

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 a pharmaceutical composition for treating a human subject suffering from plasma therapy-resistant aHUS (atypical hemolytic uremic syndrome) comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, which inhibits MASP-2-dependent complement activation

wherein the MASP-2 inhibitory monoclonal antibody comprises: (a) a heavy chain variable region comprising i) a CDR-H1 of the amino acid sequence from 31-35 of SEQ ID NO:67, ii) a CDR-H2 of the amino acid sequence from 50-65 of SEQ ID NO:67, and iii) a CDR-H3 of the amino acid sequence from 95-102 of SEQ ID NO:67; and (b) a light chain variable region comprising i) a CDR-L1 of the amino acid sequence from 24-34 of SEQ ID NO:70, ii) a CDR-L2 of the amino acid sequence from 50-56 of SEQ ID NO:70, and iii) a CDR-L3 of the amino acid sequence from 89-97 of SEQ ID NO:70, and

wherein administration of the MASP-2 inhibitory monoclonal antibody improves at least one or more of the following clinical parameters associated with aHUS: (i) an increase in platelet count, (ii) a decrease in LDH, (iii) an increase in haptoglobin, (iv) an increase in hemoglobin, and (v) a decrease in creatinine.

In one aspect, the present disclosure refers to the use of a pharmaceutical composition comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, which inhibits MASP-2-dependent complement activation, in the manufacture of a medicament for treating a human subject suffering from plasma therapy-resistant aHUS (atypical hemolytic uremic syndrome),

wherein the MASP-2 inhibitory monoclonal antibody comprises: (a) a heavy chain variable region comprising i) a CDR-H1 of the amino acid sequence from 31-35 of SEQ ID NO:67, ii) a CDR-H2 of the amino acid sequence from 50-65 of SEQ ID NO:67, and iii) a CDR-H3 of the amino acid sequence from 95-102 of SEQ ID NO:67; and (b) a light chain variable region comprising i) a CDR-L1 of the amino acid sequence from 24-34 of SEQ ID NO:70, ii) a CDR-L2 of the amino acid sequence from 50-56 of SEQ ID NO:70, and iii) a CDR-L3 of the amino acid sequence from 89-97 of SEQ ID NO:70, and

wherein administration of the MASP-2 inhibitory monoclonal antibody improves at least one or more of the following clinical parameters associated with aHUS: (i) an increase in platelet count, (ii) a decrease in LDH, (iii) an increase in haptoglobin, (iv) an increase in hemoglobin, and (v) a decrease in creatinine.

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

CLAIMS

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

1. A pharmaceutical composition for treating a human subject suffering from plasma therapy-resistant aHUS (atypical hemolytic uremic syndrome) comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, which inhibits MASP-2-dependent complement activation

wherein the MASP-2 inhibitory monoclonal antibody comprises:

- (a) a heavy chain variable region comprising
 - i) a CDR-H1 of the amino acid sequence from 31-35 of SEQ ID NO:67,
 - ii) a CDR-H2 of the amino acid sequence from 50-65 of SEQ ID NO:67,
 - and
 - iii) a CDR-H3 of the amino acid sequence from 95-102 of SEQ ID NO:67;
 - and
- (b) a light chain variable region comprising
 - i) a CDR-L1 of the amino acid sequence from 24-34 of SEQ ID NO:70,
 - ii) a CDR-L2 of the amino acid sequence from 50-56 of SEQ ID NO:70,
 - and
 - iii) a CDR-L3 of the amino acid sequence from 89-97 of SEQ ID NO:70,
 - and

wherein administration of the MASP-2 inhibitory monoclonal antibody improves at least one or more of the following clinical parameters associated with aHUS: (i) an increase in platelet count, (ii) a decrease in LDH, (iii) an increase in haptoglobin, (iv) an increase in hemoglobin, and (v) a decrease in creatinine.

2. Use of a pharmaceutical composition comprising a MASP-2 inhibitory monoclonal antibody, or antigen-binding fragment thereof, which inhibits MASP-2-dependent complement activation, in the manufacture of a medicament for treating a human subject suffering from plasma therapy-resistant aHUS (atypical hemolytic uremic syndrome),

wherein the MASP-2 inhibitory monoclonal antibody comprises:

- (a) a heavy chain variable region comprising
 - i) a CDR-H1 of the amino acid sequence from 31-35 of SEQ ID NO:67,

- ii) a CDR-H2 of the amino acid sequence from 50-65 of SEQ ID NO:67,
and
- iii) a CDR-H3 of the amino acid sequence from 95-102 of SEQ ID NO:67;
and
- (b) a light chain variable region comprising
 - i) a CDR-L1 of the amino acid sequence from 24-34 of SEQ ID NO:70,
 - ii) a CDR-L2 of the amino acid sequence from 50-56 of SEQ ID NO:70,
and
 - iii) a CDR-L3 of the amino acid sequence from 89-97 of SEQ ID NO:70,
and

wherein administration of the MASP-2 inhibitory monoclonal antibody improves at least one or more of the following clinical parameters associated with aHUS: (i) an increase in platelet count, (ii) a decrease in LDH, (iii) an increase in haptoglobin, (iv) an increase in hemoglobin, and (v) a decrease in creatinine.

3. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the MASP-2 inhibitory monoclonal 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.

4. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the subject has previously undergone, or is currently undergoing, treatment with a terminal complement inhibitor that inhibits cleavage of complement protein C5.

5. The pharmaceutical composition or use of claim 4, wherein the terminal complement inhibitor is a humanized anti-C5 antibody or antigen-binding fragment thereof.

6. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the MASP-2 inhibitory monoclonal antibody does not substantially inhibit the classical pathway.

7. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the MASP-2 inhibitory monoclonal antibody inhibits C3b deposition in 90% human serum with an IC₅₀ of 30 nM or less.

8. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the MASP-2 inhibitory monoclonal antibody is to be delivered to the subject systemically.

9. The pharmaceutical composition of claim 1 or the use of claim 2, wherein the MASP-2 inhibitory monoclonal 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:70.