

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, wherein zilucoplan is to be administered at a daily dose of 0.3 mg/kg (mg zilucoplan/kg subject body weight). 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.

CLAIMS

What is claimed is:

1. Use of zilucoplan in the manufacture of a medicament for treating myasthenia gravis (MG) in a subject, wherein zilucoplan is to be administered at a daily dose of 0.3 mg/kg (mg zilucoplan/kg subject body weight).
2. The use of claim 1, wherein the MG is generalized MG (gMG).
3. The use of claim 1 or 2, wherein at least 90% of complement activity in the subject is inhibited.
4. The use of claim 3, wherein the inhibition of complement activity in the subject is achieved through daily administration for at least 7 days.
5. The use of any of claims 1-4, wherein a steady state zilucoplan plasma concentration is achieved within the first two weeks of treatment.
36. The use of any of claims 1 or 2-5, 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.~~
- ~~57.~~ The use of any of claims 1-~~46~~, wherein the medicament is to be administered via self-administration.
- ~~68.~~ The use of any of claims 1-~~57~~, wherein the medicament is to be administered via use of a prefilled syringe.
- ~~79.~~ The use of claim ~~68~~, wherein the syringe comprises a 29-gauge needle.
- ~~810.~~ The use of any of claims 1-~~79~~, wherein the medicament is to be self-administered using a self-administration device.

911. The use of claim 810, wherein the self-administration device comprises the prefilled syringe of claim 6-8 or 79.
1012. The use of claim 911, wherein the prefilled syringe is a glass syringe.
1113. The use of claim 9-11 or 1012, wherein the prefilled syringe comprises a maximum fill volume of at least 1 ml.
1214. The use of any of claims 810-1113, wherein the self-administration device comprises an aqueous zilucoplan solution.
- ~~13. The use of claim 12, wherein the zilucoplan solution is an aqueous solution.~~
1415. The use of claim ~~12-14~~ or 13, wherein the zilucoplan solution is preservative-free.
1516. The use of ~~any of~~ claims ~~1214-14~~ or 15, 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.~~

3217. The use of any of claims 1-~~3116~~, wherein the subject is to be 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.

~~3318.~~ The use of claim ~~3217~~, wherein subject evaluation or monitoring comprises ~~assessing~~ change to be assessed in the MG characteristic during or after subject zilucoplan treatment.

~~3419.~~ The use of claim ~~3318~~, wherein treated subject QMG score is reduced.

~~3520.~~ The use of claim ~~3419~~, wherein treated subject QMG score is reduced by at least 3 points.

~~3621.~~ The use of claim ~~3419~~ or ~~3520~~, wherein treated subject QMG score is reduced at or before 12 weeks of treatment.

~~3722.~~ The use of any of claims ~~3419-3621~~, wherein treated subject QMG score is to be 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.~~

~~4023.~~ The use of claim ~~3918~~, wherein the ~~change in the MG characteristic comprises change in treated subject~~ MG Composite score is reduced by ~~of~~ at least 3 points from a baseline MG Composite score.

~~4124.~~ The use of claim ~~4023~~, wherein the ~~change-reduction~~ in MG Composite score from baseline MG Composite score occurs at or before 12 weeks of zilucoplan treatment.

~~4225.~~ The use of claim ~~3918~~, wherein the ~~change in the MG characteristic comprises change in treated subject~~ MG-ADL score ~~of~~ is reduced by at least 2 points from a baseline MG-ADL score.

~~4326.~~ The use of claim ~~4225~~, wherein the ~~change-reduction~~ in MG-ADL score from baseline MG-ADL score occurs at or before 12 weeks of zilucoplan treatment.

4427. The use of any of claims 1-~~4326~~, wherein the zilucoplan is in a solution, wherein the solution comprises phosphate-buffered saline (PBS).
4528. The use of claim 1-~~4427~~, wherein the zilucoplan is in a solution and the solution comprises from ~~about~~ 4 mg/ml to ~~about~~ 200 mg/ml zilucoplan.
4629. The use of claim 4528, wherein the solution comprises ~~about~~ 40 mg/ml zilucoplan.
4730. The use of any of claims 1-~~4629~~, wherein subject zilucoplan plasma levels reach maximum concentration (C_{max}) on the first day of treatment.
4831. The use of any of claims 1-~~4730~~, 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.
32. The use of any of claims 1-31, wherein the subject is to simultaneously receive standard of care gMG therapy.
33. The use of claim 32, wherein the standard of care gMG therapy comprises one or more of pyridostigmine treatment, corticosteroid treatment, and immunosuppressive drug treatment.
34. The use of any of claims 1-33, wherein the subject is to receive cholinesterase inhibitor treatment over the course of zilucoplan treatment.