the most potent anaphylatoxin, inducing alterations in smooth muscle and vascular tone, as well as vascular permeability. It is also a powerful chemotaxin and activator of both neutrophils and monocytes. C5a-mediated cellular activation can significantly amplify inflammatory responses by inducing the release of multiple additional inflammatory mediators, including cytokines, hydrolytic enzymes, arachidonic acid metabolites, and reactive oxygen species. C5 cleavage leads to the formation of C5b-9, also known as the membrane attack complex (MAC). There is now strong evidence that sublytic MAC deposition may play an important role in inflammation in addition to its role as a lytic pore-forming complex.

In addition to its essential role in immune defense, the complement system contributes to tissue damage in many clinical conditions. Thus, there is a pressing need to develop therapeutically effective complement inhibitors to prevent these adverse effects.

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 example, the present disclosure provides a method of inhibiting microvascular endothelial cell injury and/or thrombus formation in a subject suffering from a thrombotic microangiopathy (TMA) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody effective to inhibit MASP-2-dependent complement activation. In some examples, the subject is suffering from, or at risk for developing a TMA selected from the group consisting of hemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (HUS). In some examples, prior to administration of the composition the subject is determined to exhibit one or more symptoms selected from the group consisting of (i) anemia, (ii) thrombocytopenia (iii) renal insufficiency and (iv) rising creatinine, and the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In some examples, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof. In some examples, the MASP-2 inhibitory agent is an anti-MASP-2 monoclonal antibody, or

fragment thereof that specifically binds to a portion of SEQ ID NO:6. In some examples, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from or at risk for developing atypical hemolytic uremic syndrome (aHUS), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation. In one example, prior to administration of the composition the subject is determined to exhibit one or more symptoms selected from the group consisting of (i) anemia, (ii) thrombocytopenia (iii) renal insufficiency and (iv) rising creatinine, and the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In one example, the subject is suffering from or at risk for developing non-Factor H-dependent aHUS. In one example, the subject is suffering from aHUS associated with factor I, factor B, or membrane cofactor CD46. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-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 inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In one aspect, the present disclosure refers to the use of a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof in the manufacture of a medicament for treating a human subject suffering from plasma therapy-resistant aHUS.

In another example, the disclosure provides a method for reducing the likelihood that a subject at risk for developing atypical hemolytic uremic syndrome (aHUS) will suffer clinical symptoms associated with aHUS. The method according to this example of the disclosure comprises (a) determining the presence of a genetic marker in the subject known to be associated with aHUS; (b) periodically monitoring the subject to determine the presence or absence of at least one symptom selected from the group consisting of anemia, thrombocytopenia, renal insufficiency and rising creatinine; and (c) administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation upon the determination of the presence of at least one of anemia, thrombocytopenia, renal insufficiency or rising creatinine, wherein the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In one example of the method, step

(a) comprises performing a genetic screening test on a sample obtained from the subject and identifying the presence of at least one genetic marker associated with aHUS in a gene selected from the group consisting of complement factor H (CFH), factor I (CFI), factor B (CFB), membrane cofactor CD46, C3, complement factor H-related protein (CFHR1), anticoagulant protein thrombodulin (THBD), complement factor H-related protein 3 (CFHR3) and complement factor H-related protein 4 (CFHR4). In one example, the method further comprises monitoring the subject for the occurrence of an event known to be associated with triggering aHUS clinical symptoms and administering to the subject the composition comprising the MASP-2 inhibitory agent prior to, during, or after the occurrence of the triggering event. In one example, the event associated with triggering aHUS clinical symptoms is selected from the group consisting of drug exposure, infection, malignancy, injury, organ or tissue transplant and pregnancy. In one example, the infection is a bacterial infection. In one example, the composition is administered subcutaneously. In one example, the MASP-2 inhibitory agent inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from, or at risk for developing, atypical hemolytic uremic syndrome (aHUS) secondary to an infection, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 complement activation. In one example, the subject is suffering from, or at risk for developing non-enteric aHUS associated with an *S. pneumonia* infection. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-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 inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method of treating a subject suffering from atypical hemolytic uremic syndrome (aHUS) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered via an intravenous catheter or other catheter delivery method. In one example, the method further comprises treating the patient

with plasmapheresis. In one example, the composition comprising the MASP-2 inhibitory agent is administered in the absence of plasmapheresis. In one example, the composition comprising the MASP-2 inhibitory agent is administered via a catheter for a first time period, further comprising administering the composition comprising the MASP-2 inhibitory agent for a second time period, wherein the composition is administered subcutaneously during the second time period. In one example, the method further comprises periodically determining the level of at least one complement factor, wherein the determination of a reduced level of the at least one complement factor in comparison to a standard value or a healthy subject is indicative of the need for continued treatment with the composition. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-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 inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method of treating a subject suffering from thrombotic thrombocytopenic purpura (TTP), or exhibiting symptoms consistent with a diagnosis of TTP, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered to the subject via an intravenous catheter or other catheter delivery method. In one example,

the subject exhibits at least one or more symptoms selected from the group consisting of central nervous system involvement, thrombocytopenia, severe cardiac involvement, severe pulmonary involvement, gastro-intestinal infarction and gangrene. In one example, the subject tests positive for the presence of an inhibitor of ADAMTS13, and the method further comprises administering an immunosuppressant to the subject. In one example, the composition comprising the MASP-2 inhibitory agent is administered for a first time period in the absence of plasmapheresis. In one example, the subject tests positive for the presence of an inhibitor of ADAMTS-13, and the method further comprises administering ADAMTS-13. In one example, the method further comprises treating the patient with plasmapheresis. In one example, the composition comprising the MASP-2 inhibitory agent is administered in the presence

of plasmapheresis. In one example, the composition comprising the MASP-2 inhibitory agent is administered via a catheter for a first time period, further comprising administering the composition comprising the MASP-2 inhibitory agent for a second time period, wherein the composition is administered subcutaneously during the second time period. In one example, the method further comprises periodically determining the level of at least one complement factor, wherein the determination of a reduced level of the at least one complement factor in comparison to a standard value or a healthy subject is indicative of the need for continued treatment with the composition. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-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 inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the disclosure provides a method of treating a subject suffering from refractory thrombotic thrombocytopenic purpura (TTP) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation. In one example, the composition is administered subcutaneously. In one example, the method further comprises periodically determining the level of at least one complement factor, wherein the determination of a reduced level of the at least one complement factor in comparison to a standard value or a healthy subject is indicative of the need for continued treatment with the composition. In one example, the MASP-2 inhibitory agent is an anti-MASP-2 antibody, or fragment thereof, such as an anti-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 inhibits microvascular endothelial cell injury. In one example, the MASP-2 inhibitory agent inhibits thrombus formation.

In another example, the present disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from, or at risk for developing a thrombotic microangiopathy (TMA), wherein the TMA is at least one of (i) a TMA secondary to cancer; (ii) a TMA secondary to chemotherapy, or (iii) a TMA secondary to transplantation, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation. In some examples, the subject is suffering from, or is at risk

for developing a TMA secondary to cancer, and the MASP-2 inhibitory agent is administered systemically to the subject in an amount effective to reduce the risk of developing TMA, or reduce the severity of TMA. In some examples, the subject is suffering from, or is at risk for developing a TMA secondary to chemotherapy, and the MASP-2 inhibitory agent is administered systemically to the subject prior to, during, or after chemotherapy, in an amount effective to reduce the risk of developing TMA, or reduce the severity of TMA. In some examples, the subject is suffering from, or is at risk for developing a TMA secondary to transplantation and the MASP-2 inhibitory agent is administered systemically to the subject prior to, during, or after the transplant procedure, in an amount effective to reduce the risk of developing TMA, or reduce the severity of TMA. In some examples the transplant procedure is an allogeneic hematopoietic stem cell transplant. In some examples, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some examples, the method further comprises administering to the subject a terminal complement inhibitor that inhibits cleavage of complement protein C5, such as a humanized anti-C5 antibody or antigen-binding fragment thereof, such as eculizumab.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from or at risk for developing Upshaw-Schulman Syndrome (USS) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation. In some examples, the method comprises treating a subject at risk for developing USS, wherein the method comprises administering an amount of a MASP-2 inhibitory agent for a time period effective to ameliorate or prevent one of more clinical symptoms associated with TTP. In some examples, the method further comprises periodically monitoring the subject and administering the MASP-2 inhibitory agent upon the presence of an event known to be associated with triggering TTP clinical symptoms. In some examples, the method further comprises periodically monitoring the subject and administering the MASP-2 inhibitory agent upon the determination of the presence of anemia, thrombocytopenia or rising creatine. In some examples, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some examples, the method further

comprises administering to the subject a terminal complement inhibitor that inhibits cleavage of complement protein C5, such as a humanized anti-C5 antibody or antigen-binding fragment thereof, such as eculizumab.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from Degos disease, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation. In some examples, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some examples, the method further comprises administering to the subject a terminal complement inhibitor that inhibits cleavage of complement protein C5, such as a humanized anti-C5 antibody or antigen-binding fragment thereof, such as eculizumab.

In another example, the disclosure provides a method of inhibiting MASP-2-dependent complement activation in a subject suffering from Catastrophic Antiphospholipid Syndrome (CAPS), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation. In some examples, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In some examples, the method further comprises administering to the subject a terminal complement inhibitor that inhibits cleavage of complement protein C5, such as a humanized anti-C5 antibody or antigen-binding fragment thereof, such as eculizumab.

In some examples of any of the disclosed methods of the disclosure, the MASP-2 inhibitory agent is a MASP-2 inhibitory antibody or fragment thereof. In some examples, the MASP-2 inhibitory antibody has reduced effector function. In some examples, the MASP-2 inhibitory antibody does not substantially inhibit the classical pathway. In some examples, the MASP-2 inhibitory agent is an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In some examples, the anti-MASP-2 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 some examples, the MASP-2 inhibitory antibody is an antibody fragment selected from the group consisting of Fv, Fab, Fab', $F(ab)_2$ and $F(ab')_2$. In some examples, the MASP-2

inhibitory antibody is a single-chain molecule. In some examples, the MASP-2 inhibitory antibody is selected from the group consisting of an IgG1 molecule, an IgG2 and an IgG4 molecule. In some examples, the MASP-2 inhibitory antibody is an IgG4 molecule comprising a S228P mutation. In some examples, the MASP-2 inhibitory antibody binds human MASP-2 with a K_D of 10 nM or less. In some examples, the MASP-2 inhibitory antibody binds an epitope in the CCP1 domain of MASP-2. In some examples, the MASP-2 inhibitory antibody inhibits C3b deposition in an *in vitro* assay in 1% human serum at an IC_{50} of 10 nM or less. In some examples, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less.

In some examples of any of the disclosed methods of the disclosure the MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, comprises: (a) a heavy-chain variable region comprising: i) a heavy chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:67; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:67; and iii) a heavy-chain CDR-H3 comprising the amino acid sequence from 95-102 of SEQ ID NO:67 and (b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the amino acid sequence from 24-34 of SEQ ID NO:70; and ii) a light-chain CDR-L2 comprising the amino acid sequence from 50-56 of SEQ ID NO:70; and iii) a light-chain CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:70. In some examples, the MASP-2 inhibitory monoclonal antibody comprises a heavy-chain variable region set forth as SEQ ID NO:67 and a light-chain variable region set forth as SEQ ID NO:70. In some examples, the MASP-2 inhibitory antibody or antigen binding-fragment thereof specifically recognizes at least part of an epitope recognized by a reference antibody comprising a heavy chain variable region as set forth in SEQ ID NO:67 and a light-chain variable region as set forth in SEQ ID NO:70.

In another example of the disclosure, methods are provided for inhibiting thrombus formation in a subject suffering from atypical hemolytic uremic syndrome (aHUS), comprising administering to the subject an amount of a MASP-2 inhibitory antibody, or antigen binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In some examples, the MASP-2 inhibitory antibody inhibits thrombus formation in serum from a subject suffering from aHUS by at least 40% as compared to untreated serum. In some examples, the MASP-2 inhibitory antibody inhibits

thrombus formation in serum from a subject suffering from aHUS at a level of at least 20% greater (e.g., at least 30% greater, at least 40% greater, or at least 50% greater) than its inhibitory effect on C5b-9 deposition in the serum from the same subject. In some examples, the subject is in the acute phase of aHUS. In some examples, the subject is in the remission phase of aHUS. In some examples, the MASP-2 inhibitory antibody is a monoclonal antibody, or fragment thereof that specifically binds to a portion of SEQ ID NO:6. In some examples, 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 some examples, the MASP-2 inhibitory antibody is an antibody fragment selected from the group consisting of Fv, Fab, Fab', $F(ab)_2$ and $F(ab')_2$. In some examples, the MASP-2 inhibitory antibody is a single-chain molecule. In some examples, the MASP-2 inhibitory antibody is selected from the group consisting of an IgG1 molecule, an IgG2 and an IgG4 molecule. In some examples, the MASP-2 inhibitory antibody is an IgG4 molecule comprising a S228P mutation. In some examples, the MASP-2 inhibitory antibody binds human MASP-2 with a K_D of 10 nM or less. In some examples, the MASP-2 inhibitory antibody binds an epitope in the CCP1 domain of MASP-2. In some examples, the MASP-2 inhibitory antibody inhibits C3b deposition in an *in vitro* assay in 1% human serum at an IC_{50} of 10 nM or less. In some examples, the MASP-2 inhibitory antibody inhibits C3b deposition in 90% human serum with an IC_{50} of 30 nM or less. In some examples the MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, comprises: (a) a heavy-chain variable region comprising: i) a heavy chain CDR-H1 comprising the amino acid sequence from 31-35 of SEQ ID NO:67; and ii) a heavy-chain CDR-H2 comprising the amino acid sequence from 50-65 of SEQ ID NO:67; and iii) a heavy-chain CDR-H3 comprising the amino acid sequence from 95-102 of SEQ ID NO:67 and (b) a light-chain variable region comprising: i) a light-chain CDR-L1 comprising the amino acid sequence from 24-34 of SEQ ID NO:70; and ii) a light-chain CDR-L2 comprising the amino acid sequence from 50-56 of SEQ ID NO:70; and iii) a light-chain CDR-L3 comprising the amino acid sequence from 89-97 of SEQ ID NO:70. In some examples, the MASP-2 inhibitory monoclonal antibody comprises a heavy-chain variable region set forth as SEQ ID NO:67 and a light-chain variable region set forth as SEQ ID NO:70. In some

examples, the MASP-2 inhibitory antibody or antigen binding-fragment thereof specifically recognizes at least part of an epitope recognized by a reference antibody comprising a heavy chain variable region as set forth in SEQ ID NO:67 and a light-chain variable region as set forth in SEQ ID NO:70.

In another example, the present disclosure provides a method of treating a subject suffering from plasma therapy-resistant aHUS comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody effective to inhibit MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory antibody is an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, 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. In one example, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5, such as wherein the terminal complement inhibitor is a humanized anti-C5 antibody or antigen-binding fragment thereof. In one example, the method further comprises treating the patient with plasmapheresis. In one example, the composition comprising the MASP-2 inhibitory antibody is administered in the absence of plasmapheresis.

In another example, the present disclosure provides a method of treating a subject suffering from TMA associated with hematopoietic stem cell transplant comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody effective to inhibit MASP-2-dependent complement activation. In one example, the MASP-2 inhibitory antibody is an anti-MASP-2 monoclonal antibody, or fragment thereof that specifically binds to human MASP-2. In one example, 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. In one example, the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5. In one example, the subject is suffering from a TMA associated with hematopoietic stem cell transplant that is resistant to treatment with a platelet transfusion and/or resistant to treatment with plasmapheresis. In one example,

the MASP-2 inhibitory antibody is administered in an amount effective to improve at least one or more clinical parameters associated with TMA associated with hematopoietic stem cell transplant, such as an increase in platelet count (e.g., at least double, at least triple, at least quadruple the platelet count prior to treatment), an increase in haptoglobin, and/or a decrease in lactate dehydrogenase.

In another example, the present disclosure provides a method of treating a human subject suffering from persistent TMA associated with hematopoietic stem cell transplant (HSCT-TMA) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. In one example, the method further comprises identifying a human subject having persistent TMA associated with hematopoietic stem cell transplant prior to the step of administering to the subject a composition comprising an amount of a MASP-2 inhibitory antibody, or antigen-binding fragment thereof, effective to inhibit MASP-2-dependent complement activation. 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 antibody or antigen-binding 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 IC_{50} 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:70. In one example, the MASP-2 inhibitory antibody is administered to the patient in the absence of plasmapheresis. In one example, the subject has previously undergone, or is currently undergoing, treatment with a humanized anti-C5 antibody or antigen-binding fragment thereof, such as wherein the terminal complement inhibitor is a humanized anti-C5 antibody or antigen-binding fragment thereof. In one example, the MASP-2 inhibitory antibody is delivered to the subject systemically. In one example, the MASP-2 inhibitory antibody or antigen-binding

fragment thereof is administered in an amount effective to improve at least one or more of the following clinical parameters associated with persistent TMA associated with hematopoietic stem cell transplant: (i) an increase in platelet count (e.g., at least double, at least triple, at least quadruple the platelet count prior to treatment)); (ii) an increase in haptoglobin; (iii) a decrease in lactate dehydrogenase (LDH); and/or (iv) a decrease in creatinine.

In another example, the present disclosure provides compositions for inhibiting the adverse effects of MASP-2-dependent complement activation, comprising a therapeutically effective amount of a MASP-2 inhibitory agent, such as a MASP-2 inhibitory antibody and a pharmaceutically acceptable carrier. Methods are also provided for manufacturing a medicament for use in inhibiting the adverse effects of MASP-2-dependent complement activation in living subjects in need thereof, comprising a therapeutically effective amount of a MASP-2 inhibitory agent in a pharmaceutical carrier. Methods are also provided for manufacturing medicaments for use in inhibiting MASP-2-dependent complement activation for treatment of each of the conditions, diseases and disorders described herein below.

The methods, compositions and medicaments of the disclosure are useful for inhibiting the adverse effects of MASP-2-dependent complement activation *in vivo* in mammalian subjects, including humans suffering from or at risk for developing a thrombotic microangiopathy (TMA) as further described herein.

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;