

ensures that targets of the complement system are limited to pathogenic cells. Many complement-related disorders and diseases are associated with abnormal destruction of self cells by the complement cascade. Some complement-related disorders and diseases include neurological diseases and disorders, such as myasthenia gravis.

[0008] Myasthenia gravis is a rare complement-mediated autoimmune disease characterized by the production of autoantibodies targeting proteins that are critical for the normal transmission of electrical signals from nerves to muscles. The prevalence of MG in the United States is estimated at approximately 60,000 cases. In approximately 15% of patients with MG, symptoms are confined to the ocular muscles. The remaining patients have MG that affects multiple muscle groups throughout the body, which is typically referred to as generalized MG (gMG). Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Muscle weakness can be localized to specific muscles, but often progresses to more diffuse muscle weakness. Generalized myasthenia gravis symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalization, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within 2 years of diagnosis.

[0009] There remains a need for compositions and methods for treating complement-related diseases and disorders, including those affecting the nervous system, such as myasthenia gravis. The present disclosure meets this need by providing related compositions and methods.

SUMMARY

[0010] In one aspect, the present disclosure provides use of zilucoplan in the manufacture of a medicament for treating myasthenia gravis (MG) in a subject. In some examples, the present disclosure provides a method of treating complement-related indications and/or autoimmune indications and/or neurological disorders as disclosed herein, for example myasthenia gravis (MG), the method comprising administering a compound, or a composition comprising a compound, which modulates complement activity to a subject. Such a compound may be an inhibitor that blocks complement activation (a complement inhibitor), for example a C5 inhibitor, for example a C5 inhibitor polypeptide as described herein. The compound may be zilucoplan or active metabolites or variants thereof, as disclosed herein and the indication or disorder may be MG, as further defined herein below.

Herein, MG may include or be generalized MG (gMG). The compound (e.g., zilucoplan) administration may include subcutaneous (SC) administration. The compound (e.g., zilucoplan) may be administered at a dose of from about 0.1 mg/kg (mg compound/kg subject body weight) to about 0.6 mg/kg. Compound administration may include self-administration. Compound administration may include use of a prefilled syringe. The syringe may include a 29-gauge needle. Compound administration may include self-administration using a self-administration device. The self-administration device may include a prefilled syringe. The prefilled syringe may include glass. Optionally, the prefilled syringe is a glass syringe. The prefilled syringe may include a maximum fill volume of at least 1 ml. The self-administration device may include a solution of the compound. The solution may be an aqueous solution. The solution may be preservative-free. The self-administration device may include a solution volume of from about 0.15 ml to about 0.81 ml. The subject may be screened prior to administration of the compound (e.g., zilucoplan). The screening may include assessment of Quantitative Myasthenia Gravis (QMG) score. Subject QMG score may be ≥ 12 . The subject may be prohibited from receiving MG therapy for at least 10 hours prior to QMG score assessment. The MG therapy may be acetylcholinesterase inhibitor therapy. The screening may require that ≥ 4 QMG test items achieve a score of ≥ 2 . The subject may be between 18 and 85 years old. Screening may include selecting subjects previously diagnosed with gMG. The gMG diagnosis may be made according to Myasthenia Gravis Foundation of America (MGFA) criteria. Screening may include assessment of acetylcholinesterase receptor (AChR) autoantibody levels. Screening may include confirming no change in corticosteroid dose received by the subject for at least 30 days prior to screening. Screening may include confirming no change in subject immunosuppressive therapy for at least 30 days prior to screening. Screening may include a serum pregnancy test and/or a urine pregnancy test. Compound administration may include daily administration. The subject may simultaneously receive standard of care gMG therapy. The standard of care gMG therapy may include one or more of pyridostigmine treatment, corticosteroid treatment, and immunosuppressive drug treatment. The subject may be evaluated or monitored for an MG characteristic, wherein the MG characteristic includes one or more of QMG score, Myasthenia Gravis-Activities of Daily Living (MG-ADL) score, MG-QOL15r score, and MG Composite score. Subject evaluation or monitoring may include assessing change in the MG characteristic during or after subject treatment with a compound as described herein (e.g.: zilucoplan). The MG characteristic may include QMG score reduction. Treated subject QMG score may be reduced by at least 3 points. Treated subject QMG score may be reduced at or before 12

weeks of treatment. Treated subject QMG score may be monitored over the course of the treatment. The subject may receive cholinesterase inhibitor treatment over the course of the treatment. Cholinesterase inhibitor treatment may be withheld for at least 10 hours prior to assessment of treated subject QMG score. Change in MG characteristic may include change in MG Composite score of at least 3 points from a baseline MG Composite score. Change in MG Composite score from baseline MG Composite score may occur at or before 12 weeks of the treatment. Change in MG characteristic may include change in MG-ADL score of at least 2 points from a baseline MG-ADL score. Change in MG-ADL score from baseline MG-ADL score may occur at or before 12 weeks of the treatment. The compound may be in a solution, wherein the solution comprises phosphate-buffered saline (PBS). The solution may include from about 4 mg/ml to about 200 mg/ml of the compound (e.g.: zilucoplan). The solution may include about 40 mg/ml of the compound (e.g., zilucoplan). Subject plasma levels of the compound may reach maximum concentration ($C_{\max}$) on the first day of treatment. At least 90% hemolysis inhibition may be achieved in subject serum, wherein, optionally, hemolysis inhibition is measured by a sheep red blood cell (sRBC) hemolysis assay. The compound (e.g., zilucoplan) may be administered at a daily dose of from about 0.1 mg/kg to about 0.3 mg/kg. Zilucoplan may be administered at a dose of 0.3 mg/kg. Subject QMG score and/or MG-ADL score may be reduced. QMG score may be reduced by ≥ 3 points by 8 weeks of treatment. MG-ADL score may be reduced by ≥ 2 points by 8 weeks of treatment. Risk of need for rescue therapy may be reduced. Administration may be carried out at an MG disease stage that occurs prior to a critical or crisis stage of MG. Administration of the compound (e.g., zilucoplan) may lead to reduced subject symptom expression. The reduced subject symptom expression may exceed reduced subject symptom expression associated with eculizumab administration. Subject neuromuscular junction (NMJ) membrane attack complex (MAC) pore formation may be inhibited. Safety factor at the NMJ may be improved. Zilucoplan may be administered in combination with a therapeutic agent. The therapeutic agent may include an immunosuppressive agent. The immunosuppressive agent may include a compound selected from one or more of azathioprine, cyclosporine, cyclosporine A, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide, and rituximab. The therapeutic agent may include an inhibitor of autoantibody-mediated tissue destruction. The inhibitor of autoantibody-mediated tissue destruction may include a neonatal Fc receptor (FcRN) inhibitor. Administration of the FcRN inhibitor may include intravenous immunoglobulin (IVIG) treatment. Zilucoplan and the therapeutic agent may be administered in overlapping regimens.

[0011] In some examples, the present disclosure provides a kit that may include a syringe that includes the compound (e.g., zilucoplan) and instructions for use. The syringe may include a self-injection device. The self-injection device may include a BD ULTRASAFE PLUS™ self-administration device. The kit may include an alcohol wipe. The kit may include a wound dressing. The kit may include a disposal container. The compound may be in a solution. The solution may be an aqueous solution. The solution may include phosphate buffered saline. The solution may include from about 4 mg/ml to about 200 mg/ml of the compound (e.g., zilucoplan). The solution may include about 40 mg/ml of the compound (e.g., zilucoplan). The solution may include a preservative.

[0012] According to some examples, the present disclosure provides a method of evaluating a treatment for a complement-related indications and/or autoimmune indications and/or neurological disorders as disclosed herein, such as for MG. The method may include screening an evaluation candidate for at least one evaluation participation criteria; selecting an evaluation participant; administering the treatment for the indication or disorder (e.g., MG) to the evaluation participant; and assessing at least one efficacy endpoint, wherein, optionally, the treatment involves administration of a compound (e.g., zilucoplan) or composition as disclosed herein. The at least one evaluation participation criteria may include MG diagnosis. The MG diagnosis may include gMG diagnosis. The MG diagnosis may be gMG diagnosis. The gMG diagnosis may be made according to MGFA criteria. The at least one evaluation participation criteria may include QMG score. Evaluation participant selection may require an evaluation candidate QMG score of ≥ 12 . The evaluation candidate may have received at least one alternative MG treatment prior to screening. Evaluation candidate QMG score may be assessed at least 10 hours after receiving the at least one alternative MG treatment. The at least one alternative MG treatment may include acetylcholinesterase inhibitor administration. Evaluation participant selection may require a score of ≥ 2 for ≥ 4 QMG test items. The at least one evaluation participation criteria may include evaluation candidate age. Evaluation participant selection may require evaluation candidate age of between 18 and 85 years old. The at least one evaluation participation criteria may include AChR autoantibody level and/or anti-muscle-specific kinase autoantibody level. The at least one evaluation participation criteria may include no change in corticosteroid dose received by evaluation candidate for at least 30 days prior to screening. The at least one evaluation participation criteria may include no change in evaluation candidate immunosuppressive therapy for at least 30 days prior to screening. The at least one evaluation participation criteria may include confirmation that the evaluation candidate is not pregnant. Screening

may include a serum pregnancy test and/or a urine pregnancy test. The treatment for MG may be administered over an evaluation period. The evaluation period may be from about 1 day to about 12 weeks. The evaluation period may be about 12 weeks or longer. The evaluation participant may receive standard of care gMG therapy over the evaluation period. The standard of care gMG therapy may include one or more of pyridostigmine treatment, corticosteroid treatment, and immunosuppressive drug treatment. The at least one efficacy endpoint may include treated subject QMG score reduction. The treated subject QMG score reduction may be at least 3 points. The evaluation participant may receive cholinesterase inhibitor treatment during the evaluation period. The cholinesterase inhibitor treatment may be withheld for at least 10 hours prior to assessment of treated subject QMG score. The at least one efficacy endpoint may include a change in baseline score for one or more of MG-ADL score, MG-QOL15r score, and MG Composite score. The at least one efficacy endpoint may include a change in baseline MG Composite score of at least 3 points. The change in baseline MG Composite score may occur at or before 12 weeks of the treatment. The at least one efficacy endpoint may include a change in baseline MG-ADL score of at least 2 points. The change in baseline MG-ADL score may occur at or before 12 weeks of the treatment for MG. Assessing the at least one efficacy endpoint may include a set of assessments. The set of assessments may be carried out in the order of: (1) assessing evaluation participant MG-QOL15r score; (2) assessing evaluation participant MG-ADL score; (3) assessing evaluation participant QMG score; and (4) assessing evaluation participant MG Composite score. The set of assessments may be carried out on one or more occasions after administering the treatment for MG. The one or more occasions after administering the treatment for MG may include 1 week, 2 weeks, 4 weeks, 8 weeks, and/or 12 weeks after administering the treatment for MG.

[0013] In some examples the present disclosure provides an administration device prepared for treatment of a complement-related indication and/or neurological disorder as disclosed herein, such as MG. The administration device may include a self-injection device comprising a syringe and a needle. The administration device may include a predetermined volume of a pharmaceutical composition. The pharmaceutical composition may include a 40 mg/mL concentration of a compound as disclosed herein (e.g., zilucoplan) in an aqueous solution. The predetermined volume may be modified to facilitate administration of the compound (e.g., zilucoplan) to a subject at a dose of 0.3 mg per kg subject weight. The administration device may include a BD ULTRASAFE PLUS™ self-administration device.

[0014] In some examples, the present disclosure provides a kit prepared for treatment of MG. The kit may include a set of two or more administration devices described herein and instructions for kit usage. The kit may include an alcohol wipe. The kit may include a wound dressing. The kit may include a disposal container. Kit administration devices may include pharmaceutical compositions of the compound (e.g., zilucoplan) that are preservative free. The kit may be prepared for storage at room temperature.

BRIEF DESCRIPTION OF THE FIGURES

[0015] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale; emphasis instead being placed upon illustrating the principles of various disclosed embodiments.

[0016] Fig. 1 is a schematic showing the overlap between classical and alternative complement pathways.

[0017] Fig. 2 is a schematic showing a myasthenia gravis treatment study design.

[0018] Fig. 3 is a graph showing quantitative myasthenia gravis (QMG) score change from baseline during twelve weeks of placebo versus 0.3 mg/kg zilucoplan treatment.

[0019] Fig. 4 is a graph showing Myasthenia Gravis-Activities of Daily Living (MG-ADL) score change from baseline during twelve weeks of placebo versus 0.3 mg/kg zilucoplan treatment.

[0020] Fig. 5 is a graph showing QMG score change from baseline during twelve weeks of placebo versus 0.1 mg/kg zilucoplan treatment.

[0021] Fig. 6 is a graph showing MG-ADL score change from baseline during twelve weeks of placebo versus 0.1 mg/kg zilucoplan treatment.

[0022] Fig. 7 is a graph showing MG-ADL score change from baseline during twelve weeks of placebo versus combined average score changes from 0.1 mg/kg and 0.3 mg/kg zilucoplan treatment doses.

[0023] Fig. 8 is a graph showing point improvement in QMG score by percent of patients for 0.3 mg/kg zilucoplan treatment versus placebo.

[0024] Fig. 9 is a graph showing point improvement in MG-ADL score by percent of patients for 0.3 mg/kg zilucoplan treatment versus placebo.

CLAIMS

What is claimed is:

1. Use of zilucoplan in the manufacture of a medicament for treating myasthenia gravis (MG) in a subject.
2. The use of claim 1, wherein the MG is generalized MG (gMG).
3. The use of claim 1 or 2, wherein the medicament is to be administered via subcutaneous (SC) administration.
4. The use of any of claims 1-3, wherein zilucoplan is to be administered at a dose of from about 0.1 mg/kg (mg zilucoplan/kg subject body weight) to about 0.6 mg/kg.
5. The use of any of claims 1-4, wherein the medicament is to be administered via self-administration.
6. The use of any of claims 1-5, wherein the medicament is to be administered via use of a prefilled syringe.
7. The use of claim 6, wherein the syringe comprises a 29-gauge needle.
8. The use of any of claims 1-7, wherein the medicament is to be self-administered using a self-administration device.
9. The use of claim 8, wherein the self-administration device comprises the prefilled syringe of claim 6 or 7.
10. The use of claim 9, wherein the prefilled syringe is a glass syringe.
11. The use of claim 9 or 10, wherein the prefilled syringe comprises a maximum fill volume of at least 1 ml.
12. The use of any of claims 8-11, wherein the self-administration device comprises a zilucoplan solution.
13. The use of claim 12, wherein the zilucoplan solution is an aqueous solution.
14. The use of claim 12 or 13, wherein the zilucoplan solution is preservative-free.

15. The use of any of claims 12-14, wherein the self-administration device comprises a zilucoplan solution volume of from about 0.15 ml to about 0.81 ml.
16. The use of any of claims 1-15, wherein the subject is screened prior to zilucoplan administration.
17. The use of claim 16, wherein the screening comprises assessment of Quantitative Myasthenia Gravis (QMG) score.
18. The use of claim 17, wherein subject QMG score is ≥ 12 .
19. The use of claim 18, wherein the subject does not receive MG therapy for at least 10 hours prior to QMG score assessment.
20. The use of claim 18 or 19, wherein the subject does not receive acetylcholinesterase inhibitor therapy for at least 10 hours prior to QMG score assessment.
21. The use of any of claims 18-20, wherein ≥ 4 QMG test items achieve a score of ≥ 2 .
22. The use of any of claims 1-21, wherein the subject is between 18 and 85 years old.
23. The use of any of claims 16-22, wherein screening comprises selecting subjects previously diagnosed with gMG.
24. The use of claim 23, wherein the gMG diagnosis is made according to Myasthenia Gravis Foundation of America (MGFA) criteria.
25. The use of any of claims 16-24, wherein screening comprises assessment of acetylcholinesterase receptor (AChR) autoantibody levels.
26. The use of any of claims 16-25, wherein screening comprises confirming no change in corticosteroid dose received by subject for at least 30 days prior to screening.
27. The use of any of claims 16-26, wherein screening comprises confirming no change in subject immunosuppressive therapy for at least 30 days prior to screening.
28. The use of any of claims 16-27, wherein screening comprises a serum pregnancy test and/or a urine pregnancy test.
29. The use of any of claims 1-28, wherein zilucoplan is to be administered daily.

30. The use of any of claims 1-29, wherein the subject simultaneously receives standard of care gMG therapy.
31. The use of claim 30, wherein the standard of care gMG therapy comprises one or more of pyridostigmine treatment, corticosteroid treatment, and immunosuppressive drug treatment.
32. The use of any of claims 1-31, wherein the subject is evaluated or monitored for an MG characteristic, wherein the MG characteristic comprises one or more of QMG score, Myasthenia Gravis-Activities of Daily Living (MG-ADL) score, MG-QOL15r score, and MG Composite score.
33. The use of claim 32, wherein subject evaluation or monitoring comprises assessing change in the MG characteristic during or after subject zilucoplan treatment.
34. The use of claim 33, wherein treated subject QMG score is reduced.
35. The use of claim 34, wherein treated subject QMG score is reduced by at least 3 points.
36. The use of claim 34 or 35, wherein treated subject QMG score is reduced at or before 12 weeks of treatment.
37. The use of any of claims 34-36, wherein treated subject QMG score is monitored over the course of zilucoplan treatment.
38. The use of any of claims 34-37, wherein the subject is receiving cholinesterase inhibitor treatment over the course of zilucoplan treatment.
39. The use of claim 38, wherein cholinesterase inhibitor treatment is withheld for at least 10 hours prior to assessment of treated subject QMG score.
40. The use of claim 39, wherein the change in the MG characteristic comprises change in MG Composite score of at least 3 points from a baseline MG Composite score.
41. The use of claim 40, wherein the change in MG Composite score from baseline MG Composite score occurs at or before 12 weeks of zilucoplan treatment.
42. The use of claim 39, wherein the change in the MG characteristic comprises change in MG-ADL score of at least 2 points from a baseline MG-ADL score.

43. The use of claim 42, wherein the change in MG-ADL score from baseline MG-ADL score occurs at or before 12 weeks of zilucoplan treatment.
44. The use of any of claims 1-43, wherein the zilucoplan is in a solution, wherein the solution comprises phosphate-buffered saline (PBS).
45. The use of claim 1-44, wherein the zilucoplan is in a solution and the solution comprises from about 4 mg/ml to about 200 mg/ml zilucoplan.
46. The use of claim 45, wherein the solution comprises about 40 mg/ml zilucoplan.
47. The use of any of claims 1-46, wherein subject zilucoplan plasma levels reach maximum concentration ($C_{\max}$) on the first day of treatment.
48. The use of any of claims 1-47, wherein at least 90% hemolysis inhibition is achieved in subject serum, wherein, optionally, hemolysis inhibition is measured by a sheep red blood cell (sRBC) hemolysis assay.