Thus, there is an urgent need to develop therapeutically effective agents to treat, inhibit and/or prevent coronavirus-induced pneumonia and acute respiratory distress syndrome and influenza virus induced pneumonia and acute respiratory distress syndrome.

In addition, to maximize success in treating and protecting people against COVID-19, there is an urgent need for biomarkers and highly accurate tests to identify those persons at risk of developing acute COVID-19 and/or long term disease (post-acute COVID-19, otherwise known as Long-COVID-19 syndrome), or has developed a protective immune response versus a COVID-19 disease response. There is also a need for tests to determine the efficacy of therapeutics to treat and/or prevent COVID-19-related complications in subjects infected with SARS-CoV-2, including those suffering from, or at risk of developing Long-COVID-19.

SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

In one ~~aspect~~example, the present ~~invention~~disclosure provides a method 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, 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 or other reference standard is indicative of an increased risk of developing one or more acute manifestations of COVID-19; 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 some ~~embodiment~~examples, the subject is suffering from one or more respiratory symptoms and the method comprises administering to the subject an amount of a MASP-2 inhibitory agent effective to improve at least one respiratory symptom (i.e., improve respiratory function). In one ~~embodiment~~example, the MASP-2 inhibitory agent is a MASP-2 antibody or antigen-binding

fragment thereof. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory agent is an expression inhibitor of MASP-2. In one ~~embodiment~~example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one ~~embodiment~~example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC50 of 30 nM or less. In one ~~embodiment~~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 ~~embodiment~~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 ~~aspect~~example, the present ~~invention~~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 ~~embodiment~~example, the MASP-2 inhibitory agent is a MASP-2 antibody or antigen-binding fragment thereof. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory agent is an expression inhibitor of MASP-2. In one ~~embodiment~~example, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one ~~embodiment~~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 ~~embodiment~~example, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In one ~~embodiment~~example, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC50 of 30 nM or less. In one ~~embodiment~~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 ~~embodiment~~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 ~~aspect~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~aspect~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~aspect~~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

~~embodiment~~examples, the biological sample is a fluid sample from a human subject selected from the group consisting of whole blood, serum, plasma, urine and cerebrospinal fluid. In some ~~embodiment~~examples, the human subject is currently infected with SARS-CoV-2, or has previously been infected with SARS-CoV-2. In some ~~embodiment~~examples, the 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 ~~embodiment~~examples, the 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 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 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 another ~~aspect~~example, the present disclosure provides 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 long-term sequelae associated with COVID-19 comprising: (a) obtaining a biological sample from the subject; (b) measuring the level of MASP-2/C1-INH complex in the sample; (c) 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 (d) determining the risk of the subject for developing COVID-19-related ARDS and/or long-term sequelae associated with COVID-19 and reporting the results to the patient, physician or database; (e) optionally, administering a treatment to the subject determined to be likely to develop acute disease and/or long-term sequelae associated with COVID-19 infection. In some ~~embodiment~~examples, the level of MASP-2/C1-INH complex is measured in an immunoassay. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 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 ~~aspect~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the level of MASP-2/C1-INH complex is measured in an immunoassay. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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;

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Use of a MASP-2 inhibitory agent in the manufacture of a medicament ~~A method~~ 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) ~~administering~~ 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 ~~an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation~~, 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.

2. The ~~method~~ use of claim 1, wherein 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.

~~3. The method of claim 2, wherein 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.~~

~~4. The method of claim 2, wherein the MASP-2 antibody or fragment thereof specifically binds to a polypeptide comprising SEQ ID NO:6 with an affinity of at least 10 times greater than it binds to a different antigen in the complement system.~~

~~5. The method of claim 2, wherein the 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.~~

~~6. The method of claim 1, wherein the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation.~~

3~~7~~. The ~~method~~ use of claim 1, wherein the MASP-2 inhibitory agent is a small molecule MASP-2 inhibitory compound.

4~~8~~. The ~~method~~ use of claim 3~~7~~, wherein the MASP-2 inhibitory compound is a synthetic or semi-synthetic small molecule.

5~~9~~. The ~~method~~ use of claim 1, wherein the MASP-2 inhibitory agent is an expression inhibitor of MASP-2.

~~10. The method of claim 1, wherein the MASP-2 inhibitory agent is administered subcutaneously, intraperitoneally, intra-muscularly, intra-arterially, intravenously, orally, or as an inhalant.~~

6~~11~~. The ~~method~~ use of claim 2, wherein 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.

~~12. The method of claim 2, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO:67 and a light chain variable region comprising SEQ ID NO:69.~~

7~~13~~. Use of a MASP-2 inhibitory agent in the manufacture of a medicament~~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, 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 ~~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~~.

~~14. The method of claim 13, wherein the MASP-2 inhibitory agent is a MASP-2 antibody or fragment thereof.~~

8~~15~~. The ~~method~~ use of claim 7~~14~~, wherein 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.

~~16. The method of claim 14, wherein the MASP-2 antibody or fragment thereof specifically binds to a polypeptide comprising SEQ ID NO:6 with an affinity of at least 10 times greater than it binds to a different antigen in the complement system.~~

~~17. The method of claim 14, wherein the 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.~~

~~18. The method of claim 14, wherein the MASP-2 inhibitory agent selectively inhibits lectin pathway complement activation without substantially inhibiting C1q-dependent complement activation.~~

9~~19~~. The ~~method~~ use of claim 7~~13~~, wherein the MASP-2 inhibitory agent is a small molecule MASP-2 inhibitory compound.

10~~20~~. The ~~method~~ use of claim 7~~13~~, wherein the MASP-2 inhibitory compound is a synthetic or semi-synthetic small molecule.

11~~21~~. The ~~method~~ use of claim 7~~13~~, wherein the MASP-2 inhibitory agent is an expression inhibitor of MASP-2.

1222. The ~~method~~ use of claim 814, wherein 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.

~~23. The method of claim 14, wherein the MASP-2 inhibitory antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO:67 and a light chain variable region comprising SEQ ID NO:69.~~

1324. The ~~method~~ use of claim 713, wherein the one or more COVID-19 related long term sequelae is selected from the group consisting of a cardiovascular complication (including myocardial injury, cardiomyopathy, myocarditis, intravascular coagulation, stroke, venous and arterial complications and pulmonary thrombosis); a neurological complication (including cognitive difficulties, confusion, memory loss, also referred to as "brain fog," headache, stroke, dizziness, syncope, seizure, anorexia, insomnia, anosmia, ageusia, myoclonus, neuropathic pain, myalgias, development of neurological disease such as Alzheimer's disease, Guillian Barre Syndrome, Miller-Fisher Syndrome, Parkinson's disease) kidney injury (such as acute kidney injury (AKI); a pulmonary complication (including lung fibrosis, dyspnea, pulmonary embolism),an inflammatory condition such as Kawasaki disease, Kawasaki-like disease, multisystem inflammatory syndrome in children, multi-system organ failure, extreme fatigue, muscle weakness, low grade fever, inability to concentrate, memory lapses, changes in mood, sleep difficulties, needle pains in arms and legs, diarrhea and vomiting, loss of taste and smell, sore throat and difficulties in swallowing, new onset of diabetes and hypertension, skin rash, shortness of breath, chest pains and palpitations.

1425. 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.

~~26. The monoclonal antibody of claim 25, wherein said 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; or wherein said 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.~~

~~27. The monoclonal antibody of claim 25, wherein said antibody is a humanized, chimeric or fully human antibody.~~

15~~28~~. 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 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.

16~~29~~. The method of claim 15~~28~~, wherein the biological sample is a fluid sample selected from the group consisting of whole blood, serum, plasma, urine and cerebrospinal fluid.

1730. The method of claim 1528, wherein the antibody that specifically binds to MASP-2 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.

1831. The method of claim 1528, wherein the human subject is currently infected with SARS-CoV-2, or has previously been infected with SARS-CoV-2, or wherein the subject is suffering or at risk for developing another lectin-pathway disease or condition (e.g., HSCT-TMA, IgAN, GvHD or other lectin pathway disease or disorder).~~.~~

1932. 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) obtaining a biological sample from the subject;~~

(a~~b~~) measuring ~~the~~ a level of MASP-2/C1-INH complex in ~~the~~ a biological sample obtained from the subject;

(b~~e~~) 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~~d~~) 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;

~~(e)~~ wherein ~~optionally, administering~~ 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.

2033. The method of claim 1932, wherein the level of MASP-2/C1-INH complex is measured in an immunoassay.

~~34. The method of claim 32, wherein the method comprises performing an immunoassay to measure the level of MASP-2/C1-INH complex in the biological sample.~~

~~35. The method of claim 34, wherein the immunoassay is an ELISA assay.~~

~~36. The method of claim 35, wherein the immunoassay comprises the use of a capture 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.~~

~~37. The method of claim 34, wherein the immunoassay is a bead-based immunofluorescence assay.~~

~~38. The method of claim 37, wherein the immunoassay comprises the use of a capture 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.~~

~~39. The method of claim 37 or 38, wherein the biological sample is serum or plasma.~~

~~40. The method of claim 39, wherein the biological sample is from 1% to 5% serum or plasma.~~

2141. 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;~~

(ab) assessing a first level of MASP-2/C1-INH complex in a biological sample obtained from the subject after ~~step (a)~~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;

~~(c) treating the subject with the MASP-2 inhibitory antibody, or antigen-binding fragment thereof, at a second point in time;~~

(bd) 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~~step (c)~~; and

(ce) comparing the level of MASP-2/C1-INH complex assessed in step (ab) with the level of MASP-2/C1-INH complex assessed in step (bd) to determine the efficacy of the MASP-2 inhibitory antibody or antigen-binding fragment thereof in the mammalian subject.

2242. The method of claim 2141, wherein the method further comprises adjusting the dose of the MASP-2 inhibitory antibody or antigen-binding fragment thereof.

~~43. The method of claim 42, wherein the dose of MASP-2 inhibitory antibody or antigen-binding fragment thereof administered to the subject is increased if the level of MASP-2/C1-INH complex is higher than the control or reference standard.~~

~~44. The method of claim 43, wherein if the subject is administered an increased dose of the MASP-2 inhibitory antibody or antigen-binding fragment thereof, steps (b) to (e) are repeated to determine whether the increased dose is sufficient to adjust the level of MASP-2/C1-INH complex to the desired level as compared to the respective control or reference standard.~~

~~45. The method of claim 41, wherein steps (b) and (d) comprise assessing the concentration of MASP-2/CI-INH complex in the biological samples in an immunoassay.~~

~~46. The method of claim 45, wherein the immunoassay is a bead-based immunofluorescence assay.~~

~~47. The method of claim 46, wherein the immunoassay comprises the use of a capture 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.~~

~~48. The method of claim 46 or 47, wherein the biological sample is serum or plasma.~~

~~49. The method of claim 48, wherein the biological sample is from 1% to 5% serum or plasma.~~

~~50. The method of any one of claims 41-50, wherein the mammalian subject is a human subject.~~

~~51. The method of claim 50, wherein the human subject is suffering from, or at risk of developing a lectin pathway 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.~~

~~52. The method of claim 41, wherein the human subject is suffering from, or at risk of developing COVID-19 or long-term sequelae associated with COVID-19.~~

~~53. The method of claim 41, wherein the second point in time is from 2 to 14 days after the first point in time.~~

~~54. The method of claim 41, wherein the second point in time is within 2 to 7 days from the first point in time.~~

~~55. The method of claim 41, wherein the second point in time is within 2 to 4 days from the first point in time.~~