

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.

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Structure of the spike protein

- Coronavirus infection is a multistep process that involves enzymatic cleavage and rearrangement of the surface spike protein. The spike protein has an S1 subunit with the receptor-binding domain 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 wearing. These methods are non-specific, and efficacy largely depends on compliance.
5 Thus, there is a need for different treatments, especially treatments that simultaneously target the multitude of SARS-CoV-2 variants of concern such as, for example, broad-neutralizing antibodies (bnAbs).

Although treatment of SARS-CoV-2 infection with one, two or more antibodies is a
10 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 species known to have frequent human contact, thus increasing the risk of zoonotic transfer
15 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 -coronaviruses, as well as new SARS-CoV-2 variants of concern that are not neutralized
20 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 antibodies which are disclosed herein.

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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 coronavirus infection, especially in the prophylactic treatment of coronavirus infection.

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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.

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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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of
25 SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of
30 SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, wherein the antibody is administered to mucosal epithelium.

In a preferred embodiment, the invention provides a method for the treatment of a coronavirus infection in an individual, the method comprising administering to an individual in need thereof an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, wherein the antibody is administered to mucosal epithelium.

In a preferred embodiment, the invention provides a mucosal composition comprising an antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, wherein the antibody is administered to mucosal epithelium.

to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068,
10 a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to
15 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 013, a heavy chain CDR2 region comprising SEQ ID NO: 170, and a heavy chain CDR3 region comprising SEQ ID NO: 266, a light chain variable domain that comprises a light chain
25 CDR1 region comprising SEQ ID NO: 386, a light chain CDR2 region comprising SEQ ID NO: 439, and a light chain CDR3 region comprising SEQ ID NO: 584.

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: 013, a heavy chain CDR2 region consisting of SEQ ID NO: 170, and a heavy chain CDR3 region consisting of SEQ ID NO: 266, a light chain variable domain that comprises a light chain CDR1 region consisting of SEQ ID NO: 386, a light chain CDR2 region consisting of SEQ ID NO: 439, and a light chain CDR3 region consisting of SEQ ID NO: 584.

In a preferred embodiment, an antibody is disclosed herein for use in a method for the prophylactic treatment of a coronavirus infection, in an individual, the antibody comprising a heavy chain variable domain that comprises a heavy chain CDR1 region comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315.

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: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising
5 any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315.

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: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466,
20 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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: 006 to 011, 014 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 171 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 267 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1
30 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 387 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 440 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 585 to 589, 613 to 618, 634 to 639.

Embodiments having > 1 CDRs

Preferably, an antibody as disclosed herein comprises a heavy chain variable domain that comprises a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093
5 to 098, 115 to 120, 126 to 131, 170 to 175, 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.
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In a preferred embodiment, the invention provides an antibody as disclosed herein, or a method or composition comprising the antibody as disclosed herein, wherein the antibody is administered by 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain
5 CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID
10 NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120,
30 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466,

472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to
10 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477,
15 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639.

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: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, a heavy chain CDR2 region comprising any one of SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, and a heavy chain CDR3 region comprising any one of SEQ ID NO: 202
25 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, a light chain variable domain that comprises a light chain CDR1 region comprising any one of SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, a light chain CDR2 region comprising any one of SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, and a light chain CDR3 region comprising any one of SEQ ID NO:
30 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639, 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: 013, a heavy chain CDR2 region comprising SEQ ID NO: 170, and a heavy chain CDR3 region comprising SEQ ID NO: 266, a light chain variable domain that comprises a light chain CDR1 region comprising SEQ ID NO: 386, a light chain CDR2 region comprising SEQ ID NO: 439, and a light chain CDR3 region comprising SEQ ID NO: 584.

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: 640 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: 641 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.

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,
5 ocular administration and oropharyngeal administration.

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.

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Clause 12:

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

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Clause 13:

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 claims 1 to 12.

20

Clause 14:

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

Clause 15:

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

Dosing

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

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

10

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

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

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The flat dose, or nominal dose, of the antibody to be delivered to a human subject is preferably between 0.1 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.

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

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

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

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

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

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

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

Timing and intervals

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

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

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

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

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

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

Framework regions

Preferably, the antibody comprises a heavy chain variable domain having the sequence of SEQ ID NO: 640 and/or a light chain variable domain having the sequence of SEQ ID NO: 641.

Preferably, the heavy chain variable domain of said antibody further comprises a heavy chain framework region FR1 of SEQ ID NO: 642, a heavy chain framework region FR2 of SEQ ID NO: 643, a heavy chain framework region FR3 of SEQ ID NO: 644, and/or a heavy chain framework region FR4 of SEQ ID NO: 645.

Preferably, said light chain variable domain further comprises a light chain framework region FR1 of SEQ ID NO: 646, a light chain framework region FR2 of SEQ ID NO: 647, a light chain framework region FR3 of SEQ ID NO: 648, and/or a light chain framework region FR4 of SEQ ID NO: 649.

Combination compositions

In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 013, 170, 266, 386, 439 or 584. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 650, 651, 652, 653, 654 or SEQ ID NO.: 655. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639. More preferably wherein the First fragment comprises any one or more of SEQ ID NO: 013, 170, 266, 386, 439 or 584. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 656, 657, 658, 659, 660 or SEQ ID NO.: 661. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

15

In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196, 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639. More preferably wherein the First fragment comprises a sequence comprising any one or more of SEQ ID NO: 013, 170, 266, 386, 439 or 584. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 662, 663, 664, 665, 666 or SEQ ID NO.: 667. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

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In a preferred embodiment, we disclose a composition comprising a First binding fragment as disclosed herein and a Second binding fragment, wherein the First fragment comprises a sequence comprising any one of SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068, 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191

to 196, 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315, 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435, 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528, 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639. More preferably wherein the First fragment comprises a sequence
5 comprising any one or more of SEQ ID NO: 013, 170, 266, 386, 439 and 584. The Second binding fragment comprises a sequence comprising any one of SEQ ID NO.: 668, 669, 670, 671, 672 or SEQ ID NO.: 673. Preferably, the fragment is selected from anyone of the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, scFv-Fc, bi, tri or tetra-valent antibodies, Bis-scFv,
10 diabodies, triabodies, tetrabodies and epitope binding fragments thereof.

Bispecific antibodies

In a preferred embodiment, we disclose a bispecific antibody, wherein the bispecific antibody is capable of binding to the fusion peptide of a coronavirus. In a preferred
15 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
20 of a coronavirus and a second Fab capable of binding to the fusion peptide of a coronavirus. In a preferred embodiment, we disclose an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2.

25 In a preferred embodiment, we disclose an anti- 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 fusion
30 peptide 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: 650, 651, 652, 653, 654 to 655; alternatively wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 662, 663, 664, 665, 666 or 667; or alternatively wherein the first Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 668, 669, 670, 671, 672 to 673, and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 013, 170, 266, 386, 439 or 584; or alternatively wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 656, 657, 658, 659, 660 to 661.

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 fusion peptide 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: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 656, 657, 658, 659, 660 to 661. 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 an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the fusion peptide of SARS-CoV-2 and a second Fab 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: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 650, 651, 652, 653, 654 to 655. 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 an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the fusion peptide 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: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 662, 663, 664, 665, 666 to 667. 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 an anti-SARS-CoV-2 bispecific antibody or an antigen binding fragment thereof, having a first Fab capable of binding to the fusion peptide 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: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 668, 669, 670, 671, 672 to 673. 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 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: 013, 170 or 266, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 671, 672, or 673.

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: 013, 170 or 266, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 653, 654, or 655.

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: 013, 170 or 266, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 665, 666, or 667.

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: 668, 669, or 670, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 386, 439 or 584.

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: 650, 651, or 652, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 386, 439 or 584.

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: 662, 663 or 664, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 386, 439 or 584.

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: 013, 170 or 266, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 659, 660, or 661.

25 In a preferred embodiment, we disclose a bispecific antibody comprising a First Fab and a Second Fab, wherein the First Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 656, 657, or 658, and wherein the Second Fab comprises any one or more of sequences shown in preferred SEQ ID Numbers: 386, 439 or 584.

30 The present invention also provides construction, expression, purification methods for a bispecific antibody having a function of binding to the fusion peptide 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 sequence comprising any one or more of preferred SEQ ID Numbers: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 656, 657, 658, 659, 660 to 661.

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: 013, 170, 266, 368, 439 and/or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: 656, 657, 658, 659, 660 and/or 661.

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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, and

- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 656, a Heavy Chain CDR2 region of SEQ ID NO: 657 and a Heavy Chain CDR3 region of SEQ ID NO: 658 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 659, a Light Chain CDR2 region of SEQ ID NO: 660 and a Light Chain CDR3 region of SEQ ID NO: 661.

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 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 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 fusion peptide 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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 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: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, 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: 656, a Heavy Chain CDR2 region of SEQ ID NO: 657 and a Heavy Chain CDR3 region of SEQ ID NO: 658 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: 659, a Light Chain CDR2 region of SEQ ID NO: 660 and a Light Chain CDR3 region of SEQ ID NO: 661.

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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 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: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, 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: 656, a Heavy Chain CDR2 region of SEQ ID NO: 657 and a Heavy Chain CDR3 region of SEQ ID NO: 658 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: 659, a Light Chain CDR2 region of SEQ ID NO: 660 and a Light Chain CDR3 region of SEQ ID NO: 661.

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
- 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,
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 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
20 sequences set forth in SEQ ID NO: 640.

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
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: 684.

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: 641.

5 Clause 37:

A bispecific antibody or an antigen binding fragment thereof according to any of Clauses 26 to 33, wherein the second Fab comprises a light chain variable region having an amino acid sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequences set forth in SEQ ID NO: 685.

Clause 38:

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

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 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:

30 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 26 to 38, preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.

Claim 41:

- 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 an antigen binding fragment thereof according to any of Claims 26 to 38 and Claim 40, 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. 013, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 013,
- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 170, 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. 170,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 266, 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. 266,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ
- 20 ID NO. 368, 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. 368,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 439, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 439,
- 25 (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 584, 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. 584,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 656, 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. 656,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 657, 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. 657,

- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 658, 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. 658,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 659, 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. 659,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 660, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 660, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 661, 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. 661.

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.

5

Clause 48:

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

10

Clause 49:

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

15

Clause 50:

An inhaler device comprising the composition of Clause 43.

Clause 51:

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

20

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 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.

25

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Clauses

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

Clause 53:

- 5 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: 013, 170, 266, 368, 439 or 584
10 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: SEQ ID Numbers: 662, 663, 664, 665, 666 to 667.

Clause 54:

- A bispecific antibody or an antigen binding fragment thereof according to Clause 53,
15 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: 013, 170, 266, 368, 439 and/or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID
20 Numbers: SEQ ID Numbers: 662, 663, 664, 665, 666 and/or 667.

Clause 55:

- A bispecific antibody or an antigen binding fragment thereof according to Clauses 53 or 54, comprising a first Fab specifically binding to the fusion peptide of a coronavirus,
25 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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 and a light chain variable region
30 comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, and
b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 662, a Heavy Chain CDR2 region of SEQ ID

NO: 663 and a Heavy Chain CDR3 region of SEQ ID NO: 664 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.

5 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
10 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
15 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,
20 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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 and the VL domain of the antibody or the antigen binding fragment thereof that is capable of
25 binding to the fusion peptide of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, 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
30 as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 662, a Heavy Chain CDR2 region of SEQ ID NO: 663 and a Heavy Chain CDR3 region of SEQ ID NO: 664 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: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.

Clause 58:

- 5 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
- 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.

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,
- 20 comprises as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 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: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of
- 25 SEQ ID NO: 584, 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: 662, a Heavy Chain CDR2 region of SEQ ID NO: 663 and a Heavy Chain CDR3 region of SEQ ID NO: 664 and the VL domain of the antibody capable of binding to
- 30 the stem helix of a coronavirus, preferably SARS-CoV-2, comprises as CDRs a Light Chain CDR1 region of SEQ ID NO: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.

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
- 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 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.

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 sequences set forth in SEQ ID NO: 640.

20

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 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: 688.

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: 641.

Clause 64:

5 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
10 sequences set forth in SEQ ID NO: 689.

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
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 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
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 67:

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 53 to 65, preferably wherein the nucleic acid molecule is an isolated nucleic acid molecule.

Clause 68:

A nucleic acid molecule comprising a nucleic acid sequence, wherein the nucleic acid sequence encodes the bispecific antibody or antigen binding fragment thereof, a heavy chain variable region and/or light chain variable region of the bispecific antibody or the antigen binding fragment thereof according to any of Clauses 53 to 65 and Clause 67, 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. 013, or a first nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 013,
- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 170, 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. 170,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 266, 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. 266,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 368, 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. 368,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 439, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 439,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 584, 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. 584,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 662, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 662,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 663, 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. 663,

- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 664, 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. 664,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 665, 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. 665,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 666, or an eleventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 666, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 667, 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. 667.

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.

5

Clause 75:

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

10

Clause 76:

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

15

Clause 77:

An inhaler device comprising the composition of Clause 70.

Clause 78:

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

20

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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30

DESCRIPTION OF THE DRAWINGS

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

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: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, at day -1. At day 0, animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Lines are nudged relative to the Y-axis to improve visual representation.

Figure 2. Survival after lethal challenge – Antibody according to the invention.

Kaplan-Meier survival curves of the intranasal prophylactic treatment group. Animals (n=10 per group), treated with a dose titration with the antibody having heavy chain CDR1 as SEQ ID NO: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, at day -1. At day 0, animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Lines are nudged relative to the Y-axis to improve visual representation.

Figure 3. Bodyweight change – Antibody according to the invention.

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: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, at day -1 intranasally. At day 0 animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Bars represent the 95% CI. Of the mean. If a mouse died / was euthanized during follow-up of the study, the last observed bodyweight was carried forward.

Figure 4. Bodyweight change – Antibody according to the invention.

Bodyweight change (%) relative to day 0, for the intranasal 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: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, at day -1 intranasally. At day 0 animals were infected with $10^{3.5}$ TCID₅₀ of SARS-CoV-2 Delta. A vehicle control group was included (PBS). Bars represent the 95% CI. Of the mean. If a mouse died / was euthanized during follow-up of the study, the last observed bodyweight was carried forward.

Figure 5. Survival and bodyweight change for the intranasal administration – Antibodies according to the invention

Survival and bodyweight change for the intranasal administration of two parental antibodies and a bispecific antibody according to invention in a pre-exposure efficacy study in K18-hACE2 mice upon lethal SARS-CoV-2 Delta challenge. Animals (n=8 per group) were treated with a dose titration of either the Parental mAb 1 (Figure 5A-5C), Parental mAb 2 (Figure 5D-5F) or bispecific antibody (Figure 5G-5I) at Day -1 intranasally. At day 0 animals were infected with $10^{3.5}$ TCID₅₀ of SARS CoV-2 Delta. A vehicle control group (n=10) was included (PBS). Figures 5A, 5D, 5G: Kaplan-Meier survival curves of the treatment groups is shown. Lines are nudged relative to the Y-axis to improve visual representation. Figures 5B, 5E, 5H: Bodyweight change (%) relative to day 0 is shown. Error bars represent the mean with 95% confidence interval (CI). If a mouse died/ was euthanized during follow-up of the study, the last observed bodyweight was carried forward. Figure 5C, 5F, 5I: The survival dose response curves using Probit regression. The vehicle control group was included in the modelling at a dose of 0 mg/kg. The 95% pointwise fiducial confidence intervals for the predicted dose are indicated. Asterisk indicates significance compared to vehicle control group.

Figure 6. Linear epitope mapping against Spike fusion peptide domain of alpha and beta coronaviruses

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 and paratope hotspots for the antibody against the fusion peptide domain of SARS-CoV-2. Heavy and light chain CDRs 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.

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

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

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

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

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

Therapeutic treatment

The term '**therapeutic treatment**', as used herein, includes reference to treatment of a
10 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.

15

Coronavirus

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

20 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.

25

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,
30 preferably two or more, preferably three or more, preferably four or more, even more preferably five or more coronavirus subtypes.

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

Coronavirus infection

The term ‘**coronavirus infection**’, as used herein, includes reference to the pathological 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 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 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

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

The term ‘**individual**’, as used herein, includes reference to a mammal or human that is subject to, or a risk of suffering from viral infection. Infection may take place in any system, tissue or cell belonging to the host, including the host’s microbiome. Coronavirus

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

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).

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 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 method or antibody for use of the invention, are individuals with an elevated risk of coronavirus infection, individuals with an elevated risk of developing severe symptoms (illness), for example COVID-19, and/or individuals with an elevated risk of dying from

COVID-19. The person skilled in the art is aware of the risk factors for an elevated risk of coronavirus infection, an elevated risk of developing severe symptoms of coronavirus infection, and an elevated risk of dying from coronavirus infection.

5 **Antibody**

The term '**antibody**', as used herein, includes reference to an intact immunoglobulin, including monoclonal antibodies, such as chimeric, humanized or human monoclonal antibodies, or to a binding molecule comprising an antigen-binding domain (such as heavy chain CDRs 1-3 of a variable domain) of an antibody as disclosed herein or an antibody
10 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
15 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 subdivided
20 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
25 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
30 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
5 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,
10 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
15 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
20 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
25 as disclosed herein.

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

30 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.

15

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

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.

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

30 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.

- 5 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
- 10 inhibiting viral egress from cells. Neutralization does not specify the method of neutralization. Preferably, the antibody is cross-neutralizing, which includes reference to the ability of the antibodies of the invention to bind a set of different molecules, preferably different molecules of different subtypes belonging to the Coronaviridae family.
- 15 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.

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

20 SARS-CoV-2, and/or the stem helix of a coronavirus, in particular SARS-CoV-2 and its variants of concern. The phrases “antigen-binding fragments”, “antigen binding fragments”, “antigen fragment”, “a fragment of an antibody” or “antigen-binding molecule” as used herein, can be used interchangeably. For instance, the phrase “antigen binding fragments” as used herein is to be used interchangeably with the phrase “antibody fragments” as used herein.

30

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

IgG antibody

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

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

IgA antibody

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

Preferably, the antibody is an IgA antibody.

IgM antibody

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

Preferably, the antibody is an IgM antibody.

Anti-Coronavirus antibody

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

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

A composition

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

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

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
15 salts, for example sodium chloride. The composition of the invention may further comprise one or more buffering agents, for example sodium acetate. The composition of the invention may further comprise one or more carbohydrates, such as sucrose, or other active ingredients, such as other antibodies, neuraminidase inhibitors, endonuclease inhibitors, and adjuvants such as oils, cytokines, emulsifiers, or combinations thereof. The
20 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.

Mucosal composition

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

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

Mucosally

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

Preferably, the antibodies of the invention are administered mucosally.

Intranasally

The term 'intranasally', as used herein, may also be referred to as 'nasal administration', and includes reference to a route of administration in which a drug is provided into the upper respiratory tract and/or lower respiratory tract, preferably through the nostrils, as part of a prophylactic and/or therapeutic treatment as disclosed herein. Preferably, the administration provides for drug in the nasal cavity. The back section of the nasal cavity is 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 pressurized metered-dose inhaler (pMDI) to administer drugs through the buccal cavity during the nasal expiratory phase. Such methods allow the drug particles to enter the nasal cavities through the pharynx.

25

Preferably, the antibodies of the invention are administered intranasally.

With intranasal administration, a drug is provided through the nostrils to the upper respiratory tract as part of a prophylactic and/or therapeutic treatment as disclosed herein. Preferably, the administration provides for drug in the nasal cavity. Nasal 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

30

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

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

10 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
15 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.

20 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).

25 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.

30

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.

5 **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.
10 Oropharyngeal administration may, for example, be used for drugs in their powdered form and drugs in the form of liquid droplets or aerosols.

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

15

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.

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

Preferably, the antibody as disclosed is administered to an individual up to 48 hours prior to coronavirus exposure, for example between zero and 48 hours before the individual has
25 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
30 more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 4 days, or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 5 days or more prior to coronavirus exposure. In a preferred embodiment, the antibody is administered 6 days or more prior to coronavirus exposure.

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

Dosage

5 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
10 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).

15 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
20 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.

25

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
30 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).

5 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.

Use in a method for treatment

10 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.

15 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.

20 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.

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.

25

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

30 An antibody as disclosed herein comprises a preferred heavy chain CDR1 sequence comprising any one of the following SEQ ID NO: 006 to 011, 013 to 018, 022 to 027, 033 to 038, 053 to 058, 063 to 068. A CDR comprising the amino acid sequence SEQ ID NO: 013 is especially preferred.

An antibody as disclosed herein comprises a preferred heavy chain CDR2 sequence comprising any one of the following SEQ ID NO: 082 to 087, 093 to 098, 115 to 120, 126 to 131, 170 to 175, 191 to 196. A CDR comprising the amino acid sequence SEQ ID NO:
5 170 is especially preferred.

An antibody as disclosed herein comprises a preferred heavy chain CDR3 sequence comprising any one of the following SEQ ID NO: 202 to 207, 213 to 218, 266 to 271, 277 to 282, 299 to 304, 310 to 315. A CDR comprising the amino acid sequence SEQ ID NO:
10 266 is especially preferred.

An antibody as disclosed herein comprises a preferred light chain CDR1 sequence comprising any one of the following SEQ ID NO: 321 to 326, 353 to 358, 364 to 369, 386 to 391, 408 to 413, 430 to 435. A CDR comprising the amino acid sequence SEQ ID NO:
15 386 is especially preferred.

An antibody as disclosed herein comprises a preferred light chain CDR2 sequence comprising any one of the following SEQ ID NO: 439 to 444, 450 to 455, 461 to 466, 472 to 477, 489 to 494, 523 to 528. A CDR comprising the amino acid sequence SEQ ID NO:
20 439 is especially preferred.

An antibody as disclosed herein comprises a preferred light chain CDR3 sequence comprising any one of the following SEQ ID NO: 534 to 539, 545 to 550, 556 to 561, 584 to 589, 613 to 618, 634 to 639. A CDR comprising the amino acid sequence SEQ ID NO:
25 584 is especially preferred.

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: 642.

30 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: 643.

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: 644.

5 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: 645.

In a preferred embodiment, the heavy chain variable domain of said antibody comprises – a heavy chain framework region FR1 of SEQ ID NO: 642, a heavy chain framework region FR2 of SEQ ID NO: 643, a heavy chain framework region FR3 of SEQ ID NO: 644,
10 and/or a heavy chain framework region FR4 of SEQ ID NO: 645, preferably all said heavy chain heavy chain framework regions FR1 to FR4.

An antibody as disclosed herein comprises a heavy chain variable domain that further comprises at least a light chain framework region FR1 of SEQ ID NO: 646.
15

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: 647.

An antibody as disclosed herein comprises a heavy chain variable domain that further
20 comprises at least a light chain framework region FR3 of SEQ ID NO: 648.

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: 649.

25 In a preferred embodiment, the light chain variable domain of said antibody comprises – a heavy chain framework region FR1 of SEQ ID NO: 646, a light chain framework region FR2 of SEQ ID NO: 647, a light chain framework region FR3 of SEQ ID NO: 648, and/or a light chain framework region FR4 of SEQ ID NO: 649, preferably all said light chain framework regions are FR1 to FR4.

30 Most preferably, an antibody as disclosed herein comprises a heavy chain variable domain having the sequence of SEQ ID NO: 640 and/or a light chain variable domain having the sequence of SEQ ID NO: 641.

In treatment methods of the invention, the heavy chain variable domain (VH) of the antibody is preferably indicated as SEQ ID NO:640. In treatment methods or compositions of the invention, the light chain variable domain (VL) of the antibody is preferably indicated as SEQ ID NO:641. In treatment methods or compositions of the invention, the antibody can be an antibody as disclosed herein, or a binding molecule comprising an antigen-binding domain such as a variable domain (V) thereof.

Preferably, an antibody as disclosed herein comprises a heavy chain variable domain having the sequence of SEQ ID NO:640 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, more preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions.

Preferably, an antibody as disclosed herein comprises a light chain variable domain having the sequence of SEQ ID NO:641 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, more preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions.

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

SEQUENCES

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

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

	SEQ ID NO.: 001	DTFS
	SEQ ID NO.: 002	DTFSD
	SEQ ID NO.: 003	DTFSDY
10	SEQ ID NO.: 004	DTFSDYR
	SEQ ID NO.: 005	DTFSDYRI
	SEQ ID NO.: 006	DTFSDYRIH
	SEQ ID NO.: 007	DTFSDYRIHW
	SEQ ID NO.: 008	DTFSDYRIHWV
15	SEQ ID NO.: 009	DTFSDYRIHWVR
	SEQ ID NO.: 010	DTFSDYRIHWVRQ
	SEQ ID NO.: 011	DTFSDYRIHWVRQA
	SEQ ID NO.: 012	DYRI
	SEQ ID NO.: 013	DYRIH
20	SEQ ID NO.: 014	DYRIHW
	SEQ ID NO.: 015	DYRIHWV
	SEQ ID NO.: 016	DYRIHWVR
	SEQ ID NO.: 017	DYRIHWVRQ
	SEQ ID NO.: 018	DYRIHWVRQA
25	SEQ ID NO.: 019	FSDY
	SEQ ID NO.: 020	FSDYR
	SEQ ID NO.: 021	FSDYRI
	SEQ ID NO.: 022	FSDYRIH
	SEQ ID NO.: 023	FSDYRIHW
30	SEQ ID NO.: 024	FSDYRIHWV
	SEQ ID NO.: 025	FSDYRIHWVR

	SEQ ID NO.: 026	FSDYRIHWVRQ
	SEQ ID NO.: 027	FSDYRIHWVRQA
	SEQ ID NO.: 028	GDTFS
	SEQ ID NO.: 029	GDTFSD
5	SEQ ID NO.: 030	GDTFSDY
	SEQ ID NO.: 031	GDTFSDYR
	SEQ ID NO.: 032	GDTFSDYRI
	SEQ ID NO.: 033	GDTFSDYRIH
	SEQ ID NO.: 034	GDTFSDYRIHW
10	SEQ ID NO.: 035	GDTFSDYRIHWV
	SEQ ID NO.: 036	GDTFSDYRIHWVR
	SEQ ID NO.: 037	GDTFSDYRIHWVRQ
	SEQ ID NO.: 038	GDTFSDYRIHWVRQA
	SEQ ID NO.: 039	HWVR
15	SEQ ID NO.: 040	HWVRQ
	SEQ ID NO.: 041	HWVRQA
	SEQ ID NO.: 042	IHWV
	SEQ ID NO.: 043	IHWVR
	SEQ ID NO.: 044	IHWVRQ
20	SEQ ID NO.: 045	IHWVRQA
	SEQ ID NO.: 046	RIHW
	SEQ ID NO.: 047	RIHWV
	SEQ ID NO.: 048	RIHWVR
	SEQ ID NO.: 049	RIHWVRQ
25	SEQ ID NO.: 050	RIHWVRQA
	SEQ ID NO.: 051	SDYR
	SEQ ID NO.: 052	SDYRI
	SEQ ID NO.: 053	SDYRIH
	SEQ ID NO.: 054	SDYRIHW
30	SEQ ID NO.: 055	SDYRIHWV

	SEQ ID NO.: 056	SDYRIHWVR
	SEQ ID NO.: 057	SDYRIHWVRQ
	SEQ ID NO.: 058	SDYRIHWVRQA
	SEQ ID NO.: 059	TFSD
5	SEQ ID NO.: 060	TFSDY
	SEQ ID NO.: 061	TFSDYR
	SEQ ID NO.: 062	TFSDYRI
	SEQ ID NO.: 063	TFSDYRIH
	SEQ ID NO.: 064	TFSDYRIHW
10	SEQ ID NO.: 065	TFSDYRIHWV
	SEQ ID NO.: 066	TFSDYRIHWVR
	SEQ ID NO.: 067	TFSDYRIHWVRQ
	SEQ ID NO.: 068	TFSDYRIHWVRQA
	SEQ ID NO.: 069	WVRQ
15	SEQ ID NO.: 070	WVRQA
	SEQ ID NO.: 071	YRIH
	SEQ ID NO.: 072	YRIHW
	SEQ ID NO.: 073	YRIHWV
	SEQ ID NO.: 074	YRIHWVR
20	SEQ ID NO.: 075	YRIHWVRQ
	SEQ ID NO.: 076	YRIHWVRQA

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

25	SEQ ID NO.: 077	EWMGRMNPKSGDTNFA
	SEQ ID NO.: 078	EWMGRMNPKSGDTNFAQ
	SEQ ID NO.: 079	EWMGRMNPKSGDTNFAQK
	SEQ ID NO.: 080	EWMGRMNPKSGDTNFAQKF
	SEQ ID NO.: 081	EWMGRMNPKSGDTNFAQKFQ
30	SEQ ID NO.: 082	EWMGRMNPKSGDTNFAQKFQG
	SEQ ID NO.: 083	EWMGRMNPKSGDTNFAQKFQGR

	SEQ ID NO.: 084	EWMGRMNPKSGDTNFAQKFQGRV
	SEQ ID NO.: 085	EWMGRMNPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 086	EWMGRMNPKSGDTNFAQKFQGRVTM
	SEQ ID NO.: 087	EWMGRMNPKSGDTNFAQKFQGRVTMT
5	SEQ ID NO.: 088	GRMNPKSGDTNFA
	SEQ ID NO.: 089	GRMNPKSGDTNFAQ
	SEQ ID NO.: 090	GRMNPKSGDTNFAQK
	SEQ ID NO.: 091	GRMNPKSGDTNFAQKF
	SEQ ID NO.: 092	GRMNPKSGDTNFAQKFQ
10	SEQ ID NO.: 093	GRMNPKSGDTNFAQKFQG
	SEQ ID NO.: 094	GRMNPKSGDTNFAQKFQGR
	SEQ ID NO.: 095	GRMNPKSGDTNFAQKFQGRV
	SEQ ID NO.: 096	GRMNPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 097	GRMNPKSGDTNFAQKFQGRVTM
15	SEQ ID NO.: 098	GRMNPKSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 099	KSGDTNFA
	SEQ ID NO.: 100	KSGDTNFAQ
	SEQ ID NO.: 101	KSGDTNFAQK
	SEQ ID NO.: 102	KSGDTNFAQKF
20	SEQ ID NO.: 103	KSGDTNFAQKFQ
	SEQ ID NO.: 104	KSGDTNFAQKFQG
	SEQ ID NO.: 105	KSGDTNFAQKFQGR
	SEQ ID NO.: 106	KSGDTNFAQKFQGRV
	SEQ ID NO.: 107	KSGDTNFAQKFQGRVT
25	SEQ ID NO.: 108	KSGDTNFAQKFQGRVTM
	SEQ ID NO.: 109	KSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 110	LEWMGRMNPKSGDTNFA
	SEQ ID NO.: 111	LEWMGRMNPKSGDTNFAQ
	SEQ ID NO.: 112	LEWMGRMNPKSGDTNFAQK
30	SEQ ID NO.: 113	LEWMGRMNPKSGDTNFAQKF

	SEQ ID NO.: 114	LEWMGRMNPKSGDTNFAQKFQ
	SEQ ID NO.: 115	LEWMGRMNPKSGDTNFAQKFQG
	SEQ ID NO.: 116	LEWMGRMNPKSGDTNFAQKFQGR
	SEQ ID NO.: 117	LEWMGRMNPKSGDTNFAQKFQGRV
5	SEQ ID NO.: 118	LEWMGRMNPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 119	LEWMGRMNPKSGDTNFAQKFQGRVTM
	SEQ ID NO.: 120	LEWMGRMNPKSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 121	MGRMNPKSGDTNFA
	SEQ ID NO.: 122	MGRMNPKSGDTNFAQ
10	SEQ ID NO.: 123	MGRMNPKSGDTNFAQK
	SEQ ID NO.: 124	MGRMNPKSGDTNFAQKF
	SEQ ID NO.: 125	MGRMNPKSGDTNFAQKFQ
	SEQ ID NO.: 126	MGRMNPKSGDTNFAQKFQG
	SEQ ID NO.: 127	MGRMNPKSGDTNFAQKFQGR
15	SEQ ID NO.: 128	MGRMNPKSGDTNFAQKFQGRV
	SEQ ID NO.: 129	MGRMNPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 130	MGRMNPKSGDTNFAQKFQGRVTM
	SEQ ID NO.: 131	MGRMNPKSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 132	MNPKSGDTNFA
20	SEQ ID NO.: 133	MNPKSGDTNFAQ
	SEQ ID NO.: 134	MNPKSGDTNFAQK
	SEQ ID NO.: 135	MNPKSGDTNFAQKF
	SEQ ID NO.: 136	MNPKSGDTNFAQKFQ
	SEQ ID NO.: 137	MNPKSGDTNFAQKFQG
25	SEQ ID NO.: 138	MNPKSGDTNFAQKFQGR
	SEQ ID NO.: 139	MNPKSGDTNFAQKFQGRV
	SEQ ID NO.: 140	MNPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 141	MNPKSGDTNFAQKFQGRVTM
	SEQ ID NO.: 142	MNPKSGDTNFAQKFQGRVTMT
30	SEQ ID NO.: 143	NPKSGDTNFA

	SEQ ID NO.: 144	NPKSGDTNFAQ
	SEQ ID NO.: 145	NPKSGDTNFAQK
	SEQ ID NO.: 146	NPKSGDTNFAQKF
	SEQ ID NO.: 147	NPKSGDTNFAQKFQ
5	SEQ ID NO.: 148	NPKSGDTNFAQKFQG
	SEQ ID NO.: 149	NPKSGDTNFAQKFQGR
	SEQ ID NO.: 150	NPKSGDTNFAQKFQGRV
	SEQ ID NO.: 151	NPKSGDTNFAQKFQGRVT
	SEQ ID NO.: 152	NPKSGDTNFAQKFQGRVTM
10	SEQ ID NO.: 153	NPKSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 154	PKSGDTNFA
	SEQ ID NO.: 155	PKSGDTNFAQ
	SEQ ID NO.: 156	PKSGDTNFAQK
	SEQ ID NO.: 157	PKSGDTNFAQKF
15	SEQ ID NO.: 158	PKSGDTNFAQKFQ
	SEQ ID NO.: 159	PKSGDTNFAQKFQG
	SEQ ID NO.: 160	PKSGDTNFAQKFQGR
	SEQ ID NO.: 161	PKSGDTNFAQKFQGRV
	SEQ ID NO.: 162	PKSGDTNFAQKFQGRVT
20	SEQ ID NO.: 163	PKSGDTNFAQKFQGRVTM
	SEQ ID NO.: 164	PKSGDTNFAQKFQGRVTMT
	SEQ ID NO.: 165	RMNPKSGDTNFA
	SEQ ID NO.: 166	RMNPKSGDTNFAQ
	SEQ ID NO.: 167	RMNPKSGDTNFAQK
25	SEQ ID NO.: 168	RMNPKSGDTNFAQKF
	SEQ ID NO.: 169	RMNPKSGDTNFAQKFQ
	SEQ ID NO.: 170	RMNPKSGDTNFAQKFQG
	SEQ ID NO.: 171	RMNPKSGDTNFAQKFQGR
	SEQ ID NO.: 172	RMNPKSGDTNFAQKFQGRV
30	SEQ ID NO.: 173	RMNPKSGDTNFAQKFQGRVT

SEQ ID NO.: 174 RMNPKSGDTNFAQKFQGRVTM
SEQ ID NO.: 175 RMNPKSGDTNFAQKFQGRVTMT
SEQ ID NO.: 176 SGDTNFAQ
SEQ ID NO.: 177 SGDTNFAQK
5 SEQ ID NO.: 178 SGDTNFAQKF
SEQ ID NO.: 179 SGDTNFAQKFQ
SEQ ID NO.: 180 SGDTNFAQKFQG
SEQ ID NO.: 181 SGDTNFAQKFQGR
SEQ ID NO.: 182 SGDTNFAQKFQGRV
10 SEQ ID NO.: 183 SGDTNFAQKFQGRVT
SEQ ID NO.: 184 SGDTNFAQKFQGRVTM
SEQ ID NO.: 185 SGDTNFAQKFQGRVTMT
SEQ ID NO.: 186 WMGRMNPKSGDTNFA
SEQ ID NO.: 187 WMGRMNPKSGDTNFAQ
15 SEQ ID NO.: 188 WMGRMNPKSGDTNFAQK
SEQ ID NO.: 189 WMGRMNPKSGDTNFAQKF
SEQ ID NO.: 190 WMGRMNPKSGDTNFAQKFQ
SEQ ID NO.: 191 WMGRMNPKSGDTNFAQKFQG
SEQ ID NO.: 192 WMGRMNPKSGDTNFAQKFQGR
20 SEQ ID NO.: 193 WMGRMNPKSGDTNFAQKFQGRV
SEQ ID NO.: 194 WMGRMNPKSGDTNFAQKFQGRVT
SEQ ID NO.: 195 WMGRMNPKSGDTNFAQKFQGRVTM
SEQ ID NO.: 196 WMGRMNPKSGDTNFAQKFQGRVTMT

25 **Heavy chain CDR3 region (SEQ ID NO:197 to SEQ ID NO:315)**

SEQ ID NO.: 197 ASLLIVGGFDPL
SEQ ID NO.: 198 ASLLIVGGFDPLD
SEQ ID NO.: 199 ASLLIVGGFDPLDD
30 SEQ ID NO.: 200 ASLLIVGGFDPLDDF
SEQ ID NO.: 201 ASLLIVGGFDPLDDFE

	SEQ ID NO.: 202	ASLLIVGGFDPLDDFEV
	SEQ ID NO.: 203	ASLLIVGGFDPLDDFEVW
	SEQ ID NO.: 204	ASLLIVGGFDPLDDFEVWG
	SEQ ID NO.: 205	ASLLIVGGFDPLDDFEVWGQ
5	SEQ ID NO.: 206	ASLLIVGGFDPLDDFEVWGQG
	SEQ ID NO.: 207	ASLLIVGGFDPLDDFEVWGQGT
	SEQ ID NO.: 208	CASLLIVGGFDPL
	SEQ ID NO.: 209	CASLLIVGGFDPLD
	SEQ ID NO.: 210	CASLLIVGGFDPLDD
10	SEQ ID NO.: 211	CASLLIVGGFDPLDDF
	SEQ ID NO.: 212	CASLLIVGGFDPLDDFE
	SEQ ID NO.: 213	CASLLIVGGFDPLDDFEV
	SEQ ID NO.: 214	CASLLIVGGFDPLDDFEVW
	SEQ ID NO.: 215	CASLLIVGGFDPLDDFEVWG
15	SEQ ID NO.: 216	CASLLIVGGFDPLDDFEVWGQ
	SEQ ID NO.: 217	CASLLIVGGFDPLDDFEVWGQG
	SEQ ID NO.: 218	CASLLIVGGFDPLDDFEVWGQGT
	SEQ ID NO.: 219	GFDPLDD
	SEQ ID NO.: 220	GFDPLDDF
20	SEQ ID NO.: 221	GFDPLDDFE
	SEQ ID NO.: 222	GFDPLDDFEV
	SEQ ID NO.: 223	GFDPLDDFEVW
	SEQ ID NO.: 224	GFDPLDDFEVWG
	SEQ ID NO.: 225	GFDPLDDFEVWGQ
25	SEQ ID NO.: 226	GFDPLDDFEVWGQG
	SEQ ID NO.: 227	GFDPLDDFEVWGQGT
	SEQ ID NO.: 228	GGFDPL
	SEQ ID NO.: 229	GGFDPLD
	SEQ ID NO.: 230	GGFDPLDD
30	SEQ ID NO.: 231	GGFDPLDDF

	SEQ ID NO.: 232	GGFDPLDDFE
	SEQ ID NO.: 233	GGFDPLDDFEV
	SEQ ID NO.: 234	GGFDPLDDFEVW
	SEQ ID NO.: 235	GGFDPLDDFEVWG
5	SEQ ID NO.: 236	GGFDPLDDFEVWGQ
	SEQ ID NO.: 237	GGFDPLDDFEVWGQG
	SEQ ID NO.: 238	GGFDPLDDFEVWGQGT
	SEQ ID NO.: 239	IVGGFDPL
	SEQ ID NO.: 240	IVGGFDPLD
10	SEQ ID NO.: 241	IVGGFDPLDD
	SEQ ID NO.: 242	IVGGFDPLDDF
	SEQ ID NO.: 243	IVGGFDPLDDFE
	SEQ ID NO.: 244	IVGGFDPLDDFEV
	SEQ ID NO.: 245	IVGGFDPLDDFEVW
15	SEQ ID NO.: 246	IVGGFDPLDDFEVWG
	SEQ ID NO.: 247	IVGGFDPLDDFEVWGQ
	SEQ ID NO.: 248	IVGGFDPLDDFEVWGQG
	SEQ ID NO.: 249	IVGGFDPLDDFEVWGQGT
	SEQ ID NO.: 250	LIVGGFDPL
20	SEQ ID NO.: 251	LIVGGFDPLD
	SEQ ID NO.: 252	LIVGGFDPLDD
	SEQ ID NO.: 253	LIVGGFDPLDDF
	SEQ ID NO.: 254	LIVGGFDPLDDFE
	SEQ ID NO.: 255	LIVGGFDPLDDFEV
25	SEQ ID NO.: 256	LIVGGFDPLDDFEVW
	SEQ ID NO.: 257	LIVGGFDPLDDFEVWG
	SEQ ID NO.: 258	LIVGGFDPLDDFEVWGQ
	SEQ ID NO.: 259	LIVGGFDPLDDFEVWGQG
	SEQ ID NO.: 260	LIVGGFDPLDDFEVWGQGT
30	SEQ ID NO.: 261	LLIVGGFDPL

	SEQ ID NO.: 262	LLIVGGFDPLD
	SEQ ID NO.: 263	LLIVGGFDPLDD
	SEQ ID NO.: 264	LLIVGGFDPLDDF
	SEQ ID NO.: 265	LLIVGGFDPLDDFE
5	SEQ ID NO.: 266	LLIVGGFDPLDDFEV
	SEQ ID NO.: 267	LLIVGGFDPLDDFEVW
	SEQ ID NO.: 268	LLIVGGFDPLDDFEVWG
	SEQ ID NO.: 269	LLIVGGFDPLDDFEVWGQ
	SEQ ID NO.: 270	LLIVGGFDPLDDFEVWGQG
10	SEQ ID NO.: 271	LLIVGGFDPLDDFEVWGQGT
	SEQ ID NO.: 272	SLLIVGGFDPL
	SEQ ID NO.: 273	SLLIVGGFDPLD
	SEQ ID NO.: 274	SLLIVGGFDPLDD
	SEQ ID NO.: 275	SLLIVGGFDPLDDF
15	SEQ ID NO.: 276	SLLIVGGFDPLDDFE
	SEQ ID NO.: 277	SLLIVGGFDPLDDFEV
	SEQ ID NO.: 278	SLLIVGGFDPLDDFEVW
	SEQ ID NO.: 279	SLLIVGGFDPLDDFEVWG
	SEQ ID NO.: 280	SLLIVGGFDPLDDFEVWGQ
20	SEQ ID NO.: 281	SLLIVGGFDPLDDFEVWGQG
	SEQ ID NO.: 282	SLLIVGGFDPLDDFEVWGQGT
	SEQ ID NO.: 283	VGGFDPL
	SEQ ID NO.: 284	VGGFDPLD
	SEQ ID NO.: 285	VGGFDPLDD
25	SEQ ID NO.: 286	VGGFDPLDDF
	SEQ ID NO.: 287	VGGFDPLDDFE
	SEQ ID NO.: 288	VGGFDPLDDFEV
	SEQ ID NO.: 289	VGGFDPLDDFEVW
	SEQ ID NO.: 290	VGGFDPLDDFEVWG
30	SEQ ID NO.: 291	VGGFDPLDDFEVWGQ

SEQ ID NO.: 292 VGGFDPLDDFEVWGQG
SEQ ID NO.: 293 VGGFDPLDDFEVWGQGT
SEQ ID NO.: 294 YCASLLIVGGFDPL
SEQ ID NO.: 295 YCASLLIVGGFDPLD
5 SEQ ID NO.: 296 YCASLLIVGGFDPLDD
SEQ ID NO.: 297 YCASLLIVGGFDPLDDF
SEQ ID NO.: 298 YCASLLIVGGFDPLDDFE
SEQ ID NO.: 299 YCASLLIVGGFDPLDDFEV
SEQ ID NO.: 300 YCASLLIVGGFDPLDDFEVW
10 SEQ ID NO.: 301 YCASLLIVGGFDPLDDFEVWG
SEQ ID NO.: 302 YCASLLIVGGFDPLDDFEVWGQ
SEQ ID NO.: 303 YCASLLIVGGFDPLDDFEVWGQG
SEQ ID NO.: 304 YCASLLIVGGFDPLDDFEVWGQGT
SEQ ID NO.: 305 YYCASLLIVGGFDPL
15 SEQ ID NO.: 306 YYCASLLIVGGFDPLD
SEQ ID NO.: 307 YYCASLLIVGGFDPLDD
SEQ ID NO.: 308 YYCASLLIVGGFDPLDDF
SEQ ID NO.: 309 YYCASLLIVGGFDPLDDFE
SEQ ID NO.: 310 YYCASLLIVGGFDPLDDFEV
20 SEQ ID NO.: 311 YYCASLLIVGGFDPLDDFEVW
SEQ ID NO.: 312 YYCASLLIVGGFDPLDDFEVWG
SEQ ID NO.: 313 YYCASLLIVGGFDPLDDFEVWGQ
SEQ ID NO.: 314 YYCASLLIVGGFDPLDDFEVWGQG
SEQ ID NO.: 315 YYCASLLIVGGFDPLDDFEVWGQGT

25

Light chain CDR1 region (SEQ ID NO:316 to SEQ ID NO:435)

SEQ ID NO.: 316 CSGTSSDVGG
SEQ ID NO.: 317 CSGTSSDVGGY
30 SEQ ID NO.: 318 CSGTSSDVGGYN
SEQ ID NO.: 319 CSGTSSDVGGYNF

	SEQ ID NO.: 320	CSGTSSDVGGYNFV
	SEQ ID NO.: 321	CSGTSSDVGGYNFVS
	SEQ ID NO.: 322	CSGTSSDVGGYNFVSW
	SEQ ID NO.: 323	CSGTSSDVGGYNFVSWY
5	SEQ ID NO.: 324	CSGTSSDVGGYNFVSWYQ
	SEQ ID NO.: 325	CSGTSSDVGGYNFVSWYQH
	SEQ ID NO.: 326	CSGTSSDVGGYNFVSWYQHH
	SEQ ID NO.: 327	DVGGY
	SEQ ID NO.: 328	DVGGYN
10	SEQ ID NO.: 329	DVGGYNF
	SEQ ID NO.: 330	DVGGYNFV
	SEQ ID NO.: 331	DVGGYNFVS
	SEQ ID NO.: 332	DVGGYNFVSW
	SEQ ID NO.: 333	DVGGYNFVSWY
15	SEQ ID NO.: 334	DVGGYNFVSWYQ
	SEQ ID NO.: 335	DVGGYNFVSWYQH
	SEQ ID NO.: 336	DVGGYNFVSWYQHH
	SEQ ID NO.: 337	GTSSDVGG
	SEQ ID NO.: 338	GTSSDVGGY
20	SEQ ID NO.: 339	GTSSDVGGYN
	SEQ ID NO.: 340	GTSSDVGGYNF
	SEQ ID NO.: 341	GTSSDVGGYNFV
	SEQ ID NO.: 342	GTSSDVGGYNFVS
	SEQ ID NO.: 343	GTSSDVGGYNFVSW
25	SEQ ID NO.: 344	GTSSDVGGYNFVSWY
	SEQ ID NO.: 345	GTSSDVGGYNFVSWYQ
	SEQ ID NO.: 346	GTSSDVGGYNFVSWYQH
	SEQ ID NO.: 347	GTSSDVGGYNFVSWYQHH
	SEQ ID NO.: 348	ISCSGTSSDVGG
30	SEQ ID NO.: 349	ISCSGTSSDVGGY

	SEQ ID NO.: 350	ISCSGTSSDVGGYN
	SEQ ID NO.: 351	ISCSGTSSDVGGYNF
	SEQ ID NO.: 352	ISCSGTSSDVGGYNFV
	SEQ ID NO.: 353	ISCSGTSSDVGGYNFVS
5	SEQ ID NO.: 354	ISCSGTSSDVGGYNFVSW
	SEQ ID NO.: 355	ISCSGTSSDVGGYNFVSWY
	SEQ ID NO.: 356	ISCSGTSSDVGGYNFVSWYQ
	SEQ ID NO.: 357	ISCSGTSSDVGGYNFVSWYQH
	SEQ ID NO.: 358	ISCSGTSSDVGGYNFVSWYQHH
10	SEQ ID NO.: 359	SCSGTSSDVGG
	SEQ ID NO.: 360	SCSGTSSDVGGY
	SEQ ID NO.: 361	SCSGTSSDVGGYN
	SEQ ID NO.: 362	SCSGTSSDVGGYNF
	SEQ ID NO.: 363	SCSGTSSDVGGYNFV
15	SEQ ID NO.: 364	SCSGTSSDVGGYNFVS
	SEQ ID NO.: 365	SCSGTSSDVGGYNFVSW
	SEQ ID NO.: 366	SCSGTSSDVGGYNFVSWY
	SEQ ID NO.: 367	SCSGTSSDVGGYNFVSWYQ
	SEQ ID NO.: 368	SCSGTSSDVGGYNFVSWYQH
20	SEQ ID NO.: 369	SCSGTSSDVGGYNFVSWYQHH
	SEQ ID NO.: 370	SDVGG
	SEQ ID NO.: 371	SDVGGY
	SEQ ID NO.: 372	SDVGGYN
	SEQ ID NO.: 373	SDVGGYNF
25	SEQ ID NO.: 374	SDVGGYNFV
	SEQ ID NO.: 375	SDVGGYNFVS
	SEQ ID NO.: 376	SDVGGYNFVSW
	SEQ ID NO.: 377	SDVGGYNFVSWY
	SEQ ID NO.: 378	SDVGGYNFVSWYQ
30	SEQ ID NO.: 379	SDVGGYNFVSWYQH

	SEQ ID NO.: 380	SDVGGYNFVSWYQHH
	SEQ ID NO.: 381	SGTSSDVGG
	SEQ ID NO.: 382	SGTSSDVGGY
	SEQ ID NO.: 383	SGTSSDVGGYN
5	SEQ ID NO.: 384	SGTSSDVGGYNF
	SEQ ID NO.: 385	SGTSSDVGGYNFV
	SEQ ID NO.: 386	SGTSSDVGGYNFVS
	SEQ ID NO.: 387	SGTSSDVGGYNFVSW
	SEQ ID NO.: 388	SGTSSDVGGYNFVSWY
10	SEQ ID NO.: 389	SGTSSDVGGYNFVSWYQ
	SEQ ID NO.: 390	SGTSSDVGGYNFVSWYQH
	SEQ ID NO.: 391	SGTSSDVGGYNFVSWYQHH
	SEQ ID NO.: 392	SSDVGG
	SEQ ID NO.: 393	SSDVGGY
15	SEQ ID NO.: 394	SSDVGGYN
	SEQ ID NO.: 395	SSDVGGYNF
	SEQ ID NO.: 396	SSDVGGYNFV
	SEQ ID NO.: 397	SSDVGGYNFVS
	SEQ ID NO.: 398	SSDVGGYNFVSW
20	SEQ ID NO.: 399	SSDVGGYNFVSWY
	SEQ ID NO.: 400	SSDVGGYNFVSWYQ
	SEQ ID NO.: 401	SSDVGGYNFVSWYQH
	SEQ ID NO.: 402	SSDVGGYNFVSWYQHH
	SEQ ID NO.: 403	TISCSGTSSDVGG
25	SEQ ID NO.: 404	TISCSGTSSDVGGY
	SEQ ID NO.: 405	TISCSGTSSDVGGYN
	SEQ ID NO.: 406	TISCSGTSSDVGGYNF
	SEQ ID NO.: 407	TISCSGTSSDVGGYNFV
	SEQ ID NO.: 408	TISCSGTSSDVGGYNFVS
30	SEQ ID NO.: 409	TISCSGTSSDVGGYNFVSW

	SEQ ID NO.: 410	TISCSGTSSDVGGYNFVSWY
	SEQ ID NO.: 411	TISCSGTSSDVGGYNFVSWYQ
	SEQ ID NO.: 412	TISCSGTSSDVGGYNFVSWYQH
	SEQ ID NO.: 413	TISCSGTSSDVGGYNFVSWYQHH
5	SEQ ID NO.: 414	TSSDVGG
	SEQ ID NO.: 415	TSSDVGGY
	SEQ ID NO.: 416	TSSDVGGYN
	SEQ ID NO.: 417	TSSDVGGYNF
	SEQ ID NO.: 418	TSSDVGGYNFV
10	SEQ ID NO.: 419	TSSDVGGYNFVS
	SEQ ID NO.: 420	TSSDVGGYNFVSW
	SEQ ID NO.: 421	TSSDVGGYNFVSWY
	SEQ ID NO.: 422	TSSDVGGYNFVSWYQ
	SEQ ID NO.: 423	TSSDVGGYNFVSWYQH
15	SEQ ID NO.: 424	TSSDVGGYNFVSWYQHH
	SEQ ID NO.: 425	VTISCSGTSSDVGG
	SEQ ID NO.: 426	VTISCSGTSSDVGGY
	SEQ ID NO.: 427	VTISCSGTSSDVGGYN
	SEQ ID NO.: 428	VTISCSGTSSDVGGYNF
20	SEQ ID NO.: 429	VTISCSGTSSDVGGYNFV
	SEQ ID NO.: 430	VTISCSGTSSDVGGYNFVS
	SEQ ID NO.: 431	VTISCSGTSSDVGGYNFVSW
	SEQ ID NO.: 432	VTISCSGTSSDVGGYNFVSWY
	SEQ ID NO.: 433	VTISCSGTSSDVGGYNFVSWYQ
25	SEQ ID NO.: 434	VTISCSGTSSDVGGYNFVSWYQH
	SEQ ID NO.: 435	VTISCSGTSSDVGGYNFVSWYQHH

Light chain CDR2 region (SEQ ID NO:436 to SEQ ID NO:528)

30	SEQ ID NO.: 436	EVTK
	SEQ ID NO.: 437	EVTKR

	SEQ ID NO.: 438	EVTKRP
	SEQ ID NO.: 439	EVTKRPS
	SEQ ID NO.: 440	EVTKRPSG
	SEQ ID NO.: 441	EVTKRPSGV
5	SEQ ID NO.: 442	EVTKRPSGVP
	SEQ ID NO.: 443	EVTKRPSGVPD
	SEQ ID NO.: 444	EVTKRPSGVPDR
	SEQ ID NO.: 445	ILIYEV
	SEQ ID NO.: 446	ILIYEVT
10	SEQ ID NO.: 447	ILIYEVTK
	SEQ ID NO.: 448	ILIYEVTKR
	SEQ ID NO.: 449	ILIYEVTKRP
	SEQ ID NO.: 450	ILIYEVTKRPS
	SEQ ID NO.: 451	ILIYEVTKRPSG
15	SEQ ID NO.: 452	ILIYEVTKRPSGV
	SEQ ID NO.: 453	ILIYEVTKRPSGVP
	SEQ ID NO.: 454	ILIYEVTKRPSGVPD
	SEQ ID NO.: 455	ILIYEVTKRPSGVPDR
	SEQ ID NO.: 456	IYEV
20	SEQ ID NO.: 457	IYEVT
	SEQ ID NO.: 458	IYEVTK
	SEQ ID NO.: 459	IYEVTKR
	SEQ ID NO.: 460	IYEVTKRP
	SEQ ID NO.: 461	IYEVTKRPS
25	SEQ ID NO.: 462	IYEVTKRPSG
	SEQ ID NO.: 463	IYEVTKRPSGV
	SEQ ID NO.: 464	IYEVTKRPSGVP
	SEQ ID NO.: 465	IYEVTKRPSGVPD
	SEQ ID NO.: 466	IYEVTKRPSGVPDR
30	SEQ ID NO.: 467	KILIYEV

	SEQ ID NO.: 468	KILIYEVT
	SEQ ID NO.: 469	KILIYEVTK
	SEQ ID NO.: 470	KILIYEVTKR
	SEQ ID NO.: 471	KILIYEVTKRP
5	SEQ ID NO.: 472	KILIYEVTKRPS
	SEQ ID NO.: 473	KILIYEVTKRPSG
	SEQ ID NO.: 474	KILIYEVTKRPSGV
	SEQ ID NO.: 475	KILIYEVTKRPSGVP
	SEQ ID NO.: 476	KILIYEVTKRPSGVPD
10	SEQ ID NO.: 477	KILIYEVTKRPSGVPDR
	SEQ ID NO.: 478	KRPS
	SEQ ID NO.: 479	KRPSG
	SEQ ID NO.: 480	KRPSGV
	SEQ ID NO.: 481	KRPSGVP
15	SEQ ID NO.: 482	KRPSGVPD
	SEQ ID NO.: 483	KRPSGVPDR
	SEQ ID NO.: 484	LIYEV
	SEQ ID NO.: 485	LIYEVT
	SEQ ID NO.: 486	LIYEVTK
20	SEQ ID NO.: 487	LIYEVTKR
	SEQ ID NO.: 488	LIYEVTKRP
	SEQ ID NO.: 489	LIYEVTKRPS
	SEQ ID NO.: 490	LIYEVTKRPSG
	SEQ ID NO.: 491	LIYEVTKRPSGV
25	SEQ ID NO.: 492	LIYEVTKRPSGVP
	SEQ ID NO.: 493	LIYEVTKRPSGVPD
	SEQ ID NO.: 494	LIYEVTKRPSGVPDR
	SEQ ID NO.: 495	PSGV
	SEQ ID NO.: 496	PSGVP
30	SEQ ID NO.: 497	PSGVPD

	SEQ ID NO.: 498	PSGVPDR
	SEQ ID NO.: 499	RPSG
	SEQ ID NO.: 500	RPSGV
	SEQ ID NO.: 501	RPSGVP
5	SEQ ID NO.: 502	RPSGVPD
	SEQ ID NO.: 503	RPSGVPDR
	SEQ ID NO.: 504	TKRP
	SEQ ID NO.: 505	TKRPS
	SEQ ID NO.: 506	TKRPSG
10	SEQ ID NO.: 507	TKRPSGV
	SEQ ID NO.: 508	TKRPSGVP
	SEQ ID NO.: 509	TKRPSGVPD
	SEQ ID NO.: 510	TKRPSGVPDR
	SEQ ID NO.: 511	VTKR
15	SEQ ID NO.: 512	VTKRP
	SEQ ID NO.: 513	VTKRPS
	SEQ ID NO.: 514	VTKRPSG
	SEQ ID NO.: 515	VTKRPSGV
	SEQ ID NO.: 516	VTKRPSGVP
20	SEQ ID NO.: 517	VTKRPSGVPD
	SEQ ID NO.: 518	VTKRPSGVPDR
	SEQ ID NO.: 519	YEV
	SEQ ID NO.: 520	YEVTK
	SEQ ID NO.: 521	YEVTKR
25	SEQ ID NO.: 522	YEVTKRP
	SEQ ID NO.: 523	YEVTKRPS
	SEQ ID NO.: 524	YEVTKRPSG
	SEQ ID NO.: 525	YEVTKRPSGV
	SEQ ID NO.: 526	YEVTKRPSGVP
30	SEQ ID NO.: 527	YEVTKRPSGVPD

SEQ ID NO.: 528 YEVTKRPSGVPDR

Light chain CDR3 region (SEQ ID NO:529 to SEQ ID NO:639)

5 SEQ ID NO.: 529 ADYYCSSYGG
SEQ ID NO.: 530 ADYYCSSYGGT
SEQ ID NO.: 531 ADYYCSSYGGTN
SEQ ID NO.: 532 ADYYCSSYGGTNN
SEQ ID NO.: 533 ADYYCSSYGGTNNL
10 SEQ ID NO.: 534 ADYYCSSYGGTNNLL
SEQ ID NO.: 535 ADYYCSSYGGTNNLLF
SEQ ID NO.: 536 ADYYCSSYGGTNNLLFG
SEQ ID NO.: 537 ADYYCSSYGGTNNLLFGG
SEQ ID NO.: 538 ADYYCSSYGGTNNLLFGGG
15 SEQ ID NO.: 539 ADYYCSSYGGTNNLLFGGGT
SEQ ID NO.: 540 CSSYGG
SEQ ID NO.: 541 CSSYGGT
SEQ ID NO.: 542 CSSYGGTN
SEQ ID NO.: 543 CSSYGGTNN
20 SEQ ID NO.: 544 CSSYGGTNNL
SEQ ID NO.: 545 CSSYGGTNNLL
SEQ ID NO.: 546 CSSYGGTNNLLF
SEQ ID NO.: 547 CSSYGGTNNLLFG
SEQ ID NO.: 548 CSSYGGTNNLLFGG
25 SEQ ID NO.: 549 CSSYGGTNNLLFGGG
SEQ ID NO.: 550 CSSYGGTNNLLFGGGT
SEQ ID NO.: 551 DYYCSSYGG
SEQ ID NO.: 552 DYYCSSYGGT
SEQ ID NO.: 553 DYYCSSYGGTN
30 SEQ ID NO.: 554 DYYCSSYGGTNN
SEQ ID NO.: 555 DYYCSSYGGTNNL

	SEQ ID NO.: 556	DYYCSSYGGTNNLL
	SEQ ID NO.: 557	DYYCSSYGGTNNLLF
	SEQ ID NO.: 558	DYYCSSYGGTNNLLFG
	SEQ ID NO.: 559	DYYCSSYGGTNNLLFGG
5	SEQ ID NO.: 560	DYYCSSYGGTNNLLFGGG
	SEQ ID NO.: 561	DYYCSSYGGTNNLLFGGGT
	SEQ ID NO.: 562	GGTN
	SEQ ID NO.: 563	GGTNN
	SEQ ID NO.: 564	GGTNNL
10	SEQ ID NO.: 565	GGTNNLL
	SEQ ID NO.: 566	GGTNNLLF
	SEQ ID NO.: 567	GGTNNLLFG
	SEQ ID NO.: 568	GGTNNLLFGG
	SEQ ID NO.: 569	GGTNNLLFGGG
15	SEQ ID NO.: 570	GGTNNLLFGGGT
	SEQ ID NO.: 571	GTNN
	SEQ ID NO.: 572	GTNNL
	SEQ ID NO.: 573	GTNNLL
	SEQ ID NO.: 574	GTNNLLF
20	SEQ ID NO.: 575	GTNNLLFG
	SEQ ID NO.: 576	GTNNLLFGG
	SEQ ID NO.: 577	GTNNLLFGGG
	SEQ ID NO.: 578	GTNNLLFGGGT
	SEQ ID NO.: 579	SSYGG
25	SEQ ID NO.: 580	SSYGGT
	SEQ ID NO.: 581	SSYGGTN
	SEQ ID NO.: 582	SSYGGTNN
	SEQ ID NO.: 583	SSYGGTNNL
	SEQ ID NO.: 584	SSYGGTNNLL
30	SEQ ID NO.: 585	SSYGGTNNLLF

	SEQ ID NO.: 586	SSYG GTNNLLFG
	SEQ ID NO.: 587	SSYG GTNNLLFGG
	SEQ ID NO.: 588	SSYG GTNNLLFGGG
	SEQ ID NO.: 589	SSYG GTNNLLFGGGT
5	SEQ ID NO.: 590	SYGG
	SEQ ID NO.: 591	SYGGT
	SEQ ID NO.: 592	SYGGTN
	SEQ ID NO.: 593	SYGGTNN
	SEQ ID NO.: 594	SYGGTNNL
10	SEQ ID NO.: 595	SYGGTNNLL
	SEQ ID NO.: 596	SYGGTNNLLF
	SEQ ID NO.: 597	SYGGTNNLLFG
	SEQ ID NO.: 598	SYGGTNNLLFGG
	SEQ ID NO.: 599	SYGGTNNLLFGGG
15	SEQ ID NO.: 600	SYGGTNNLLFGGGT
	SEQ ID NO.: 601	TNNL
	SEQ ID NO.: 602	TNNLL
	SEQ ID NO.: 603	TNNLLF
	SEQ ID NO.: 604	TNNLLFG
20	SEQ ID NO.: 605	TNNLLFGG
	SEQ ID NO.: 606	TNNLLFGGG
	SEQ ID NO.: 607	TNNLLFGGGT
	SEQ ID NO.: 608	YCSSYGG
	SEQ ID NO.: 609	YCSSYGGT
25	SEQ ID NO.: 610	YCSSYGGTN
	SEQ ID NO.: 611	YCSSYGGTNN
	SEQ ID NO.: 612	YCSSYGGTNNL
	SEQ ID NO.: 613	YCSSYGGTNNLL
	SEQ ID NO.: 614	YCSSYGGTNNLLF
30	SEQ ID NO.: 615	YCSSYGGTNNLLFG

SEQ ID NO.: 616 YCSSYGGTNNLLFGG
SEQ ID NO.: 617 YCSSYGGTNNLLFGGG
SEQ ID NO.: 618 YCSSYGGTNNLLFGGGT
SEQ ID NO.: 619 YGGT
5 SEQ ID NO.: 620 YGGTN
SEQ ID NO.: 621 YGGTNN
SEQ ID NO.: 622 YGGTNNL
SEQ ID NO.: 623 YGGTNNLL
SEQ ID NO.: 624 YGGTNNLLF
10 SEQ ID NO.: 625 YGGTNNLLFG
SEQ ID NO.: 626 YGGTNNLLFGG
SEQ ID NO.: 627 YGGTNNLLFGGG
SEQ ID NO.: 628 YGGTNNLLFGGGT
SEQ ID NO.: 629 YYCSSYGG
15 SEQ ID NO.: 630 YYCSSYGGT
SEQ ID NO.: 631 YYCSSYGGTN
SEQ ID NO.: 632 YYCSSYGGTNN
SEQ ID NO.: 633 YYCSSYGGTNNL
SEQ ID NO.: 634 YYCSSYGGTNNLL
20 SEQ ID NO.: 635 YYCSSYGGTNNLLF
SEQ ID NO.: 636 YYCSSYGGTNNLLFG
SEQ ID NO.: 637 YYCSSYGGTNNLLFGG
SEQ ID NO.: 638 YYCSSYGGTNNLLFGGG
SEQ ID NO.: 639 YYCSSYGGTNNLLFGGGT

25

Heavy chain variable domain (SEQ ID NO: 640)

QMQLMQSGAEVKKPGASVTVSCKASGDTFSDYRIHWVRQAPGQGLEWMGRMNPKS
GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
VWGQGTMTVISS

30

Light chain variable domain (SEQ ID NO: 641)

QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNFVSWYQHHPGKAPKILIYEVTKRPS
GVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVL

Heavy chain FR1 region (SEQ ID NO:642)

5 SEQ ID NO:642 QMQLMQSGAEVKKPGASVTVSCKASGDTFS

Heavy chain FR2 region (SEQ ID NO:643)

SEQ ID NO:643 WVRQAPGQGLEWMG

10 **Heavy chain FR3 region (SEQ ID NO:644)**

SEQ ID NO:644 RVTMTRDMSINTAYMTLSGLTFDDTALYYCAS

Heavy chain FR4 region (SEQ ID NO:645)

SEQ ID NO:645 WGQGTMTVISS

15

Light chain FR1 region (SEQ ID NO:646)

SEQ ID NO:646 QSALTQPPSASGSPGQSVTISC

Light chain FR2 region (SEQ ID NO:647)

20 SEQ ID NO:647 WYQHHPGKAPKILY

Light chain FR3 region (SEQ ID NO:648)

SEQ ID NO:648 GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC

25

Light chain FR4 region (SEQ ID NO:649)

SEQ ID NO:649 FGGGTKLTVL

Heavy chain CDR1 region (SEQ ID NO:650)

5 SEQ ID NO.: 650 YFYLH

Heavy chain CDR2 region (SEQ ID NO: 651)

SEQ ID NO.: 651 IINPRGDGTRYAQKFQG

10 **Heavy chain CDR3 region (SEQ ID NO: 652)**

SEQ ID NO.: 652 GADHGAFDI

Light chain CDR1 region (SEQ ID NO: 653)

SEQ ID NO.: 653 RASQSVRRNYFA

15

Light chain CDR2 region (SEQ ID NO: 654)

SEQ ID NO.: 654 DASTRAT

Light chain CDR3 region (SEQ ID NO: 655)

20 SEQ ID NO.: 655 QQYDSSPPMYI

Heavy chain CDR1 region (SEQ ID NO: 656)

SEQ ID NO.: 656 GYAMH

25 **Heavy chain CDR2 region (SEQ ID NO: 657)**

SEQ ID NO.: 657 VISRDARNKYYADSVKG

Heavy chain CDR3 region (SEQ ID NO: 658)

SEQ ID NO.: 658 LIIPGITEPGSPDALDI

30

Light chain CDR1 region (SEQ ID NO: 659)

SEQ ID NO.: 659 RASQDISKWLA

Light chain CDR2 region (SEQ ID NO: 660)

SEQ ID NO.: 660 AASSLQS

5

Light chain CDR3 region (SEQ ID NO: 661)

SEQ ID NO.: 661 QQASSFPWSIT

Heavy chain CDR1 region (SEQ ID NO: 662)

10 SEQ ID NO.: 662 SHYMH

Heavy chain CDR2 region (SEQ ID NO: 663)

SEQ ID NO.: 663 IINPSGSGTAYGQKFQG

15 **Heavy chain CDR3 region (SEQ ID NO: 664)**

SEQ ID NO.: 664 GSGGLFAY

Light chain CDR1 region (SEQ ID NO: 665)

SEQ ID NO.: 665 RASQIVRSNYLA

20

Light chain CDR2 region (SEQ ID NO: 666)

SEQ ID NO.: 666 GASSRAT

Light chain CDR3 region (SEQ ID NO: 667)

25 SEQ ID NO.: 667 LQYDSSPPTYI

Heavy chain CDR1 region (SEQ ID NO: 668)

SEQ ID NO.: 668 SYMH

Heavy chain CDR2 region (SEQ ID NO: 669)

SEQ ID NO.: 669 LITPSGDDTYYAQRFQG

Heavy chain CDR3 region (SEQ ID NO: 670)

5 SEQ ID NO.: 670 MSRAGGFVDV

Light chain CDR1 region (SEQ ID NO: 671)

SEQ ID NO.: 671 RASQSITGRYLA

10 **Light chain CDR2 region (SEQ ID NO: 672)**

SEQ ID NO.: 672 GESSRVT

Light chain CDR3 region (SEQ ID NO: 673)

SEQ ID NO.: 673 QHFASSPPTYT

15 **Heavy chain (SEQ ID NO: 674)**

SEQ ID NO.: 674

QEQLVQSGAEVKKPGASVKVSCKSSGFTFSYFYLHWVRQAPGQGLEWMGIIN
PRGDGTRYAQKFQGRVTMTRDASTGTLYMELRSLRSEDVAVYYCARGADHGAFDIW
GQGTMTVTSSASVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL
20 QSGNSQESVTEQDSKDSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR
GECDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVCTLPSPRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQP
ENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
25 SPGK

Light chain (SEQ ID NO: 675)

SEQ ID NO.: 675

EIVLTQSPGTLSPGERATLSCRASQSVRRNYFAWYQQKRGQAPRLLIYDASTRATG
30 IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSSPPMYIFGQGTKLEIKSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

Heavy chain of arm (SEQ ID NO: 676)

SEQ ID NO.: 676

QMQLMQSGAEVKKPGASVTVSCKASGDTFSDYRIHWVRQAPGQGLEWMGRMNPKS
5 GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
VWGQGTMTVISSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
10 KTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K

Light chain of arm (SEQ ID NO: 677)

15 SEQ ID NO.: 677

QSALTQPPSASGSPGQSVTISCSTSSDVGGYNFVSWYQHHPGKAPKILYEVTKRPS
GVPDFRFGSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVLGQPKA
APSVTLFPSSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN
NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

20

Heavy chain arm (SEQ ID NO: 678)

SEQ ID NO.: 678

QEQLVQSGAEVKKPGASVKVSCKSSGFTFSYFYLHWVRQAPGQGLEWMGIINPRGD
GTRYAQKFQGRVTMTRDASTGTLYMELRSLRSEDVAVYYCARGADHGAFDIWGQGT
25 MVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTTP
30 PVLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Light chain arm (SEQ ID NO: 679)

SEQ ID NO.: 679

EIVLTQSPGTLSSLSPGERATLSCRASQSVRRNYFAWYQQKRGQAPRLLIYDASTRATG
 IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDSSPPMYIFGQGTKLEIKRTVAAPS
 VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
 TYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

5

Heavy chain of arm (SEQ ID NO: 680)

SEQ ID NO.: 680

QMQLMQSGAEVKKPGASVTVSCKASGDTFSDYRIHWVRQAPGQGLEWMGRMNPKS
 GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
 10 VWGQGTMTVISGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS
 SPVKAGVETTTTPSKQSNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT
 ECSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
 NWWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
 PIEKTISKAKGQPREPQVCTLPISRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPE
 15 NNYKTTTPVLDSGSEFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
 PGK

Light chain of arm (SEQ ID NO: 681)

SEQ ID NO.: 681

QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNFVSWYQHHPGKAPKILYEVTKRPS
 20 GVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVLSSAST
 KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
 LYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

Heavy chain of arm (SEQ ID NO: 682)

SEQ ID NO.: 682

QSALTQPPSASGSPGQSVTISCSGTSSDVGGYNFVSWYQHHPGKAPKILYEVTKRPS
 GVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYGGTNNLLFGGGTKLTVLGQPKA
 APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSN
 30 NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECSDKTHTCPPCPAPEL
 LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWWYVDGVEVHNAKTK
 PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ

VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLVSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

Light chain o (SEQ ID NO: 683)

5 SEQ ID NO.: 683

QMQLMQSGAEVKKPGASVTVSCKASGDTFSDYRIHWVRQAPGQGLEWMGRMNPKS
GDTNFAQKFQGRVTMTRDMSINTAYMTLSGLTFDDTALYYCASLLIVGGFDPLDDFE
VWQGQTMVTISSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

10

Heavy chain variable domain arm (SEQ ID NO: 684)

SEQ ID NO.: 684

QVQLVESGGGVVQPGRSLRLSCAASGLTFSGYAMHWVRQAPGKGLEWVAVISR
DAR NKYYADSVKGRFTISRDNSSKKTIVYLEMNSLRVEDTAVYYCAILIPGITEPGSPDALDI
15 WGQGTMTVS

Light chain variable domain (SEQ ID NO: 685)

SEQ ID NO.: 685

DIQMTQSPSSMSASVGDRVTITCRASQDISKWLAWYQQRPGKAPKLLIYAASSLQSGV
20 PSRFGSGSGTDFTLTISSQLPEDFATYYCQQASSFPWSITFGQGTRLEIR

Heavy chain variable domain arm (SEQ ID NO: 686)

SEQ ID NO.: 686

QEQLVQSGAEVKKPGASVKVSCSSGFTFSYFYLHWVRQAPGQGLEWMGIINPRGD
25 GTRYAQKFQGRVTMTRDASTGTLYMELRSLRSEDVAVYYCARGADHGAFDIWGQGT
MVTVSS

Light chain variable domain (SEQ ID NO: 687)

SEQ ID NO.: 687

30 EIVLTQSPGTLSPGERATLSCRASQSVRRNYFAWYQQKRGQAPRLLIYDASTRATG
IPDRFSGSGSGTDFTLISRLEPEDFAVYYCQQYDSSPPMYIFGQGTKLEIK

Heavy chain variable domain arm (SEQ ID NO: 688)

SEQ ID NO.: 688

QVQLVQSGAEVKKPAASVKVSCASGDTFSSHYMHWVRQAPGQGPEWMGIINPSGS
 5 GTAYGQKFQGRLTMTRDTSTSTVYMELSSLTSDDTAVYYCGGGSGGLFAYWGQGTL
 VTVSS

Light chain variable domain (SEQ ID NO: 689)

SEQ ID NO.: 689

10 EIVLTQSPGTLSSLSPGERATLSCRASQIVRSNYLAWYQQKPGQAPRLLIYGASSRATGT
 PDRFSGGGSGTDFTLTINRLEPEDFAVYYCLQYDSSPPTYIFGQGTKLEIK

15 EXAMPLES**Example 1: Antibody according to the invention (Intraperitoneal)**

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: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as
 20 SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, 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
 25 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, which 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 a monoclonal antibody dilution.

5

The monoclonal antibody dilution was made up at various concentrations so that 200 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.

10

The antibody was stored at $-85^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and dilutions were stored at 4°C until usage and the temperature of the storage unit was monitored.

15

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

20

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. 16-21 g on day -5. 60 mice were used at the age of 8-9 weeks on the day of test article administration 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. Food and water were inspected daily and topped up as needed. Each animal was weighed daily beginning at the day of infection (Day 0).

30

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

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

5 **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 formulated assuming 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 μ L of antibody solution into the intraperitoneal cavity, mice were scruffed and held inverted at a -45 deg angle for administration (200 μ L per mouse). Mice in the vehicle group receiving PBS 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. 50uL of compound or vehicle control was then slowly administered to the nares of each mouse (25 μ L 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

5 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 $10^{3.5}$
10 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
15 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.

20

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.
25 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 $\alpha = 0.05$.

30

Survival

Prophylactic treatment with ≥ 0.5 mg/kg test antibody provided a statistically significant increase in survival compared to vehicle (See Figure 1). The animals that were treated with with 0.5 mg/kg had a 60% survival rate, with 1.7 and 5 mg/kg test antibody a 100% survival rate and with 10 mg/kg a rate of 90%. Whereas the control group showed 0% survival at day 7 with a median survival time of 6 days.

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

Body weight

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

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intraperitoneal administration of ≥ 0.5 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.

Example 2: Antibody according to the invention (Intranasal)

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

Animals (n=10 per group) were treated with an intranasal dose range of the test 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.

Materials and Methods

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

5

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 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.

- 10 The antibody was stored at $-85^{\circ}\text{C} \pm 10^{\circ}\text{C}$ 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.

15

Animals

The animal species used was the SARS-CoV-2 Delta K18 hACE2 Tg mouse model, at a weight of c. 16-22 g on the day of test article administration. 60 mice were used at the age of 8-9 weeks on the day of test article administration and were exclusively female. Ten
20 animals were allocated to 6 treatment groups based on Day -5 weights to create groups with similar 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
25 every 14 days. Food and water were inspected daily and topped up as needed.

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
30 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 at the test article dosing time, 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

5

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.

10

Antibody administration

The test antibody was stored at -80°C upon arrival. The appropriate dose, according to the treatment schedule (Table 2), was formulated based upon average weight per cage.

15

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. 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.

20

Virus administration

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
5 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
10 titrating replicate samples on Vero cells.

Terminal investigations

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

Data analysis and statistical methods

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

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

Survival

Prophylactic treatment with >0.5 mg/kg test antibody provided a statistically significant increase in survival compared to vehicle control (See Figure 2). Whereas the control group
30 showed 0% survival at Day 7 with a median survival time of 6 days.

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

Body weight

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

Conclusion

In this lethal SARS-CoV-2 Delta K18 hACE2 Tg mouse model, the prophylactic intranasal administration of ≥ 0.5 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 control group had died by day 7.

Example 3: Antibody according to the invention

The aim of this study is to assess the pre- and post- exposure efficacy of a monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584, following intranasal administration in a NHP model in which each subject is pre-screened for the absence of serum antibodies against SARS-CoV-2 viruses.

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

Materials and Methods

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

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

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.

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).

Samples are analyzed as required for viral quantification (by RT-PCR and / or TCID₅₀) and / or antibody titers and neutralization titers by ELISA, HPLC or similar method and in-vitro neutralization assay (e.g. Pseudovirion neutralization).

Animals

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

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 3: Intranasal experimental detail per antibody

Test group	Antibody	Admin. route	Dose (mg)	Day of admin.	No. of Animals
High dose		I.N.	2.0 – 10	-1	5 – 12

Low dose	As disclosed above.	I.N.	0.01 – 2.0	-1	5 – 12
Vehicle	---	I.N.	0	-1	5 – 12

The NHP subjects receive intranasal administrations with compositions comprising the antibody at a dose between 0.01 mg to 2.0 mg or 2.0 mg to 10 mg (Nominal Dose). On Day 0, all NHP subjects are challenged with a dose of the SARS-CoV-2 and observed for clinical
5 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)
10 according to the treatment schedule (Table 3), 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
15 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

20 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
25 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.

5 Conclusion

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

10

Example 4: 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
15 CDR1 as SEQ ID NO: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584 ("First Antibody"), and a second monoclonal antibody according to the invention, having a heavy chain CDR1 as SEQ ID NO: 656, heavy chain CDR2 as SEQ ID NO: 657, heavy chain CDR3 as SEQ ID NO: 658,
20 a light chain CDR1 as SEQ ID NO: 659, a light chain CDR2 as SEQ ID NO: 660, and a light chain CDR3 as SEQ ID NO: 661 ("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.

25 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

30 Materials and Methods

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

to the final concentration for administration ranging from 0.003 mg and 5 mg nominal dose, administered as 50 µL to 500 µL per nare.

5 The NHP subjects allocated to the Control Group (Sodium acetate buffer) are administered with vehicle (e.g. 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.

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

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

Animals

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

Study design

25 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 4: 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	4 – 12

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

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

10

Antibody administration

The antibody compositions (Treatment Groups 1 to 3) or vehicle only are administered to each nare (e.g. pipette or spray) according to the treatment schedule (Table 4), using volumes of between 50 µL to 500 µL per nare.

15

Virus administration

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

20

Data analysis and statistical methods

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

25

Results – Clinical Manifestations

Prophylactic treatment with treatments (as indicated in Table 4) 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 4) 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 4) according to the invention provides a reduction in
15 clinical manifestations and /or a reduction in virological measurements, as compared with control group NHPs and within treatments.

Example 5: Bi-specific antibody according to the invention

20 The aim of this intranasal murine study is to assess the pre- and post- exposure efficacy of a bispecific monoclonal antibody in comparison with the parental antibodies, according to the invention, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2, wherein the first Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 013, 170,
25 266, 386, 439 or 584; wherein the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 656, 657, 658, 659, 660 to 661.

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
30 above, or vehicle control at study day -1.

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
5 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.

10

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

25

Table 5: Intranasal experimental detail per antibody

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

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

5

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 5), using volumes of between 25 µL to 50 µL per nare.

10

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).

15

Laboratory analysis

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

20

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).

25

Data analysis and statistical methods

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

30

Combination index

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

Survival

Prophylactic treatment with Parental mAb 1, Parental mAb 2 or bispecific antibody (as indicated in Table 5) compared to the control group provides statistically significant protection against mortality and a significant improvement in survival time compared to the control group.

Body weight

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

Prophylactic treatment with the parental or bispecific antibodies (as indicated in Table 5) provides a statistically significant reduction in weight loss, compared to the control group.

Conclusion

In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of a bispecific antibody (as indicated in Table 5) according to the invention provides significant improvement in survival and a reduction in body weight loss compared with Control Group. The outcome of the combination index is suggestive of at least a comparable, an additive or potentially synergistic effect for the bispecific compared to the parental antibodies.

Example 5a: Bi-specific antibody according to the invention

The aim of this intranasal murine study was to assess the pre- and post- exposure efficacy of a bispecific monoclonal antibody in comparison with the parental antibodies, according

to the invention, having a first Fab capable of binding to the stem helix of SARS-CoV-2 and a second Fab capable of binding to the fusion peptide of SARS-CoV-2. The first parental antibody ("Parental mAb 1") has the following CDRs as described in SEQ ID Numbers: 013, 170, 266, 386, 439, and 584. The second parental antibody ("Parental mAb 2") has the following CDRs as described in SEQ ID Numbers: 650, 651, 652, 653, 654 and 655. The bi-specific antibody according to the invention has a first Fab that comprises a sequence comprising any one or more of SEQ ID Numbers: 013, 170, 266, 386, 439, and 584; the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 650, 651, 652, 653, 654 and 655.

Animals (n= 8 per group) were treated with an intranasal dose comprising either 0.007 mg/kg to 1.7 mg/kg (Parental mAb 1 or Parental mAb 2), or 0.002 mg/kg to 10 mg/kg (bispecific antibody) described above, or vehicle control at study Day -1.

Materials and Methods

The monoclonal parental antibodies and the bispecific antibody according to the invention were provided in a sodium acetate buffer (20mM Sodium Acetate, 75mM Sodium Chloride, 5% sucrose, pH 5.5) and the bispecific antibody according to the invention was provided in phosphate buffered saline (PBS) and all antibodies were diluted to the final concentration for administration ranging from either 0.007 mg/kg to 1.7 mg/kg (Parental mAb 1 or Parental mAb 2), or 0.002 mg/kg to 10 mg/kg (bispecific antibody), administered as 25 µL per nare.

The mice allocated to the control group were administered with vehicle (phosphate buffered saline, PBS), administered as 25 µL per nare.

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. 13.6- 22.6 g at Day 0. A total of 144 mice were used at the age of 7-11 weeks and were exclusively

female. Eight animals were allocated to 17 treatment groups to create groups with similar mean weight. Eight mice were allocated to a vehicle control group. 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).

Study design

The dose level of the parental antibodies and a combination thereof applied in the current example was based on previous experience with these antibodies intranasally showing protection IN at doses ≥ 0.5 mg/kg (Parental mAb 1) and ≥ 0.2 mg/kg (Parental mAb 2). The potency of the bispecific antibody of the two parental antibodies is expected to be similar, and one dose step up and down from the dose range for the parental antibodies was included for the bispecific antibody. A total number of 144 mice, 7-11 weeks of age, were allocated to 18 experimental groups according to Table 6 (see below). Mice were given a period of > 3 days for acclimatization.

Table 6: Intranasal experimental detail for parental antibodies and bispecific antibody.

Test group	Antibody	Dose (mg/kg)	Day of admin.	No. of Animals
1	Parental mAb 1	1.7	-1	8
2	Parental mAb 1	0.43	-1	8
3	Parental mAb 1	0.11	-1	8
4	Parental mAb 1	0.03	-1	8
5	Parental mAb 1	0.007	-1	8
6	Parental mAb 2	1.7	-1	8
7	Parental mAb 2	0.43	-1	8
8	Parental mAb 2	0.11	-1	8
9	Parental mAb 2	0.03	-1	8
10	Parental mAb 2	0.007	-1	8
11	Bispecific mAb	10	-1	8

12	Bispecific mAb	2.5	-1	8
13	Bispecific mAb	0.63	-1	8
14	Bispecific mAb	0.16	-1	8
15	Bispecific mAb	0.039	-1	8
16	Bispecific mAb	0.010	-1	8
17	Bispecific mAb	0.002	-1	8
Vehicle control	---	0	-1	8

The mice were treated via the intranasal route of administration with compositions comprising either parental antibodies or the bispecific antibody at dose ranges between 0.002 and 10 mg/kg. On Day 0, all mice were challenged with a dose of the SARS-CoV-2 and observed for survival and body weight until the end of the study (Day 14).

Antibody administration

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

Just prior to dosing, the material was drawn into a 1 mL syringe with a 26G needle, and then administered to each mouse. Mice were anaesthetized with isoflurane (4% v/v with 2 L/min O_2) for two minutes. The mice were then scruffed and held at a +45 deg angle. 50 μL of compound or vehicle control was then slowly administered to the nares of each mouse (25 μL each nare). The mice were held for an additional 5 to 10 seconds to ensure compound delivery to the lower respiratory tract before being put back into the home box.

Virus administration

The virus material was stored at $-80^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and was defrosted prior to administration. Once defrosted, the material was diluted in cold PBS corresponding to approximately $10^{3.5}$ TCID₅₀/ 50 μL . As required, the animals were anesthetized by isoflurane (4% v/v with 2 L/min O_2) and each animal received approximately 50 μL (25 μL each nare) of virus corresponding with approximately $10^{3.5}$ TCID₅₀ by intranasal inoculation.

Terminal investigations

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

5 Data analysis and statistical methods

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

Survival proportions at Day 14 were used to estimate the survival dose response curve using Probit regression without assuming a parallel dose response curve for the treatments. The model was used to estimate the median effective dose and the ratio between the treatments was determined.

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

20 Survival

The vehicle control group showed 0% survival with a median survival time of 7 days. Prophylactic intranasal treatment with ≥ 0.11 mg/kg of either parental antibody intranasally provided a statistically significant increase in survival compared to control group (See Figure 5A and 5D). Prophylactic treatment with ≥ 0.16 mg/kg of the bispecific antibody provides statistically significant increase in survival compared to control group (See Figure 5G).

Prophylactic intranasal treatment with ≥ 0.03 mg/kg of either parental antibody or ≥ 0.039 mg/kg of the bispecific antibody intranasally provides statistically significant increase in survival time compared to control group.

Survival dose response curves

The survival dose response curves were estimated using Probit regression without assuming a parallel dose response curve between treatments. The vehicle control group was included in the modelling at a dose of 0 mg/kg. The Probit regression model was used to estimate the antibody dose corresponding to 50% survival (ED₅₀) (see Table 7 and Figure 5C, 5F and 5I). The intranasal median effective dose was lowest for the bispecific antibody, with 0.013 mg/kg and both parental antibodies were within a 4-fold ratio and no significant difference in ED₅₀ compared to the bispecific antibody was determined.

Table 7: Estimated ED₅₀'s (in mg/kg, rounded to 3 decimals).

Treatment	ED₅₀ (mg/kg, 95% confidence interval (CI.))
Parental mAb 1	0.046 (0.012 – 0.169)
Parental mAb 2	0.023 (0.005 – 0.104)
Bispecific antibody	0.013 (0.004 – 0.040)

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 with the net AUC defined as the summation of the were a above and below the baseline using the percentage change per day.

Prophylactic intranasal treatment with ≥ 0.03 mg/kg of either parental antibody and ≥ 0.039 mg/kg of the bispecific antibody resulted in a significant reduction in weight loss compared to the control group (Figure 5B, 5E and 5H).

Conclusion

In this SARS-CoV-2 Delta mouse model, the prophylactic intranasal administration of a bispecific antibody (as indicated in Table 6) according to the invention at doses ≥ 0.16 mg/kg provides significant increases in survival and at doses ≥ 0.039 mg/kg a reduction

in body weight loss compared with control group. Moreover, median effective doses of the bispecific antibody were not significantly different to the parental antibodies (Table 7).

Example 6: 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: 013, heavy chain CDR2 as SEQ ID NO: 170, heavy chain CDR3 as SEQ ID NO: 266, a light chain CDR1 as SEQ ID NO: 386, a light chain CDR2 as SEQ ID NO: 439, and a light chain CDR3 as SEQ ID NO: 584. The second antibody ("Second mAb") having a heavy chain CDR1 as SEQ ID NO: 662, heavy chain CDR2 as SEQ ID NO: 663, heavy chain CDR3 as SEQ ID NO: 664, a light chain CDR1 as SEQ ID NO: 665, a light chain CDR2 as SEQ ID NO: 666, and a light chain CDR3 as SEQ ID NO: 667.

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 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

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

14	<u>Combination mAb (dose 6)</u>	<u>0.001-15</u> <u>(e.g. 5.0)</u>	<u>-1</u>	<u>6 – 10</u>
<u>Vehicle</u>	<u>---</u>	<u>0</u>	<u>-1</u>	<u>6 – 10</u>

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

Antibody administration

The First or Second antibodies or the composition comprising the combination or vehicle only is administered to each nare (e.g. pipette or spray) according to the treatment 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 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. 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).

5

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 calculation of the combination index.

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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 statistically significant protection against mortality and a significant improvement in survival time compared to the control group.

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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 composition comprising the combination (as indicated in Table 8) 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 the composition comprising the combination (as indicated in Table 8) 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

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at least a comparable, an additive or potentially synergistic effect for the combination compared to the First or Second antibodies administered alone.

Example 7: ELISA binding assessment of an antibody according to the invention

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

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

Table 10: ELISA EC₅₀ values (nM) for the antibody according to invention. N/D = no EC₅₀ value was determined, due to lack of binding

	CoV-2 Delta	CoV-2 XBB.1.5	NL63
Parental mAb 1	0.0014	1.2	0.00084
Anti - S1 antibody DZIF-10c	6.9	N/D	N/D
Anti - S1 antibody Imdevimab	0.010	N/D	N/D
isotype control	N/D	N/D	N/D

The ELISA binding assay (Table 10) shows 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. The anti-S1 antibodies tested only bound the SARS-CoV-2 Delta, as expected from literature and did not show breadth amongst alpha coronavirus NL63. The isotype control antibody did not show any binding to the coronavirus antigens.

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Example 8. Affinity binding assessment by MSD of an antibody according to the invention

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

	SARS-CoV-2	SARS-CoV-1	MERS-CoV	hCoV-OC43	hCoV-HKU1	hCoV-NL63	hCoV-229E	SARS-CoV-2 S1 RBD
Parental mAb 1	6.73	7.00	2.77	65.11	92.04	0.70	5.44	N/D
Anti-S1 mAb DZIF-10c	0.16	N/D	N/D	N/D	N/D	N/D	N/D	0.09
isotype control	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D

- 5 The MSD binding array (see Table 11) showed that the antibody was able to effectively bind Spike antigens from beta coronaviruses SARS-CoV-2, SARS-CoV-1, MERS, HKU1 and OC43. Alpha coronaviruses including 229E and NL63 were bound as well. The antibody did not bind the SARS-CoV-2 receptor binding domain (RBD) on the S1 part of the Spike used in this study. On the contrary, the anti-S1 antibody tested here bound well
- 10 the RBD domain and the wildtype SARS-CoV-2, as expected from literature and did not show breadth amongst other coronaviruses. This suggests that the antibody according to invention shows breadth in binding across all tested beta and alpha coronavirus Spikes, while the anti-RBD antibody only bound SARS-CoV-2 Spike and RBD domain. The isotype control did not show any binding to the coronavirus antigens

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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 = antibody concentration could not be determined.

	SARS-CoV-2	SARS-CoV-2 BA.1	SARS-CoV-2 BA.2.75	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
Parental mAb 1	7670	4349	10501	8726	10235	9696	10421	7638	6502	10134

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

The MSD binding array showed that the antibody according to invention can bind all Omicron variants tested in this assay at high concentrations up to 10 ng/ml (Table 12), therefore retaining activity among the tested Omicron mutants, as also confirmed for XBB.1.5 in the ELISA binding assay (Table 10). While the anti-S1 control antibody bound SARS-CoV-2 Spike at a lower concentration than the antibody according to invention, the earlier Omicron mutants were only bound at high extrapolated concentrations, indicating lower affinity for these mutants and the later Omicron mutants such as BQ.1 and XBB.1 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 negative isotype control antibody did not show any binding to the coronavirus antigens..

Example 9. Live virus neutralization of an antibody according to the invention

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

Table 13: Live virus neutralization assay. IC₅₀ values in µg/ml are displayed for the antibody according to invention against three different beta coronaviruses. A pooled

convalescent serum from SARS-CoV-2 patients was used as a comparator and SARS-CoV-2 positive control, MN₅₀ titers are shown. N/D = IC₅₀ could not be determined

Live virus neutralization	SARS-CoV-2 Wuhan	SARS-CoV-1	MERS-CoV
Parental mAb 1	39.92	15.80	38.94
SARS-CoV-2 pooled convalescent serum	142	N/D	N/D

- 5 Overall, the antibody according to invention was able to neutralize the tested viruses SARS-CoV-1, SARS-CoV-2 and MERS at varying concentrations (see Table 13), with the lowest IC₅₀ concentrations for SARS-CoV-1. This confirms that the antibody has neutralizing activity across these beta coronaviruses, as indicated by the binding assessment via MSD (Table 11). The positive serum control for SARS-CoV-2 requires a
10 high MN₅₀ titer.

Example 10. Pseudovirion neutralization of an antibody according to the invention

- 15 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
20 expression plasmids with the pHIV-1NL43 ΔEnv-NanoLuc reporter virus plasmid in HEK293T cells. Then, dilution series of the antibody were pre-incubated with the corresponding pseudovirus and then added to HEK 293T cells expressing ACE2, the entry receptor for SARS-CoV-2, SARS-CoV-1 and NL63. For hCoV 229E, the diluted antibody mixed with virus was added to Huh7 cells which express the aminopeptidase N (APN
25 receptor which facilitates entry of hCoV 229E into host cells. After incubation, cells were washed and lysed to measure the luciferase activity in cell lysates using the Nano-Glo Luciferase Assay System and GloMax system, with a readout of relative light units (RLUs). The 50% inhibitory concentrations (IC₅₀) were determined as the antibody concentration at which infectivity was inhibited by 50% using a four Parameter Logistic

Regression (4PL) curve fit. The bispecific antibody was tested for neutralizing activity in the range of 0.0042 to 250 µg/ml against SARS-CoV-1, SARS-CoV-2 Wuhan, Delta, Omicron BA4, Omicron BQ.1.1, Omicron XBB.1, hCoV NL63 and hCoV 229E.

- 5 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 the 95% normal range is shown.

	SARS-CoV-1	SARS-CoV-2 Wuhan	SARS-CoV-2 Delta	SARS-CoV-2 BA4	SARS-CoV-2 XBB.1	SARS-CoV-2 BQ.1.1	CoV 229E	CoV NL63
Parental mAb 1	10.058 (2.212-45.728)	0.068 (0.029-0.160)	0.488 (0.061-3.882)	7.563 (1.189-48.096)	20.619 (9.245-45.987)	10.090 (1.779-60.640)	1.946 (0.474-7.986)	3.880 (0.586-25.679)

- Overall, the antibody according to invention was able to neutralize all tested alpha and beta viruses at varying concentrations (see Table 14), with an overall trend of higher IC₅₀ concentrations for the Omicron variants. This indicates that the antibody according to invention shows neutralization breadth across alpha and beta coronaviruses, as expected based on the binding data.

15 Example 11. Epitope mapping of an antibody according to the invention

- 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 antibody. The library of peptides consists of overlapping 15-amino acid fragments, with an overlap of 14 amino acids. Binding of the antibody to each of the synthesized peptide chips was tested in an enzyme-linked immunosorbent assay (ELISA) assay via incubation of the peptide arrays with antibody solutions. After washing, peptide arrays were incubated with an antibody peroxidase conjugate and substrate was added, and the reaction was then stopped using hydrogen peroxide. Colour development was measured and intensity was reported.

The antibody according to invention bound the peptide array of alpha and beta coronaviruses in a specific epitope of a 10- 20 amino acids (see Figure 6). The method allowed for a high confidence in the epitope definition, with certain variance in the outer
5 areas of the epitope, indicated by asterisk for the respective strain.

Example 13. Affinity binding assessment by MSD of a bispecific antibody

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
10 antibody was tested in a multiplexed assay, Meso Scale Discovery (MSD), which uses electrochemiluminescent labels that were conjugated to detection antibodies.

The first parental antibody ("Parental mAb 1") has the following CDRs as described in SEQ ID Numbers: 013, 170, 266, 386, 439, and 584. The second parental antibody
15 ("Parental mAb 2") has the following CDRs as described in SEQ ID Numbers: 650, 651, 652, 653, 654, and 655. The bi-specific antibody according to the invention has a first Fab that comprises a sequence comprising any one or more of SEQ ID Numbers: 013, 170, 266, 386, 439, and 584; the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 650, 651, 652, 653, 654, and 655.

20 Three versions of bispecific antibodies have been produced and tested, all with the combination of the Parental mAb 1 and Parental mAb 2.

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
25 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- (current) chemi- (buffer substrate) luminescent (light) cascade is initiated which results in light emission. The intensity of emitted light is measured per spot, revealing
30 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 20), 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 21). 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 (ng/ml) corresponding to the midpoint of the dynamic range (that is, the range between the lower and upper limit of quantification, LLOQ and ULOQ) was reported.

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Table 20: Antibody concentrations corresponding to the midpoint of the dynamic range ($(\text{LOQ} + \text{ULOQ})/2$ ng/ml) for the bispecific antibodies compared to the parental antibodies against different SARS-CoV-2 Omicron variants. 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	6.73	7.00	2.77	65.11	92.04	0.70	5.44	N/D
Parental mAb 2	0.40	0.21	0.16	5.17	7.63	N/D	44.48	30.05
BISPECIFIC 1	1.10	0.70	0.43	10.64	14.1	2.98	22.36	30.19
BISPECIFIC 2	1.10	0.68	0.42	10.73	16.46	2.43	20.83	40.55
BISPECIFIC 3	1.19	0.80	0.48	10.11	16.01	2.58	23.12	25.70
Anti-S1 mAb DZIF-10c	0.16	N/D	N/D	N/D	N/D	N/D	N/D	0.09

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The MSD binding array (see Table 20) showed that the bispecific antibodies were able to effectively bind all Spike antigens from alpha and beta coronaviruses. Alpha coronavirus NL63 was not bound by the Parental mAb 2 anti-stem helix antibody, but only by the anti-fusion peptide Parental mAb 1 and the bispecific antibodies, albeit at slightly higher

concentrations than the Parental antibody 1. Alpha coronavirus 229E was bound by all tested antibodies, with lower concentrations for Parental mAb 1. The SARS-CoV-2 Spike RBD antigen was only bound at high concentrations by the Parental mAb 2 (stem-helix mAb) and the bispecific antibodies. The control anti-S1 mAb only bound SARS-CoV-2 Spike and RBD, at low concentrations. The data suggests that the bispecific antibodies retain the binding capacity from each parental antibody, here demonstrated by the ability to utilize the Fab arm of the Parental mAb 1 and retaining alpha coronavirus binding activity.

- Table 21: Antibody concentrations corresponding to the midpoint of the dynamic range (LOQ+ULOQ)/2 (pg/ml) for the bispecific antibodies compared to the Parental antibodies against different SARS-CoV-2 Omicron variants. N/D = antibody concentration could not be determined.

	SAR S- CoV- 2	SAR S- CoV- 2 BA.1	SARS- CoV-2 BA.2.75	SARS -CoV- 2 BA.5	SARS- CoV-2 BF.7	SAR S- CoV- 2 BN.1	SARS- CoV-2 BQ.1	SAR S- CoV- 2 BQ.1 .1	SARS -CoV- 2 XBB. 1	SARS- CoV-2 XBB.1. 5
Parental mAb 1	7670	4349	10501	8726	10235	9696	10421	7638	6502	10134
Parental mAb 2	842	169	229	263	238	182	303	269	215	321
BISPEC IFIC 1	690	121	162	169	172	130	209	182	161	215
BISPEC IFIC 2	1286	239	342	364	337	270	426	361	318	477
BISPEC IFIC 3	1173	196	281	304	275	233	365	308	269	394

- The MSD binding array (see Table 21) showed that the three bispecific antibodies were able to effectively bind all Spike antigens from SARS-CoV-2 Omicron variants at varying concentrations. While only the Parental mAb 2 retains efficient binding against later Omicron variants (< 1000 pg/ml) and the Parental mAb 1 requires high antibody concentrations, the bispecific antibodies retain binding at low concentrations, suggesting that the bispecific antibodies can leverage the Fab arm of Parental mAb 2.

Example 14: Live virus neutralization of a bispecific antibody

The objective of this study was to assess the ability of the bispecific antibody to neutralize live corona viruses and pseudovirions. The bispecific antibody was tested for functional activity in a live virus microneutralization assay against MERS, SARS-CoV-1, SARS-CoV-2 Wuhan, Delta and Omicron BA.4/5.

The first parental antibody (“Parental mAb 1”) has the following CDRs as described in SEQ ID Numbers:013, 170, 266, 386, 439, and 584. The second parental antibody (“Parental mAb 2”) has the following CDRs as described in SEQ ID Numbers: 650, 651, 652, 653, 654 and 655. The bispecific antibody according to the invention has a first Fab that comprises a sequence comprising any one or more of SEQ ID Numbers: 013, 170, 266, 386, 439, and 584; the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 650, 651, 652, 653, 654 and 655.

The bispecific antibody BISPECIFIC 1 comprises the first Fab and the second Fab as described above.

Briefly, dilution series of antibodies were pre-incubated with the corresponding virus and then added to the respective cell line (Vero: MERS and SARS-CoV-1, all other Vero E6 cells). After incubation, cells were fixed, stained with an anti-nucleocapsid antibody, and an enzymatically tagged and a detection antibody was added. Colored precipitate signaling nucleocapsid presence was read out via an Immunospot analyzer and 50% inhibitory concentration (IC₅₀), was reported. The bispecific antibody was tested for neutralizing activity in the range of 0.02 to 500 µg/ml compared to the individual control antibodies.

Table 22: Live virus neutralization assay. IC₅₀ values in ug/ml are displayed for against three different beta coronaviruses. Parental antibodies are assayed alongside the bispecific antibody as comparator.

	SARS-CoV-2 Wuhan	SARS-CoV-2 Delta	SARS-CoV-2 BA.4/5	SARS- CoV-1	MERS- CoV
BISPECIFIC 1	11.92	14.17	4.85	6.67	1.32

Parental mAb 2	6.44	14.77	2.92	4.18	0.86
Parental mAb 1	21.70	16.08	4.62	5.94	11.59

Overall, the bispecific antibody was able to neutralize the tested viruses SARS-CoV-1, SARS-CoV-2 Wuhan, Delta and Omicron BA.4/5 and MERS at varying concentrations (see Table 22). The anti-stem helix Parental antibody 2 was able to neutralize SARS-CoV-2 Wuhan and MERS at lower IC₅₀ concentrations compared to the anti-fusion peptide antibody Parental mAb 1, this trend was also observed for the bispecific antibody, indicating that the antibody can leverage the anti-stem helix Fab arm. For SARS-CoV-2 Delta, Omicron BA4.5 and SARS-CoV-1, the parental and the bispecific antibodies neutralize at similar IC₅₀ concentrations. Overall, this indicates that the bispecific antibody retains affinity from both parental Fab arms and retain neutralizing activity across tested beta coronaviruses.

Example 15: Pseudovirion neutralization of a bispecific antibody

The pseudovirion neutralization assay was performed against pseudotyped virus particles.

The first parental antibody (“Parental mAb 1”) has the following CDRs as described in SEQ ID Numbers: 013, 170, 266, 386, 439, and 584. The second parental antibody (“Parental mAb 2”) has the following CDRs as described in SEQ ID Numbers: 650, 651, 652, 653, 654 and 655. The bi-specific antibody according to the invention has a first Fab that comprises a sequence comprising any one or more of SEQ ID Numbers: 013, 170, 266, 386, 439, and 584; the second Fab comprises a sequence comprising any one or more of SEQ ID Numbers: 650, 651, 652, 653, 654 and 655.

The bispecific antibody BISPECIFIC 1 comprises the first Fab and the second Fab as described above.

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. Briefly, pseudovirions were produced by co-transfecting virus expression plasmids with the pHIV-1NL43 Δ Env-NanoLuc reporter virus plasmid in HEK293T cells. Then, dilution series of antibodies 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. 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. The 50% inhibitory concentrations (IC_{50}) were determined as the antibody 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 0.01 to 250 μ g/ml compared to the individual control antibodies against SARS-CoV-2 Wuhan, Delta, Omicron BA4/5, BQ.1 and XBB.1, hCoV NL63 and hCoV 229E.

Table 23: Pseudovirion neutralization assay. IC_{50} values in μ g/ml were displayed for the anti-stem helix and anti-fusion peptide antibodies against different beta coronaviruses. For multiple runs, the geometric mean with 95% normal range is shown.

	CoV-2 Wuhan	CoV-2 Delta	CoV-2 Omicron BA4/5	CoV-2 Omicron BQ.1	CoV-2 Omicron XBB.1.1
BISPECIFIC 1	0.000342	0.307	5.14	8.09	11.9
Parental mAb 2	0.072 (0.054- 0.097)	2.858 (1.503- 5.436)	4.134 (3.583- 4.769)	4.921 (2.833- 8.547)	4.851 (2.613- 9.005)
Parental mAb 1	0.068 (0.029- 0.160)	0.488 (0.061- 3.882)	7.563 (1.189- 48.096)	10.090 (1.779- 60.640)	20.619 (9.245- 45.987)

The Pseudovirion neutralization assay (see Table 23) shows that for the Omicron variants, especially the ones arising later such as XBB.1.1, the Parental antibody 2 according to invention was able to neutralize at lower concentrations than the anti-fusion peptide Parental mAb 1, with the bispecific antibody retaining the neutralizing activity with IC_{50} concentrations in the middle of each Parental mAb, except for SARS-CoV-2 Wuhan, which was neutralized by the bispecific antibody at the lowest concentration compared to the Parental antibodies. The overall trends of the bispecific antibody retaining neutralizing

activity of its parental antibodies was confirmed from the live virus assay (Table 22). This indicates that the bispecific antibody retains neutralizing affinity from each Fab arm of the parental antibodies.

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: 013, 170, 266, 368, 439 or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: SEQ ID Numbers: 662, 663, 664, 665, 666 to 667.
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: 013, 170, 266, 368, 439 and/or 584 and wherein the second Fab comprises a sequence comprising any one or more of preferred SEQ ID Numbers: SEQ ID Numbers: 662, 663, 664, 665, 666 and/or 667.
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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID NO: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, and
- b.) the second Fab comprises a heavy chain variable region comprising as CDRs, a Heavy Chain CDR1 region of SEQ ID NO: 662, a Heavy Chain CDR2 region of SEQ ID NO: 663 and a Heavy Chain CDR3 region of SEQ ID NO: 664 and a light chain variable region comprising as CDRs a Light Chain CDR1 region of SEQ ID

NO: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.

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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 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: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, and
20
- 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: 662, a Heavy Chain CDR2 region of SEQ ID NO: 663 and a Heavy Chain CDR3 region of SEQ ID NO: 664 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: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.
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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 Claim 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: 013, a Heavy Chain CDR2 region of SEQ ID NO: 170 and a Heavy Chain CDR3 region of SEQ ID NO: 266 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: 368, a Light Chain CDR2 region of SEQ ID NO: 439 and a Light Chain CDR3 region of SEQ ID NO: 584, 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: 662, a Heavy Chain CDR2 region of SEQ ID NO: 663 and a
- 25 Heavy Chain CDR3 region of SEQ ID NO: 664 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: 665, a Light Chain CDR2 region of SEQ ID NO: 666 and a Light Chain CDR3 region of SEQ ID NO: 667.
- 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: 640.
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: 688.
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: 641.
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: 689.

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 Claims
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 65
and Claim 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. 013, or a first nucleic acid sequence encoding the amino acid sequence having
at most 1 or 2 amino acids different from SEQ ID NO. 013,
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- (ii) a second nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 170, 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. 170,
- (iii) a third nucleic acid sequence encoding the amino acid sequence as set forth in
5 SEQ ID NO. 266, 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. 266,
- (iv) a fourth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 368, 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. 368,
- (v) a fifth nucleic acid sequence encoding the amino acid sequence as set forth in
10 SEQ ID NO. 439, or a fifth nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 439,
- (vi) a sixth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 584, 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. 584,
- (vii) a seventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 662, or a seventh nucleic acid sequence encoding the amino acid sequence having at most 1 or 2 amino acids different from SEQ ID NO. 662,
- (viii) an eighth nucleic acid sequence encoding the amino acid sequence as set forth
20 in SEQ ID NO. 663, 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. 663,
- (ix) a ninth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 664, 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. 664,
- (x) a tenth nucleic acid sequence encoding the amino acid sequence as set forth in
25 SEQ ID NO. 665, 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. 665,
- (xi) an eleventh nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 666, 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. 666, and
- (xii) a twelfth nucleic acid sequence encoding the amino acid sequence as set forth in SEQ ID NO. 667, 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. 667.

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 Claim 18 further comprising a second medicament, for simultaneous, separate, or sequential administration.
- 10 20. A composition according to Claim 19, wherein the second medicament comprises a second antibody or antigen binding fragment thereof.
21. A composition according to Claim 19, wherein the second medicament comprises a bispecific antibody or bispecific antigen binding fragment thereof.
- 15 22. A composition according to Claim 19, wherein the composition further comprises a pharmaceutically acceptable excipient or carrier.
- 20 23. A composition according to Claim 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 Claim 18, for use as a medicament.
25. An inhaler device comprising the composition of Claim 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.