NO.: 491	LQSGV
25	SEQ ID NO.: 492	LQSGVP
	SEQ ID NO.: 493	LQSGVPS
	SEQ ID NO.: 494	LQSGVPSR
	SEQ ID NO.: 495	QSGV
	SEQ ID NO.: 496	QSGVP
30	SEQ ID NO.: 497	QSGVPS

SEQ ID NO.: 498 QSGVPSR
SEQ ID NO.: 499 SLQS
SEQ ID NO.: 500 SLQSG
SEQ ID NO.: 501 SLQSGV
5 SEQ ID NO.: 502 SLQSGVP
SEQ ID NO.: 503 SLQSGVPS
SEQ ID NO.: 504 SLQSGVPSR
SEQ ID NO.: 505 SSLQ
SEQ ID NO.: 506 SSLQS
10 SEQ ID NO.: 507 SSLQSG
SEQ ID NO.: 508 SSLQSGV
SEQ ID NO.: 509 SSLQSGVP
SEQ ID NO.: 510 SSLQSGVPS
SEQ ID NO.: 511 SSLQSGVPSR
15 SEQ ID NO.: 512 YAAS
SEQ ID NO.: 513 YAASS
SEQ ID NO.: 514 YAASSL
SEQ ID NO.: 515 YAASSLQ
SEQ ID NO.: 516 YAASSLQS
20 SEQ ID NO.: 517 YAASSLQSG
SEQ ID NO.: 518 YAASSLQSGV
SEQ ID NO.: 519 YAASSLQSGVP
SEQ ID NO.: 520 YAASSLQSGVPS
SEQ ID NO.: 521 YAASSLQSGVPSR

25

Light chain CDR3 region (SEQ ID NO:522 to SEQ ID NO:632)

SEQ ID NO.: 522 ASSF
SEQ ID NO.: 523 ASSFP
30 SEQ ID NO.: 524 ASSFPW
SEQ ID NO.: 525 ASSFPWS

	SEQ ID NO.: 526	ASSFPWSI
	SEQ ID NO.: 527	ASSFPWSIT
	SEQ ID NO.: 528	ASSFPWSITF
	SEQ ID NO.: 529	ASSFPWSITFG
5	SEQ ID NO.: 530	ASSFPWSITFGQ
	SEQ ID NO.: 531	ASSFPWSITFGQG
	SEQ ID NO.: 532	ASSFPWSITFGQGT
	SEQ ID NO.: 533	ATYYCQQASSF
	SEQ ID NO.: 534	ATYYCQQASSFP
10	SEQ ID NO.: 535	ATYYCQQASSFPW
	SEQ ID NO.: 536	ATYYCQQASSFPWS
	SEQ ID NO.: 537	ATYYCQQASSFPWSI
	SEQ ID NO.: 538	ATYYCQQASSFPWSIT
	SEQ ID NO.: 539	ATYYCQQASSFPWSITF
15	SEQ ID NO.: 540	ATYYCQQASSFPWSITFG
	SEQ ID NO.: 541	ATYYCQQASSFPWSITFGQ
	SEQ ID NO.: 542	ATYYCQQASSFPWSITFGQG
	SEQ ID NO.: 543	ATYYCQQASSFPWSITFGQGT
	SEQ ID NO.: 544	CQQASSF
20	SEQ ID NO.: 545	CQQASSFP
	SEQ ID NO.: 546	CQQASSFPW
	SEQ ID NO.: 547	CQQASSFPWS
	SEQ ID NO.: 548	CQQASSFPWSI
	SEQ ID NO.: 549	CQQASSFPWSIT
25	SEQ ID NO.: 550	CQQASSFPWSITF
	SEQ ID NO.: 551	CQQASSFPWSITFG
	SEQ ID NO.: 552	CQQASSFPWSITFGQ
	SEQ ID NO.: 553	CQQASSFPWSITFGQG
	SEQ ID NO.: 554	CQQASSFPWSITFGQGT
30	SEQ ID NO.: 555	FPWS

	SEQ ID NO.: 556	FPWSI
	SEQ ID NO.: 557	QASSF
	SEQ ID NO.: 558	QASSFP
	SEQ ID NO.: 559	QASSFPW
5	SEQ ID NO.: 560	QASSFPWS
	SEQ ID NO.: 561	QASSFPWSI
	SEQ ID NO.: 562	QASSFPWSIT
	SEQ ID NO.: 563	QASSFPWSITF
	SEQ ID NO.: 564	QASSFPWSITFG
10	SEQ ID NO.: 565	QASSFPWSITFGQ
	SEQ ID NO.: 566	QASSFPWSITFGQG
	SEQ ID NO.: 567	QASSFPWSITFGQGT
	SEQ ID NO.: 568	QQASSF
	SEQ ID NO.: 569	QQASSFP
15	SEQ ID NO.: 570	QQASSFPW
	SEQ ID NO.: 571	QQASSFPWS
	SEQ ID NO.: 572	QQASSFPWSI
	SEQ ID NO.: 573	QQASSFPWSIT
	SEQ ID NO.: 574	QQASSFPWSITF
20	SEQ ID NO.: 575	QQASSFPWSITFG
	SEQ ID NO.: 576	QQASSFPWSITFGQ
	SEQ ID NO.: 577	QQASSFPWSITFGQG
	SEQ ID NO.: 578	QQASSFPWSITFGQGT
	SEQ ID NO.: 579	SFPW
25	SEQ ID NO.: 580	SFPWS
	SEQ ID NO.: 581	SFPWSI
	SEQ ID NO.: 582	SFPWSIT
	SEQ ID NO.: 583	SFPWSITF
	SEQ ID NO.: 584	SFPWSITFG
30	SEQ ID NO.: 585	SFPWSITFGQ

	SEQ ID NO.: 586	SFPWSITFGQG
	SEQ ID NO.: 587	SFPWSITFGQGT
	SEQ ID NO.: 588	SSFP
	SEQ ID NO.: 589	SSFPW
5	SEQ ID NO.: 590	SSFPWS
	SEQ ID NO.: 591	SSFPWSI
	SEQ ID NO.: 592	SSFPWSIT
	SEQ ID NO.: 593	SSFPWSITF
	SEQ ID NO.: 594	SSFPWSITFG
10	SEQ ID NO.: 595	SSFPWSITFGQ
	SEQ ID NO.: 596	SSFPWSITFGQG
	SEQ ID NO.: 597	SSFPWSITFGQGT
	SEQ ID NO.: 598	TYYCQQASSF
	SEQ ID NO.: 599	TYYCQQASSFP
15	SEQ ID NO.: 600	TYYCQQASSFPW
	SEQ ID NO.: 601	TYYCQQASSFPWS
	SEQ ID NO.: 602	TYYCQQASSFPWSI
	SEQ ID NO.: 603	TYYCQQASSFPWSIT
	SEQ ID NO.: 604	TYYCQQASSFPWSITF
20	SEQ ID NO.: 605	TYYCQQASSFPWSITFG
	SEQ ID NO.: 606	TYYCQQASSFPWSITFGQ
	SEQ ID NO.: 607	TYYCQQASSFPWSITFGQG
	SEQ ID NO.: 608	TYYCQQASSFPWSITFGQGT
	SEQ ID NO.: 609	YCQQASSF
25	SEQ ID NO.: 610	YCQQASSFP
	SEQ ID NO.: 611	YCQQASSFPW
	SEQ ID NO.: 612	YCQQASSFPWS
	SEQ ID NO.: 613	YCQQASSFPWSI
	SEQ ID NO.: 614	YCQQASSFPWSIT
30	SEQ ID NO.: 615	YCQQASSFPWSITF

SEQ ID NO.: 616 YCQQASSFPWSITFG
SEQ ID NO.: 617 YCQQASSFPWSITFGQ
SEQ ID NO.: 618 YCQQASSFPWSITFGQG
SEQ ID NO.: 619 YCQQASSFPWSITFGQGT
5 SEQ ID NO.: 620 YYCQQASSF
SEQ ID NO.: 621 YYCQQASSFP
SEQ ID NO.: 622 YYCQQASSFPW
SEQ ID NO.: 623 YYCQQASSFPWS
SEQ ID NO.: 624 YYCQQASSFPWSI
10 SEQ ID NO.: 625 YYCQQASSFPWSIT
SEQ ID NO.: 626 YYCQQASSFPWSITF
SEQ ID NO.: 627 YYCQQASSFPWSITFG
SEQ ID NO.: 628 YYCQQASSFPWSITFGQ
SEQ ID NO.: 629 YYCQQASSFPWSITFGQG
15 SEQ ID NO.: 630 YYCQQASSFPWSITFGQGT

Heavy chain variable domain (SEQ ID NO: 631)

QVQLVESGGGVVQPGRLRLSCAASGLTFSGYAMHWVRQAPGKGLEWVAVISR
DAR
NKYYADSVKGRFTISRDNSSKKTIVYLEMNSLRVEDTAVYYCAILIPGITEPGSPD
ALDI
20 WGQGTMSVSS

Light chain variable domain (SEQ ID NO: 632)

DIQMTQSPSSMSASVGDRVTITCRASQDISKWLAWYQQRPGKAPKLLIYAASSLQSGV
PSRFGSGSGTDFTLTISSLQPEDFATYYCQQASSFPWSITFGQGTRLEIR
25

Heavy chain FR1 region (SEQ ID NO:633)

SEQ ID NO:633 QVQLVESGGGVVQPGRLRLSCAASGLTFS

Heavy chain FR2 region (SEQ ID NO:634)

30 SEQ ID NO:634 WVRQAPGKGLEWVA

Heavy chain FR3 region (SEQ ID NO:635)

SEQ ID NO:635 RFTISRDNSKKTVYLEMNSLRVEDTAVYYCAI

Heavy chain FR4 region (SEQ ID NO:636)

5 SEQ ID NO:636 WGQGTMTVSVSS

Light chain FR1 region (SEQ ID NO:637)

SEQ ID NO:637 DIQMTQSPSSMSASVGDRVTTTC

10 **Light chain FR2 region (SEQ ID NO:638)**

SEQ ID NO:638 WYQQRPGKAPKLLIY

Light chain FR3 region (SEQ ID NO:639)

SEQ ID NO:639 GVPSRFSGSGSGTDFTLTISLQPEDFATYYC

15

Light chain FR4 region (SEQ ID NO:640)

SEQ ID NO:640 FGQGTRLEIR

Heavy chain CDR1 region (SEQ ID NO:641)

20 SEQ ID NO.: 641 DYRIH

Heavy chain CDR2 region (SEQ ID NO: 642)

SEQ ID NO.: 642 RMNPKSGDTNFAQKFQG

25 **Heavy chain CDR3 region (SEQ ID NO: 643)**

SEQ ID NO.: 643 LLIVGGFDPLDDFEV

Light chain CDR1 region (SEQ ID NO: 644)

SEQ ID NO.: 644 SGTSSDVGGYNFVS

30

Light chain CDR2 region (SEQ ID NO: 645)

SEQ ID NO.: 645 EVTKRPS

Light chain CDR3 region (SEQ ID NO: 646)

SEQ ID NO.: 646 SSYGGTNNLL

5

Heavy chain CDR1 region (SEQ ID NO: 647)

SEQ ID NO.: 647 YFYLH

Heavy chain CDR2 region (SEQ ID NO: 648)

10 SEQ ID NO.: 648 IINPRGDGTRYAQKFQG

Heavy chain CDR3 region (SEQ ID NO: 649)

SEQ ID NO.: 649 GADHGAFDI

15 **Light chain CDR1 region (SEQ ID NO: 650)**

SEQ ID NO.: 650 RASQSVRRNYFA

Light chain CDR2 region (SEQ ID NO: 651)

SEQ ID NO.: 651 DASTRAT

20

Light chain CDR3 region (SEQ ID NO: 652)

SEQ ID NO.: 652 QQYDSSPPMYI

Heavy chain CDR1 region (SEQ ID NO: 653)

SEQ ID NO.: 653 SHYMH

25

Heavy chain CDR2 region (SEQ ID NO: 654)

SEQ ID NO.: 654 IINPSGSGTAYGQKFQG

Heavy chain CDR3 region (SEQ ID NO: 655)

30 SEQ ID NO.: 655 GSGGLFAY

Light chain CDR1 region (SEQ ID NO: 656)

SEQ ID NO.: 656 RASQIVRSNYLA

Light chain CDR2 region (SEQ ID NO: 657)

5 SEQ ID NO.: 657 GASSRAT

Light chain CDR3 region (SEQ ID NO: 658)

SEQ ID NO.: 658 LQYDSSPPTYI

10 **Heavy chain CDR1 region (SEQ ID NO: 659)**

SEQ ID NO.: 659 SYVMH

Heavy chain CDR2 region (SEQ ID NO: 660)

SEQ ID NO.: 660 LITPSGDDTYAQRFGG

15

Heavy chain CDR3 region (SEQ ID NO: 661)

SEQ ID NO.: 661 MSRAGGFVDV

Light chain CDR1 region (SEQ ID NO: 662)

20 SEQ ID NO.: 662 RASQSITGRYLA

Light chain CDR2 region (SEQ ID NO: 663)

SEQ ID NO.: 663 GESSRVT

Light chain CDR3 region (SEQ ID NO: 664)

25 SEQ ID NO.: 664 QHFASSPPTYT

Heavy chain variable domain (SEQ ID NO: 665)

SEQ ID NO.: 665

30 QMQLMQSGAEVKKPGASVTVSCKASGDTFSDYRIHWVRQAPGQGLEWMGRMNPKS
GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
VWGQGTMTVISS

Light chain variable domain (SEQ ID NO: 666)

SEQ ID NO.: 666

QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNFVSWYQHHPGKAPKILIYEVTKRPS
5 GVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVL

Heavy chain variable domain (SEQ ID NO: 667)

SEQ ID NO.: 667

10 QEQLVQSGAEVKKPGASVKVSCKSSGFTFSYFYLHWVRQAPGQGLEWMGIINPRGD
GTRYAQKFQGRVTMTRDASTGTLYMELRSLRSEDVAVYYCARGADHGAFDIWGQGT
MVTVSS

Light chain variable domain (SEQ ID NO: 668)

15 SEQ ID NO.: 668

EIVLTQSPGTLSSLSPGERATLSCRASQSVRRNYFAWYQQKRGQAPRLLIYDASTRATG
IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSSPPMYIFGQGTKLEIK

Heavy chain variable domain (SEQ ID NO: 669)

20 SEQ ID NO.: 669

QVQLVQSGAEVKKPAASVKVSCKASGDTFSSHMHWVRQAPGQGPEWMGIINPSGS
GTAYGQKFQGRLTMTRDTSTSTVYMELSSLTSDDTAVYYCGGGSGGLFAYWGQGT
LTVSS

25 **Light chain variable domain (SEQ ID NO: 670)**

SEQ ID NO.: 670

EIVLTQSPGTLSSLSPGERATLSCRASQIVRSNYLAWYQQKPGQAPRLLIYGASSRATGT
PDRFSGGGSGTDFTLTINRLEPEDFAVYYCLQYDSSPPTYIFGQGTKLEIK

30 **Heavy chain variable domain (SEQ ID NO: 671)**

SEQ ID NO.: 671

QVQLVQSGAEVKKPGASVKVSCQTSGYTFSTSYMHWRQAPGQGLEWMGLITPSGD
DTYYAQRFFQGRVTMTRDTSTSPYMESSLTSEDVAVYYCAKMSRAGGFDVWGQGT
LTVVSS

5 **Light chain variable domain (SEQ ID NO: 672)**

SEQ ID NO.: 672

EIVLTQSPGTLSPGERATLSCRASQIVRSNYLAWYQQKPGQAPRLLIYGASSRATGT
PDRFSGGGSGTDFTLINRLEPEDFAVYYCLQYDSSPPTYIFGQGTKLEIK

10

EXAMPLES

Example 1: Antibody according to the invention (Intraperitoneals)

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: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, 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 monoclonal antibody (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 antibody according to the invention, is buffered in phosphate-buffered saline PBS was diluted with (PBS) to the final concentrations for administration (10 to 0.2mg/kg in 200 µL), thereby preparing an antibody dilution.

The antibody dilution was made up at various concentrations so that 200 µL administration to the mean weight per cage of the dosing group at day -5 resulted in 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 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 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. 15.8-20.9 g. 60 mice were used at the age of 8-9 weeks and were exclusively female. Ten animals were allocated to 6 treatment groups based on day -5 weight to create groups with similar mean

weight. 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.

- 5 Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at the day of infection (Day 0).

Study design

The dose level of 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 IP at doses ≥ 0.5 mg/kg. A total number of 60 mice, 8-9 weeks of age were allocated to 6 experimental groups according to Table 1 (see below). Mice were given a period of >3 days for acclimatization.

15

Table 1: Intraperitoneal experimental detail

Test group	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	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 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 weight loss and mortality until the end of the study at day 14.

Antibody administration

The test antibody was stored at -80°C upon arrival. The appropriate dose, according to the treatment schedule (Table1), was based upon the average weight per cage.

Prior to dosing, the material was drawn into a 1mL 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 deg angle for administration (200 µL per mouse). Mice in the vehicle group received PBS intranasally by administering 25 µL of PBS into the left and right nare (50 µL per mouse).

Virus administration

The virus material was stored at -80°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 2L/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 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) 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 $\alpha = 0.05$.

5

Survival

Prophylactic treatment with ≥ 1.7 mg/kg test antibody provide statistically significant increase in survival compared to vehicle (See Figure 1). The animals that were treated with 1.7 mg/kg test antibody had an 80% survival rate, with 5 mg/kg a rate of 100% and with 10 mg/kg a 90% survival, whereas the survival proportion at day 7 in the control group was 0%. The median survival time of the control group was 6 days.

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

15

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 ≥ 1.7 mg/kg test antibody resulted in a significant reduction in weight loss compared to the control group.

25

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of ≥ 1.7 mg/kg test antibody provides significant improvement in survival compared to vehicle and a reduction in weight loss whereas all the animals in the control group died.

30

Example 2: Antibody according to the invention (Intranasal)

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: 027, heavy chain

CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573 following systemic intranasal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

5

Animals (n=10 per group, except 10 mg/kg where n=9) were treated with an intranasal dose range of the test monoclonal antibody (10 to 0.2 mg/kg) or PBS control at study day -1. At study day 0, animals were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

10

Materials and Methods

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

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

20 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 has been passed three times through Vero-hSLAM cells.

25

Animals

30 The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg mouse model, at a weight of c. 16.0-22.4 g on day -5. 60 mice were used at the age of 8-9 weeks and were exclusively female. Ten animals were allocated to 6 treatment groups based on creating groups with similar mean weight and weight variability based on Day -5 weights. 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. Each animal was weighed daily beginning at the day of infection (Day 0).

5 Study design

The dose level of 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, 8-9 weeks of age, 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	Admin. route	Dose (mg/kg)	Day of admin.	No. of Animals
10	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

15 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 average 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.

20

Antibody administration

The test antibody was stored at -80°C upon arrival. The appropriate dose, according to the treatment schedule (Table1), was formulated based upon the average weight per cage

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

Virus administration

10 The virus material was stored at -80°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 2L/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
15 material was frozen at -20 to -80°C for back titration.

Laboratory analysis

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

20

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

25 One animal in the 10 mg/kg monoclonal antibody group died from non-infection related causes on day 8 post challenge. This animal was excluded from the statistical analysis. 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
30 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).

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

Survival

- 5 Prophylactic treatment with ≥ 0.2 mg/kg test antibody provides statistically significant increase in survival compared to vehicle (See Figure 2). The median survival time of the control group was 6 days with 0% survival at day 7.

Prophylactic treatment with ≥ 0.2 mg/kg test antibody resulted in a significant
10 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
15 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.

20

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal administration of ≥ 0.2 mg/kg test antibody provides significant improvement in survival compared to vehicle and a reduction in weight loss whereas all the animals in the control
25 group died.

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: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as
30 SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, 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.

5 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 µL). thereby preparing the test antibody dilution.

10 The test antibody dilution was made up at various concentrations so that 200 µL administrations on the basis of 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.

15 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.

20

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. 17-22 g at day -5. 60 mice were used at the age of 7-11 weeks and were exclusively female. Ten
25 animals were allocated to 6 treatment groups based on day -5 weight to create 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
30 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).

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 and previous experience with an anti-S2 antibody (CV3-25) showing protection IP at doses
 5 > 0.5 mg/kg. A total number of 60 mice, 7-11 weeks of age, 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

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 at day -5. 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
 15 until the end of the study at day 14.

Antibody administration

The test antibody was stored at -80°C ± 10°C upon arrival. The appropriate dose, according to the treatment schedule (Table 3), was formulated using the average weight
 20 per cage and group at day -5 (18.5 to 19.9g).

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 deg 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 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°C ± 10°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 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 corresponding 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).

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

Survival - Intraperitoneal

5 Prophylactic treatment with ≥ 1.7 mg/kg test antibody provides statistically significant protection compared to vehicle (See Figure 3). The animals that were treated with 1.7 mg/kg test antibody had a 100% survival rate, with 5 mg/kg a rate of 70% and with 10 mg/kg a 90% survival, whereas the survival proportion at day 6 in the control group was 0%. The median survival time of the control group was 6 days.

10

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.

15

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
20 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.

Conclusion

25 In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of ≥ 1.7 mg/kg test antibody provides significant improvement in survival compared to vehicle and a reduction in weight loss whereas all the animals in the control group died.

30

Example 4: 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: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as

SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573, following intranasal administration in a SARS-CoV-2 Delta K18 hACE2 Tg mouse model.

- 5 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 were challenged with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta variant.

Materials and Methods

- 10 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)

- 15 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.

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.

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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.

Animals

- 25 The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg mouse model, at a weight of c. 16.4-21.8 g on the day of test article administration. 60 mice were used at the age of 7-11 weeks and were exclusively female. Ten animals were allocated to 6 treatment groups based on creating groups with similar mean weight and weight variability based on Day -5 weights. All mice were housed in individually ventilated cages (IVCs), with corn
30 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 (Day 0).

Study design

- 5 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, 7-11 weeks of age were transported to the animal facility and allocated to 6 experimental groups according to Table 4 (see below).
- 10 Mice were given a period of >3 days for acclimatization.

Table 4: 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 at day -5. 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 4), was formulated based upon the average weight per cage and group at day -5 (18.7 to 20.0g).

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°C ± 10°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 to -80°C for back titration.

Laboratory analysis

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 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 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).

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

Survival - Intranasal

Prophylactic treatment with ≥ 0.2 mg/kg test antibody provides statistically significant
5 protection compared to vehicle (See Figure 4). 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
10 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
15 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.

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Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal
administration of ≥ 0.2 mg/kg test antibody provides significant improvement in survival
and a reduction in weight loss compared to vehicle. In contrast, all the animals in the
25 control group had died by day 6.

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Example 7: Antibody according to the invention

The aim of this study is to assess the pre- and post- exposure efficacy of a monoclonal
30 antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 027,
heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light
chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain
CDR3 as SEQ ID NO: 573, 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.

5 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

10 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.

15 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.

20

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 (7 to 21 days follow-up period).

25

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

Animals

30 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.

Study design

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.

Table 5: 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	4 – 12
Low dose		I.N.	0.01 – 2.0	-1	4 – 12
Vehicle	---	I.N.	0	-1	4 – 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 5), 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 10² and 10⁸ TCID₅₀ of SARS-CoV-2 (e.g. 10⁵ 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 along with 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: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573 ("First Antibody"), and a second monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 647, heavy chain CDR2 as SEQ ID NO: 648, heavy chain CDR3 as SEQ ID NO: 649, a light chain CDR1 as SEQ ID NO: 650, a light chain CDR2 as SEQ ID NO: 651, and a light chain CDR3 as SEQ ID NO: 652 ("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

5 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 5 mg nominal dose, administered as 50 µL to 500 µL per nare.

10 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.

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

15

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 (7 to 21 days follow-up period).

20

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

Animals

25 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.

Study design

30 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.

Table 6: Intranasal experimental detail

Treatment group	Antibody	Admin. route	Dose (mg)	Day of admin	No. of Animals
1	First Antibody only	I.N.	0.003 -5	-1	4 – 12
2	Second Antibody only	I.N.	0.003 - 5	-1	4 – 12
3	First and Second Antibody	I.N.	0.003 - 5	-1	4 – 12
Vehicle	---	I.N.	0	-1	5 – 12

The NHP subjects receive intranasal administrations with compositions comprising either single antibody nominal doses of between 0.003 mg to 5 mg (Treatment Groups 1 or 2) . Different NHP subjects receive intranasal administrations with compositions comprising the First and Second Antibody at nominal doses between 0.003 mg to 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).

Antibody administration

The antibody compositions (Treatment Groups 1 to 6) or vehicle only are administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 6), 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 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).

Results – Clinical Manifestations

Prophylactic treatment with treatments (as indicated in Table 6) 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 6) 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 6) according to the invention provides a reduction in
15 clinical manifestations and / or a reduction in virological measurements, as compared with control group NHPs or within treatments.

Example 9: Bi-specific antibody according to the invention

The aim of this intranasal murine study is to assess the pre- and post- exposure efficacy
20 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, wherein the first Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 027, 180, 275, 379, 432 or 573; wherein the second Fab comprises a sequence comprising any one or
25 more of SEQ ID Numbers: 647, 648, 649, 650, 651 to 652.

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

30

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.

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.

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.

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.

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Table 7: 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	-1	6 – 10

		(e.g. 1.7, 1.25)		
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 Delta 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 7), 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 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 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 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.

5 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).

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

10

Survival

Prophylactic treatment with Parental mAb 1, Parental mAb 2 or bispecific antibody (as indicated in Table 7) compared to the control group provides statistically significant protection against mortality and a significant improvement in survival time compared to the control group.

15

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.

20

Prophylactic treatment with the parental or bispecific antibodies (as indicated in Table 7) provides a statistically significant reduction in weight loss, compared to the control group.

25

Conclusion

In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of a bispecific antibody (as indicated in Table 7) 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

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additive or potentially synergistic effect for the bispecific compared to the parental antibodies.

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") having a heavy chain CDR1 as SEQ ID NO: 027, heavy chain CDR2 as SEQ ID NO: 180, heavy chain CDR3 as SEQ ID NO: 275, a light chain CDR1 as SEQ ID NO: 379, a light chain CDR2 as SEQ ID NO: 432, and a light chain CDR3 as SEQ ID NO: 573. The second antibody ("Second mAb") having a heavy chain CDR1 as SEQ ID NO: 647, heavy chain CDR2 as SEQ ID NO: 648, heavy chain CDR3 as SEQ ID NO: 649, a light chain CDR1 as SEQ ID NO: 650, a light chain CDR2 as SEQ ID NO: 651, and a light chain CDR3 as SEQ ID NO: 652.

Animals are treated with an intranasal dose (0.001 mg/kg to 15 mg/kg) of the 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

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.

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.

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.

5 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
10 each the parental or bispecific antibody is applied.

Table 8: 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	-1	6 – 10

		(e.g.- 1.7)		
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
5 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
10 only is administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 8), 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
15 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).

Laboratory analysis

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

Clinical monitoring

General health observations are performed on each animal from the day of arrival until
10 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).

Data analysis and statistical methods

Survival proportions and survival times and change in bodyweight (Area Under the
15 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).

20

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

Survival

Prophylactic treatment with the First or Second antibodies or the composition comprising
the combination (as indicated in Table 8) compared to the control group provides
30 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
5 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 composition comprising the combination (as indicated in Table 8) provides a statistically significant reduction in weight loss, compared to the
10 control group.

Conclusion

In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of the composition comprising the combination (as indicated in Table 8) according to the
15 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 combination compared to the First or Second antibodies administered alone.

Example 12. ELISA binding

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
25 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
30 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 (EC_{50}) was calculated for each antibody on each antigen as an estimate of binding affinity.

Table 10: ELISA EC_{50} values (nM) for the antibody according to invention.

5 N/D = no EC_{50} value was determined, due to lack of binding.

	CoV-2 Delta	CoV-2 XBB.1.5	NL63
Parental mAb 1	0.0068	2.8	0.011
Anti - S1 antibody DZIF-10c	6.9	N/D	N/D
Anti - S1 antibody	0.010	N/D	N/D
Human IgG1 Isotype	N/D	N/D	N/D

The ELISA binding assay (Table 10) showed that the antibody according to invention was able to effectively bind all tested Spike antigens from alpha and beta coronaviruses, including SARS-CoV-2 Delta, Omicron XBB.1.5 and hCoV NL63, suggesting binding across alpha and beta coronaviruses. The anti-S1 antibodies tested only bound the SARS-CoV-2 Delta, as expected from literature and did not show breadth amongst the alpha coronavirus NL63. The isotype control antibody did not show any binding to the coronavirus antigens.

15 **Example 13: 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 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-
25 (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

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 11), 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 12). The antibody was tested in a dilution range starting from 555 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 the lower limit of detection (LLOQ) and the upper limit of detection (ULOQ). The concentration (pg/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 11: Antibody concentrations corresponding to the midpoint of the dynamic range $(\text{LOQ} + \text{ULOQ})/2$ (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.

	SARS-CoV-2	SARS-CoV-1	MERS-CoV	hCoV-OC43	hCoV-HKU1	hCoV-NL63	hCoV-229E	SARS-CoV-2 S1 RBD
Parental mAb 1	2.66	5.11	1.89	N/D	N/D	1.39	N/D	N/D
Anti-S1 mAb DZIF-10c	0.16	N/D	N/D	N/D	N/D	N/D	N/D	0.90
isotype control	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D

The MSD binding array (see Table 11) showed that the antibody according to invention was able to effectively bind Spike antigens from alpha and beta coronaviruses, including SARS-CoV-1, SARS-CoV-2, MERS and NL63. The seasonal beta coronaviruses HKU1 and OC43 and alpha coronavirus 229E were not bound, as well as the receptor binding domain (RBD) on S1 domain of the Spike. On the contrary, the anti-S1 antibody tested here bound very well to the RBD domain and the wildtype SARS-CoV-2 at low concentrations, as expected from literature and did not show breadth amongst other coronaviruses. This

suggests that the antibody according to invention shows efficient binding across all tested beta and for one of two tested alpha coronaviruses, while the anti-RBD antibody only bound SARS-CoV-2 Spike and RBD domain. The isotype negative control antibody directed against influenza did not show any binding to the coronavirus antigens.

5

Table 12: 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: half-dynamic range was not able to be determined.

	SARS -CoV- 2	SARS -CoV- 2 BA.1	SARS- CoV-2 BA.2.7 5	SARS -CoV- 2 BA.5	SARS -CoV- 2 BF.7	SARS -CoV- 2 BN.1	SARS -CoV- 2 BQ.1	SARS -CoV- 2 BQ.1 1	SARS -CoV- 2 XBB 1	SARS- CoV-2 XBB.1 5
Parent al mAb 1	2155	1056	2250	2435	3000	2957	3909	2394	2154	4841
Anti-S1 mAb DZIF- 10c	117	93	81	630	13625	11558	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

10

The MSD binding array showed that the antibody according to invention can bind all Omicron variants tested in this assay, albeit at higher concentrations (Table 12), therefore retaining activity among the Omicron mutants. While the anti-S1 control antibody bound the SARS-CoV-2 Spike at lower concentrations than the antibody according to invention, the earlier Omicron mutants were only bound by this antibody at very high concentrations and the later Omicron mutants such as BQ.1 and XBB were not bound. This indicates that the antibody according to invention was able to bind to the latest Omicron mutants while the anti-RBD antibody did not bind these variants. The isotype control antibody did not show any binding to the coronavirus antigens.

20

Example 14. 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
 5 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:
 10 <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 13: 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
 15 patients was used as a comparator and SARS-CoV-2 positive control, MN₅₀ titers are shown. N/D = not determined

Live virus neutralization	SARS-CoV-2 Wuhan	SARS-CoV-1	MERS-CoV
Parental mAb 1	16.52	9.25	>500
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 and SARS-CoV-2 but not MERS (see Table 13). This suggests that while MERS Spike was bound in
 20 the highly sensitive MSD binding assay by this antibody (Table 11), it is not neutralized at the tested concentration in this study. The positive serum control for SARS-CoV-2 shows a high MN₅₀ titer.

Example 15. Pseudovirion neutralization

25 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

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
 5 mixed with virus was added to Huh7 cells which express the aminopeptidase N (APN 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
 10 concentration at which infectivity was inhibited by 50% using a four Parameter Logistic 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, hCoV NL63 and hCoV 229E.

15 Table 14: Pseudovirion neutralization assay. IC₅₀ values in ug/ml were displayed for the anti-stem helix antibody against different alpha and beta coronaviruses. For multiple runs, the geometric mean with 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	2.809 (1.058-7.461)	0.314 (0.125-0.790)	1.102 (0.122-9.912)	11.759 (1.613-85.703)	32.318 (9.466-110.341)	13.665 (2.156-86.611)	54.752 (31.471-95.256)	4.820 (0.822-28.258)

Overall, the antibody was able to neutralize all tested alpha and beta viruses at varying
 20 concentrations (see Table 14), with an overall trend of higher IC₅₀ concentrations for the Omicron variants and alpha coronavirus 229E. SARS-CoV-1, SARS-CoV-2 and the hCoV NL63 are neutralized effectively at low concentrations, this suggests breadth of neutralizing activity of the antibody according to the invention across alpha and beta coronaviruses including variants of concern, as expected based on the binding data.

25

Example 16. Epitope mapping

The goal of this study was to precisely determine the amino acid sequence that the antibody according to the invention 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
5 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
10 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 5). The method allowed for a high confidence in the
15 epitope definition, with certain variance in the outer areas of the epitope, indicated by asterisk for the respective strain.

CLAIMS

1. 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 fusion peptide of a coronavirus, preferably SARS-CoV-2 and a second Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 647, 648, 649, 650, 651 to 652, alternatively SEQ ID Numbers: 659, 660, 661, 662, 663 to 664, or alternatively 647, 648, 649, 650, 651 to 652.
2. A bispecific antibody or an antigen binding fragment thereof according to Claim 1, comprising a first Fab capable of binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, and a second Fab capable of binding to the stem helix of a coronavirus, preferably SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 027, 180, 275, 379, 432 and/or 573 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 647, 648, 649, 650, 651 and/or 652.
3. A bispecific antibody or an antigen binding fragment thereof according to Claims 1 or 2, comprising a first Fab specifically binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, and a second Fab specifically binding to the stem helix 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: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and
 - b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a Heavy Chain CDR3 region of SEQ ID NO: 649 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID

NO: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.

4. A bispecific antibody or an antigen binding fragment thereof according to any of
5 Claims 1 to 3, comprising:
- 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 fusion peptide 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
10 of binding to the stem helix 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 fusion peptide of a coronavirus, preferably SARS-CoV-2, are replaced by each other.
- 15
5. A bispecific antibody or an antigen binding fragment thereof according to Claim 4, 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: 027, a Heavy Chain
20 CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO:
25 573, and
- 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: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a Heavy Chain CDR3 region of SEQ ID NO:
30 649 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: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.

6. A bispecific antibody, or an antigen binding fragment thereof according to any of Claims 1 to 3, comprising:
- 5 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 fusion peptide of a coronavirus, preferably SARS-CoV-2; and
- 10 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 stem helix 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.
7. A bispecific antibody or an antigen binding fragment thereof according to Clause 6, wherein the VH domain of the antibody or the antigen binding fragment thereof that
- 15 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: 027, a Heavy Chain CDR2 region of SEQ ID NO: 180 and a Heavy Chain CDR3 region of SEQ ID NO: 275 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
- 20 region of SEQ ID NO: 379, a Light Chain CDR2 region of SEQ ID NO: 432 and a Light Chain CDR3 region of SEQ ID NO: 573, and
- wherein the VH domain of the antibody 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: 647, a Heavy Chain CDR2 region of SEQ ID NO: 648 and a
- 25 Heavy Chain CDR3 region of SEQ ID NO: 649 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: 650, a Light Chain CDR2 region of SEQ ID NO: 651 and a Light Chain CDR3 region of SEQ ID NO: 652.
- 30
8. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 3, 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 fusion peptide 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 stem helix 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.
9. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 8, 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, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 631.
10. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 8, 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: 667.
11. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 8, 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, 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: 632.
12. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 8, 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: 668.

13. A bispecific antibody or an antigen binding fragment thereof according to any of
5 Claims 1 to 8, 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.
- 10 14. A method for the production of a bispecific antibody or an antigen binding fragment
thereof according to any of Claims 1 to 13, 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
15 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.
- 15 15. 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 Claims 1 to 13,
preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.
- 20 16. 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 Claims 1 to 13
and Clause 15, wherein the nucleic acid sequence comprises at least anyone of:
- 25 (i) a first nucleic acid sequence encoding the amino acid sequence as set forth in SEQ
ID NO. 027, or a first nucleic acid sequence encoding the amino acid sequence having
at most 1 or 2 amino acids different from SEQ ID NO. 027,
- 30

- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 180, 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. 180,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in
5 SEQ ID NO. 275, or a third nucleic acid sequence encoding the amino acid sequence having at most 1, 2 or 3 amino acids different from SEQ ID NO. 275,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 379, 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. 379,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in
10 SEQ ID NO. 432, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 432,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 573, or a sixth nucleic acid sequence encoding the amino acid sequence
15 having at most 1, 2, 3, or 4 amino acids different from SEQ ID NO. 573,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 647, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 647,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth
20 in SEQ ID NO. 648, or an eighth nucleic acid sequence encoding the amino acid sequence having at most 1, 2, 3, 4, or 5 amino acids different from SEQ ID NO. 648,
- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 649, 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. 649,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in
25 SEQ ID NO. 650, 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. 650,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 651, or an eleventh nucleic acid sequence encoding the amino acid
30 sequence having at most 1 or 2 amino acids different from SEQ ID NO. 651, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 652, 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. 652.

17. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 13 for use in a method of treating a coronavirus infection in a subject.
- 5 18. A composition comprising the bispecific antibody and/or an antigen binding fragment thereof according to any of Claims 1 to 13.
19. A composition according to Clause 18 further comprising a second medicament, for simultaneous, separate, or sequential administration.
- 10 20. A composition according to Clause 19, wherein the second medicament comprises a second antibody or antigen binding fragment thereof.
21. A composition according to Clause 19, wherein the second medicament comprises a bispecific antibody or bispecific antigen binding fragment thereof.
- 15 22. A composition according to Clause 18, wherein the composition further comprises a pharmaceutically acceptable excipient or carrier.
- 20 23. A composition according to Clause 18, 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 excipient or carrier.
- 25 24. The composition of Clause 18, for use as a medicament.
25. An inhaler device comprising the composition of Clause 18.
- 30 26. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 13, wherein the bispecific antibody or an antigen binding fragment thereof is bivalent.

27. A bispecific antibody or an antigen binding fragment thereof according to any of Claims 1 to 13, 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.