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°C and 8°C for at least one month. In some embodiments, the concentration of the antibody in the formulation is from about 150 mg/mL to about 200 mg/mL. In some embodiments, the viscosity of the formulation less than 25 cP. In some embodiments, the buffering system comprises histidine. In some embodiments, the buffering system comprises citrate. In some embodiments, the formulation further comprises an excipient, such as a tonicity modifying agent in a sufficient amount for the formulation to be hypertonic. In some embodiments, the formulation further comprises a surfactant. In

some embodiments, 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, there is provided 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 or histidine;

(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 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

(c) a tonicity modifying agent in a sufficient amount for the formulation to be hypertonic;

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 six months.

In another aspect, there is provided 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 about 0.01 to about 0.08% w/v;

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

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

(d) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of about 150 mg/mL to about 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 about 5.0 to about 7.0, 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 six months.

In another aspect, there is provided a sealed container containing a formulation as described herein.

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

In another aspect, there is provided 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, there is provided 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, such as 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, optionally wherein the kit further comprises at least one injection device suitable for administering the formulation in the sealed vial to a human subject.

In another aspect, there is provided 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 2^{o}C and 8^{o}C for at least six months. In some embodiments, 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, there is provided 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 about 350mg to about 400mg of MASP-2 inhibitory antibody, wherein the composition comprises about 1.8mL to about 2.2 mL of a 185mg/mL antibody formulation, wherein the antibody 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 composition is stable when stored at between 2°C and 8°C for at least six months.

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, there is provided 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-

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 or histidine;

(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 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

(c) a tonicity modifying agent in a sufficient amount for the formulation to be hypertonic;

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 six months.

2. The pharmaceutical formulation of claim 1, wherein at least one or more of the following applies:

(a) wherein the concentration of the antibody in the formulation is from about 100 mg/mL to about 225 mg/mL, or from about 150 mg/mL to about 200 mg/mL, or from about 175 mg/mL to about 195 mg/mL;

(b) wherein the viscosity of the formulation is from about 2 cP to about 40 cP, or from about 2 cP to about 30 cP, or from about 2 cP to about 25 cP, or from about 2 cP to about 20 cP, or from about 2 cP to about 18 cP;

(c) wherein the viscosity is less than about 25 cP, or such as less than about 20 cP, or such as less than about 18 cP;

(d) wherein the concentration of the antibody is about 185 mg/mL;

(e) wherein the formulation is stable when stored between 2°C and 8°C for at least 12 months;

(f) wherein the injection glide force of the formulation is about 25 Newton or less when injected through a 27GA 1.25" needle at room temperature; and/or

(g) wherein the injection glide force of the formulation is about 20 Newton or less when injected through a 25GA 1" needle at room temperature.

3. The pharmaceutical formulation of claim 1, wherein the at least one buffering agent is citrate, such as sodium citrate, such as wherein citrate is present in the solution at a concentration of 10 mM to 50 mM.

4. The pharmaceutical formulation of claim 1, wherein the tonicity modifying agent is an amino acid with a charged side chain selected from the group consisting of:

(a) wherein the amino acid with a charged side chain is present in the formulation at a concentration of from about 150 mM to about 300 mM;

(b) wherein the tonicity modifying agent is an amino acid with a negatively charged side chain, such as glutamate;

(c) wherein the tonicity modifying agent is an amino acid with a positively charged side chain,

such as arginine or L-arginine HCl, and

(d) wherein arginine is present in the solution at a hypertonic level of from 200 mM to 300 mM.

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

6. The pharmaceutical formulation of claim 1, wherein the solution further comprises a surfactant at a concentration from about 0.001% (w/v) and about 0.1% (w/v), optionally wherein the surfactant is a nonionic surfactant such as a polysorbate or a poloxamer, e.g., polysorbate 80.

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

about 20 mM sodium citrate, about 200 mM L-arginine HCl, wherein the concentration of the antibody in the formulation is from about 175 mg/mL to about 195 mg/mL, and wherein the viscosity is less than about 25cP, optionally wherein the formulation further comprises from 0.001% w/v to 0.05% w/v polysorbate 80.

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

9. The pharmaceutical formulation of claim 1, wherein the monoclonal antibody is a full length monoclonal antibody, optionally wherein the antibody is a human IgG4 full length antibody, such as a human IgG4 antibody comprising a mutation in the hinge region.

10. The pharmaceutical formulation of claim 1, wherein one or more the following applies:

(a) wherein the formulation does not include sucrose or sorbitol;

(b) wherein the formulation does not include $CaCl_2$;

(c) wherein the formulation does not include $MgCl_2$;

(d) wherein the formulation does not include $CaCl_2$ and wherein the formulation does not include $MgCl_2$; and/or

(e) wherein the formulation does not include a divalent cation additive.

11. 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 about 0.01 to about 0.08% w/v;

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

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

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

(ii) a formulation comprising:

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

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

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

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

12. 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 about 0.01 to about 0.08% w/v;

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

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

(d) a monoclonal antibody or fragment thereof that specifically binds to human MASP-2 at a concentration of about 150 mg/mL to about 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 about 5.0 to about 7.0, 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 six months.

13. A sealed container containing a formulation according to claim 1or 12.

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

15. A kit comprising a pre-filled container comprising the pharmaceutical formulation comprising the MASP-2 antibody of claim 1 or 12 and instructions for use of the formulation, such as 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, optionally wherein the kit further comprises at least one injection device suitable for administering the formulation in the sealed vial to a human subject.

16. A pharmaceutical unit dosage form suitable for parental administration to a human, comprising a formulation according to claim 1 or 12 in a suitable container.

17. Use of a formulation of claim 1 or 12 in the manufacture of a medicament for treating a subject suffering from a MASP-2-dependent complement-associated disease or disorder.

18. The use of claim 17, wherein the formulation is suitable for subcutaneous administration.

19. The use of claim 18, wherein the formulation is contained within a pre-filled syringe.

20. 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 about 350mg to about 400mg of MASP-2 inhibitory antibody, wherein the composition comprises about 1.8mL to about 2.2 mL of a 185mg/mL antibody formulation, wherein the antibody 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 composition is stable when stored at between 2°C and 8°C for at least six months.