affinity and blocks the lectin pathway complement activity and is therefore useful to treat various lectin complement pathway-associated diseases and disorders.

As further described in U.S. Patent No. 7,919,094, U.S. Patent No. 8,840,893, U.S. Patent No.8,652,477, U.S. Patent No. 8,951,522, U.S. Patent No. 9,011,860; U.S. Patent No. 9,644,035, U.S. Patent Application Publication Nos. US2013/0344073, US2013/0266560, US 2015/0166675; US2017/0189525; and co-pending U.S. Patent Application Serial Nos. 15/476,154, 15/347,434, 15/470,647, 62/315,857, 62/275,025 and 62/527,926 (each of which is assigned to Omeros Corporation, the assignee of the instant application, each of which is hereby incorporated by reference), MASP-2-dependent complement activation has been implicated as contributing to the pathogenesis of numerous acute and chronic disease states. Therefore, a need exists for a stable, high-concentration, low-viscosity formulation of a MASP-2 monoclonal antibody that is suitable for parenteral (e.g., subcutaneous) administration, for treatment of subject suffering from MASP-2 complement pathway-associated diseases and disorders.

SUMMARY

Disclosed is a stable pharmaceutical formulation suitable for parenteral administration to a mammalian subject, comprising: (a) an aqueous solution comprising a buffer system having a pH of 5.0 to 7.0; and (b) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of about 50 mg/mL to about 250 mg/mL, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising CDR-H1, CDR-H2 and CDR-H3 of SEQ ID NO:2 and (ii) a light chain variable region comprising CDR-L1, CDR-L2 and CDR-L3 of SEQ ID NO:3, or a variant thereof comprising a heavy chain variable region having at least 95% identity to SEQ ID NO:2 and a light chain variable region having at least 95% identity to SEQ ID NO:3; wherein the formulation has a viscosity of between 2 and 50 centipoise (cP), and wherein the formulation is stable when stored at between 2^{o}C and 8^{o}C for at least one month. In some examples, the concentration of the antibody in the formulation is from about 150 mg/mL to about 200 mg/mL. In some examples, the viscosity of the formulation less than 25 cP. In some examples, the buffering system comprises histidine. In some examples, the buffering system comprises citrate. In some examples, the formulation further comprises an excipient, such as a tonicity modifying agent in a sufficient amount for the formulation to be hypertonic. In some examples, the formulation further comprises a surfactant. In

some examples, the formulation further comprises a hyaluronidase enzyme in an amount effective to increase the dispersion and/or absorption of the antibody following subcutaneous administration.

In one aspect, the present disclosure refers to a stable pharmaceutical formulation suitable for parenteral administration to a mammalian subject, comprising:

(a) an aqueous solution comprising a buffer system having a pH of 5.0 to 7.0, wherein the buffer system comprises at least one buffering agent selected from the group consisting of citrate at a concentration of 10 mM to 50 mM or histidine at a concentration of 10 mM to 50 mM;

(b) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of from 100 mg/mL to 225 mg/mL, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and (ii) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:3;

(c) arginine at a concentration of from 200 mM to 300 mM; and

(d) a nonionic surfactant selected from the group consisting of a polysorbate or a poloxamer at a concentration of from 0.01% (w/v) to 0.1% (w/v);

wherein the formulation has a viscosity of between 2 and 50 millipascal-second (mPa s) when measured at 25°C with a shear rate in the range of 100,000 to 250,000 1/sec, and wherein the formulation is stable when stored at between 2ºC and 8ºC for at least six months.

In another aspect, the present disclosure refers to a stable aqueous pharmaceutical formulation suitable for parenteral administration to a mammalian subject, the formulation consisting essentially of:

(a) polysorbate 80 at a concentration from 0.01 to 0.08% w/v;

(b) L-arginine HCl at a concentration from 150 mM to 200 mM;

(c) sodium citrate at a concentration from 10 mM to 50 mM; and

(d) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of 150 mg/mL to 200 mg/mL, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and (ii) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:3;

wherein the formulation has a pH from 5.0 to 7.0, a viscosity of between 2 and 50 millipascal-second (mPa s) when measured at 25°C with a shear rate in the range of 100,000 to 250,000 1/sec, and wherein the formulation is stable when stored at between 2ºC and 8ºC for at least six months.

In another aspect, the present disclosure refers to a sealed container containing a formulation as described herein.

In another example, the formulation is contained within a subcutaneous administration device, such as a pre-filled syringe.

In another aspect, the present disclosure refers to a subcutaneous administration device containing the formulation as described herein therein.

Disclosed is a kit comprising a pre-filled container containing the formulation.

In another aspect, the present disclosure refers to a kit comprising a pre-filled container comprising the pharmaceutical formulation comprising the MASP-2 antibody as described herein and instructions for use of the formulation, wherein the pre-filled container is selected from the group consisting of: a syringe, a pen injector, a sealed vial, an auto-injector and a pump device.

In another aspect, the present disclosure refers to a pharmaceutical unit dosage form suitable for parental administration to a human, comprising a formulation as described herein in a suitable container.

Disclosed is a pharmaceutical composition for use in treating a patient suffering from, or at risk for developing a MASP-2-dependent disease or condition, wherein the composition is a sterile, single-use dosage form comprising from about 350 mg to about 400 mg (i.e., 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, or 400 mg) of MASP-2 inhibitory antibody, wherein the composition comprises about 1.8 mL to about 2.2 mL (i.e., 1.8 mL, 1.9mL, 2.0 mL, 2.1 mL or 2.2 mL) of a 185 mg/mL antibody formulation, such as disclosed herein, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and (ii) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:3; and wherein the formulation is stable when stored at between 2ºC and 8ºC for at least six months. In some examples, the MASP-2 dependent disease or condition is selected from the group consisting of aHUS, HSCT-TMA, IgAN and Lupus Nephritis (LN).

In another aspect, the present disclosure refers to a pharmaceutical composition for use in treating a patient suffering from, or at risk for developing a MASP-2-dependent complement-associated disease or disorder, wherein the composition is a sterile, single-use dosage form comprising from 350mg to 400mg of MASP-2 inhibitory antibody, wherein the composition comprises 1.8mL to 2.2 mL of an antibody formulation as disclosed herein.

Disclosed is a method of treating a subject suffering from a disease or disorder amenable to treatment with a MASP-2 inhibitory antibody comprising administering the formulation comprising a MASP-2 antibody, as disclosed herein.

In another aspect, the present disclosure refers to use of a formulation as described herein in the manufacture of a medicament for treating a subject suffering from a MASP-2-dependent complement-associated disease or disorder.

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 1A graphically illustrates the amount of lectin pathway-dependent membrane attack complex (MAC) deposition in the presence of different amounts of human MASP-2 monoclonal antibody (OMS646), demonstrating that OMS646 inhibits lectin-

on the properties of the composition. If reference is made to no amount of a substance, it should be understood as "no detectable amount."

The term "viscosity" refers to the measure of the resistance of a fluid which is being deformed by either shear stress or tensile stress; it can be evaluated using a viscometer (e.g., a rolling ball viscometer) or rheometer. Unless otherwise indicated, the viscosity measurement (centipoise, cP, which is the equivalent of one millipascal-second (mPa s) in SI units) is that at about 25°C with a shear rate in the range of 100,000 to 250,000 1/sec.

The term "parenteral administration" refers to a route of administration other than by way of the intestines and includes injection of a dosage form into the body by a syringe or other mechanical device such as an infusion pump. Parenteral routes can include intravenous, intramuscular, subcutaneous and intraperitoneal routes of administration. Subcutaneous injection is a preferred route of administration.

The term "treatment" refers to therapeutic treatment and/or prophylactic or preventative measures. Those in need of treatment include the subjects already having the disease as well as those in which the disease is to be prevented. Hence, the patient to be treated herein may have been diagnosed as having the disease or may be predisposed or susceptible to the disease.

The term "effective amount" refers to an amount of a substance that provides the desired effect. In the case of a pharmaceutical drug substance it is the amount of active ingredient effective to treat a disease in the patient. In the case of a formulation ingredient, for example, a hyaluronidase enzyme, an effective amount is the amount necessary to increase the dispersion and absorption of the co-administered MASP-2 inhibitory antibody in such a way that the MASP-2 inhibitory antibody can act in a therapeutically effective way as outlined above.

As used herein, the term "about" as used herein is meant to specify that the specific value provided may vary to a certain extent, such as a variation in the range of ±10%, preferably ±5%, most preferably ±2% are included in the given value. For example, the phrase "a pharmaceutical formulation having about 200 mg/mL MASP-2 inhibitory antibody" is understood to mean that the formulation can have from 180 mg/mL to 220 mg/mL MASP-2 inhibitory antibody (e.g., OMS646). Where ranges are stated, the endpoints are included within the range unless otherwise stated or otherwise evident from the context.

As used herein the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" includes a plurality of such excipients and equivalents thereof known to those skilled in the art,

CLAIMS

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

1. A stable pharmaceutical formulation suitable for parenteral administration to a mammalian subject, comprising:

(a) an aqueous solution comprising a buffer system having a pH of 5.0 to 7.0, wherein the buffer system comprises at least one buffering agent selected from the group consisting of citrate at a concentration of 10 mM to 50 mM or histidine at a concentration of 10 mM to 50 mM;

(b) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of from 100 mg/mL to 225 mg/mL, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and (ii) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:3;

(c) arginine at a concentration of from 200 mM to 300 mM; and

(d) a nonionic surfactant selected from the group consisting of a polysorbate or a poloxamer at a concentration of from 0.01% (w/v) to 0.1% (w/v);

wherein the formulation has a viscosity of between 2 and 50 millipascal-second (mPa s) when measured at 25°C with a shear rate in the range of 100,000 to 250,000 1/sec, and wherein the formulation is stable when stored at between 2°C and 8°C for at least six months.

2. The pharmaceutical formulation of claim 1, wherein the concentration of the antibody in the formulation is from 150 mg/mL to 200 mg/mL.

3. The pharmaceutical formulation of claim 1, wherein the at least one buffering agent is citrate.

4. The pharmaceutical formulation of claim 3, wherein the solution comprises 20 mM citrate and has a pH from 5.5 to 6.5, and wherein the solution comprises arginine at a concentration of 200 mM.

5. The pharmaceutical formulation of claim 1, wherein the nonionic surfactant is polysorbate 80.

6. The pharmaceutical formulation of claim 1, wherein the formulation comprises:

20 mM sodium citrate, 200 mM L-arginine HCl, wherein the concentration of the antibody in the formulation is from 175 mg/mL to 195 mg/mL, wherein the viscosity is less than 25 millipascal-second (mPa s), and wherein the formulation comprises from 0.001% w/v to 0.05% w/v polysorbate 80.

7. The pharmaceutical formulation of claim 1, wherein the formulation is sterile.

8. The pharmaceutical formulation of claim 1, wherein the monoclonal antibody is a full length monoclonal antibody.

9. The pharmaceutical formulation of claim 1, wherein the formulation is selected from the group consisting of:

(i) a formulation comprising:

(a) polysorbate 80 at a concentration from 0.01 to 0.08% w/v;

(b) L-arginine HCl at a concentration of 200 mM;

(c) sodium citrate at a concentration from 10 mM to 50 mM; and

(d) 150 mg/mL to 200 mg/mL of the antibody; and

(ii) a formulation comprising:

(a) polysorbate 80 at a concentration of 0.01 w/v;

(b) L-arginine HCl at a concentration of 200 mM;

(c) sodium citrate at a concentration of 20 mM; and

(d) 175 mg/mL to 195 mg/mL of the antibody.

10. A stable aqueous pharmaceutical formulation suitable for parenteral administration to a mammalian subject, the formulation consisting essentially of:

(a) polysorbate 80 at a concentration from 0.01 to 0.08% w/v;

(b) L-arginine HCl at a concentration from 150 mM to 200 mM;

(c) sodium citrate at a concentration from 10 mM to 50 mM; and

(d) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of 150 mg/mL to 200 mg/mL, wherein said antibody or fragment thereof comprises (i) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and (ii) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:3;

wherein the formulation has a pH from 5.0 to 7.0, a viscosity of between 2 and 50 millipascal-second (mPa s) when measured at 25°C with a shear rate in the range of 100,000 to 250,000 1/sec, and wherein the formulation is stable when stored at between 2ºC and 8ºC for at least six months.

11. A sealed container containing a formulation according to claim 1or 10.

12. A subcutaneous administration device containing the formulation of claim 1 or 10 therein.

13. A kit comprising a pre-filled container comprising the pharmaceutical formulation comprising the MASP-2 antibody of claim 1 or 10 and instructions for use of the formulation, wherein the pre-filled container is selected from the group consisting of: a syringe, a pen injector, a sealed vial, an auto-injector and a pump device.

14. A pharmaceutical unit dosage form suitable for parental administration to a human, comprising a formulation according to claim 1 or 10 in a suitable container.

15. Use of a formulation of claim 1 or 10 in the manufacture of a medicament for treating a subject suffering from a MASP-2-dependent complement-associated disease or disorder.

16. The use of claim 15, wherein the formulation is suitable for subcutaneous administration.

17. The use of claim 16, wherein the formulation is contained within a pre-filled syringe.

18. A pharmaceutical composition for use in treating a patient suffering from, or at risk for developing a MASP-2-dependent complement-associated disease or disorder,

wherein the composition is a sterile, single-use dosage form comprising from 350mg to 400mg of MASP-2 inhibitory antibody, wherein the composition comprises 1.8mL to 2.2 mL of an antibody formulation of Claim 1 or Claim 10.

19. The pharmaceutical composition of Claim 8, wherein the full length antibody is a human IgG4 full length antibody.

20. The kit according to Claim 13, wherein the kit further comprises at least one injection device suitable for administering the formulation in the sealed vial to a human subject.