fragment thereof. In one example, the MASP-2 inhibitory agent is a MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one example, the MASP-2 inhibitory agent is a small molecule, such as a synthetic or semi-synthetic small molecule that inhibits MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory agent is an expression inhibitor of MASP-2. In one example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, the MASP-2 inhibitory antibody or fragment thereof is selected from the group consisting of a recombinant antibody, an antibody having reduced effector function, a chimeric antibody, a humanized antibody, and a human antibody. In one example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC50 of 30 nM or less. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof, comprises a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:69. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69.

~~In one aspect, the present disclosure refers to use of a MASP-2 inhibitory agent in the manufacture of a medicament for treating, inhibiting, alleviating or preventing acute respiratory distress syndrome, pneumonia or some other pulmonary or other acute manifestation of COVID-19, such as thrombosis, in a mammalian subject infected with SARS-CoV-2, the use comprising (i) determining the level of MASP-2/C1-INH complex in a biological sample obtained from the subject, wherein an increased level of MASP-2/C1-INH complex as compared to a healthy control sample is indicative of an increased risk of developing one or more acute manifestations of COVID-19; and (ii) wherein an amount of the MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation is to be administered to the subject having an increased level of MASP-2/C1-INH complex, optionally, wherein the amount of said MASP-2 inhibitory agent is sufficient to reduce the level of MASP-2/C1-INH to a control level or reference standard.~~

In another example, the present disclosure provides a method for treating, ameliorating, preventing or reducing the risk of developing one or more COVID-19-related long-term sequelae in a mammalian subject that has been infected with SARS-CoV-2, comprising (i) determining the level of MASP-2/C1-INH complex in a biological sample obtained from the subject, wherein an increased level of MASP-2/C1-INH complex as compared to a healthy control sample is indicative of an increased risk of developing one or more COVID-19-related long term sequelae; and (ii) administering to the subject having an increased level of MASP-2/C1-INH complex an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation.

In one example, the MASP-2 inhibitory agent is a MASP-2 antibody or antigen-binding fragment thereof. In one example, the MASP-2 inhibitory agent is a MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one example, the MASP-2 inhibitory agent is a small molecule, such as a synthetic or semi-synthetic small molecule that inhibits MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory agent is an expression inhibitor of MASP-2. In one example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, the MASP-2 inhibitory antibody or fragment thereof is selected from the group consisting of a recombinant antibody, an antibody having reduced effector function, a chimeric antibody, a humanized antibody, and a human antibody. In one example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC50 of 30 nM or less. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof, comprises a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of the amino acid sequence set forth as SEQ ID NO:69. In one example, the MASP-2 inhibitory antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence set forth as SEQ ID NO:67 and a light chain variable region comprising the amino acid sequence set forth as SEQ ID NO:69.

~~In one aspect, the present disclosure refers to use of a MASP-2 inhibitory agent in the manufacture of a medicament for treating, ameliorating, preventing or reducing the risk of developing one or more COVID-19 related long-term sequelae in a mammalian subject that has been infected with SARS-CoV-2, the use comprising (i) determining the level of MASP-2/C1-INH complex in a biological sample obtained from the subject, wherein an increased level of MASP-2/C1-INH complex as compared to a healthy control sample is indicative of an increased risk of developing one or more COVID-19 related long-term sequelae; and (ii) wherein an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation is to be administered to the subject having an increased level of MASP-2/C1-INH complex.~~

In another example, the present disclosure provides a monoclonal antibody, or antigen binding fragment thereof, that specifically binds to human MASP-2 in complex with C1-INH, wherein the antibody comprises a binding domain comprising HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:87 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:88, wherein the CDRs are numbered according to the Kabat numbering system. In one example, the MASP-2 specific antibody comprises a heavy chain variable region having at least 95% identify with the amino acid sequence set

forth as SEQ ID NO:87 and a light chain variable region having at least 95% identify with the amino acid sequence set forth as SEQ ID NO:88. In one example, the MASP-2 specific antibody or antigen-binding fragment thereof is labeled with a detectable moiety, for example a detectable moiety suitable for use in an immunoassay as further described herein. In one example, the MASP-2 specific antibody or fragment thereof is immobilized on a substrate, such as a substrate suitable for use in an immunoassay, such as an immunoassay for detecting MASP-2/C1-INH complex.

~~In one aspect, the present disclosure refers to a monoclonal antibody, or antigen binding fragment thereof, that specifically binds to human MASP-2 in complex with C1-INH, wherein the antibody comprises a binding domain comprising (a) HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:87 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:88, or (b) HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:97 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:98, wherein the CDRs are numbered according to the Kabat numbering system.~~

In another example, the present disclosure provides a monoclonal antibody, or antigen binding fragment thereof, that specifically binds to human MASP-2 in complex with C1-INH, wherein the antibody comprises a binding domain comprising HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:97 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:98, wherein the CDRs are numbered according to the Kabat numbering system. In one example, the MASP-2 specific antibody comprises a heavy chain variable region having at least 95% identify with the amino acid sequence set forth as SEQ ID NO:97 and a light chain variable region having at least 95% identify with the amino acid sequence set forth as SEQ ID NO:98. In one example, the MASP-2 specific antibody or antigen-binding fragment thereof is labeled with a detectable moiety, for example a detectable moiety suitable for use in an immunoassay as further described herein. In one example, the MASP-2 specific antibody or fragment thereof is immobilized on a substrate, such as a substrate suitable for use in an immunoassay, such as an immunoassay for detecting MASP-2/C1-INH complex.

In another example, the present disclosure provides a method of measuring the amount of MASP-2/C1-INH in a biological sample comprising: (a) providing a test biological sample from a human subject; (b) performing an immunoassay comprising capturing and detecting MASP-2/C1-INH complex in the test sample, wherein MASP-2/C1-INH complex is captured with a monoclonal antibody that specifically binds to human MASP-2; and the MASP-2/C1-INH complex is detected directly or indirectly with an antibody that specifically binds to C1-INH; and (c) comparing the level of MASP-2/C1-INH complex detected in accordance with (b) with a predetermined level or control sample wherein the level of MASP-2/C1-INH complex detected in the test sample is indicative of the extent of Lectin Pathway Complement activation. In some

an antibody that specifically binds to MASP-2 comprises a binding domain comprising HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:97 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:98, wherein the CDRs are numbered according to the Kabat numbering system.

~~In one aspect, the present disclosure refers to a method of determining the risk of a subject that is or has been infected with SARS-CoV-2 for developing COVID-19-related ARDS or other poor outcome, or long term sequelae associated with COVID-19 comprising: (a) measuring a level of MASP-2/C1-INH complex in a biological sample obtained from the subject; (b) comparing the measured level with a predetermined level of MASP-2/C1-INH complex or a reference standard to assess the risk of developing COVID-19 related ARDS and/or long term sequelae associated with COVID-19; and (c) determining the risk of the subject for developing COVID-19 related ARDS or other poor outcome and/or long term sequelae associated with COVID-19 and reporting the results to the patient, physician or database; wherein a treatment is to be optionally administered to the subject determined to be likely to develop acute disease and/or long term sequelae associated with COVID-19 infection.~~

In another example, the present disclosure provides a method for monitoring the efficacy of treatment with a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, in a mammalian subject in need thereof, the method comprising:(a) administering a dose of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, to a mammalian subject at a first point in time;(b) assessing a first level of MASP-2/C1-INH complex in a biological sample obtained from the subject after step (a);(c) treating the subject with the MASP-2 inhibitory antibody, or antigen-binding fragment thereof, at a second point in time;(d) assessing a second level of MASP-2/C1-INH complex in a biological sample obtained from the subject after step (c); and (e) comparing the level of MASP-2/C1-INH complex assessed in step (b) with the level of MASP-2/C1-INH complex assessed in step (d) to determine the efficacy of the MASP-2 inhibitory antibody or antigen-binding fragment thereof in the mammalian subject. In some examples, the subject is a human subject suffering from, or at risk of developing COVID-19 or long-term sequelae associated with COVID-19. In some examples, the subject is a human subject suffering from, or at risk of developing a disease or disorder selected from the group consisting of HSCT-TMA, IgAN, Lupus Nephritis and Graft-versus-Host Disease or some other lectin pathway disease or disorder. In some examples, the level of MASP-2/C1-INH complex is measured in an immunoassay. In some examples, step (b) comprises performing an immunoassay such as an ELISA assay to measure the level of MASP-2/C1-INH complex in the biological sample. In some examples, the immunoassay comprises the use of an antibody that specifically binds to MASP-2 comprises a binding domain comprising HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:87 and comprising LC-CDR1, LC-CDR2 and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:88, wherein the CDRs are numbered according to the Kabat numbering system. In some examples, the immunoassay comprises the use of an antibody that specifically binds to MASP-2 comprises a binding domain comprising HC-CDR1, HC-CDR2 and HC-CDR3 in a heavy chain variable region set forth as SEQ ID NO:97 and comprising LC-CDR1, LC-CDR2

and LC-CDR3 in a light chain variable region set forth as SEQ ID NO:98, wherein the CDRs are numbered according to the Kabat numbering system.

~~In one aspect, the present disclosure refers to a method for monitoring the efficacy of treatment with a MASP-2 inhibitory antibody, or antigen binding fragment thereof, in a mammalian subject in need thereof, the method comprising: (a) assessing a first level of MASP-2/C1-INH complex in a biological sample obtained from the subject after a dose of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, has been administered to the subject at a first point in time; (b) assessing a second level of MASP-2/C1-INH complex in a biological sample obtained from the subject after the subject has been treated with the MASP-2 inhibitory antibody, or antigen binding fragment thereof, at a second point in time; and (c) comparing the level of MASP-2/C1-INH complex assessed in step (a) with the level of MASP-2/C1-INH complex assessed in step (b) to determine the efficacy of the MASP-2 inhibitory antibody or antigen binding fragment thereof in the mammalian subject.~~

Description of the Drawings

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is a diagram illustrating the genomic structure of human MASP-2;

FIGURE 2A is a schematic diagram illustrating the domain structure of human MASP-2 protein;

FIGURE 2B is a schematic diagram illustrating the domain structure of human MAp19 protein;

FIGURE 3 is a diagram illustrating the murine MASP-2 knockout strategy;

FIGURE 4 is a diagram illustrating the human MASP-2 minigene construct;

FIGURE 5A presents results demonstrating that MASP-2-deficiency leads to the loss of lectin-pathway-mediated C4 activation as measured by lack of C4b deposition on mannan, as described in Example 2;

FIGURE 5B presents results demonstrating that MASP-2-deficiency leads to the loss of lectin-pathway-mediated C4 activation as measured by lack of C4b deposition on zymosan, as described in Example 2;

FIGURE 5C presents results demonstrating the relative C4 activation levels of serum samples obtained from MASP-2+/-; MASP-2-/- and wild-type strains as measure by C4b deposition on mannan and on zymosan, as described in Example 2;

FIGURE 6 presents results demonstrating that the addition of murine recombinant MASP-2 to MASP-2-/- serum samples recovers lectin-pathway-mediated C4 activation in a protein concentration dependent manner, as measured by C4b deposition on mannan, as described in Example 2;

FIGURE 7 presents results demonstrating that the classical pathway is functional in the MASP-2-/- strain, as described in Example 8;

FIGURE 8A presents results demonstrating that anti-MASP-2 Fab2 antibody #11 inhibits C3 convertase formation, as described in Example 10;