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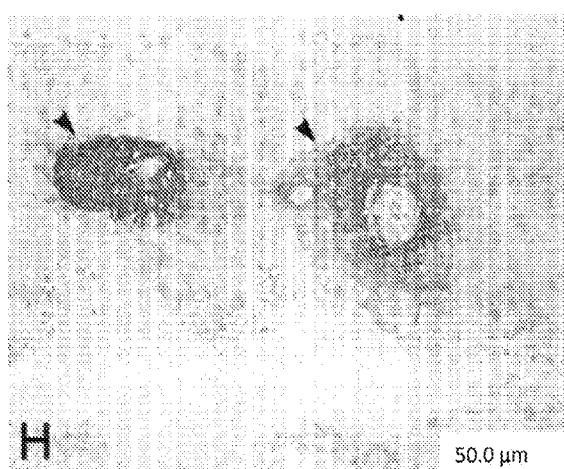
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(54) Title: COMPOSITIONS AND METHODS USEFUL FOR THE TREATMENT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS



(57) Abstract: Compositions and methods useful for the treatment of neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD) are disclosed.



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## COMPOSITIONS AND METHODS USEFUL FOR THE TREATMENT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS

### Field of the Invention

The invention relates to the fields of central nervous system and neuromyelitis optica (NMO) spectrum disorders. More specifically, the invention provides an anti-inflammatory formulation and methods of use thereof which ameliorate or reduce the symptoms of NMO.

### Background of the Invention

Numerous publications and patent documents, including both published applications and issued patents, are cited throughout the specification in order to describe the state of the art to which this invention pertains. Each of these citations is incorporated herein by reference as though set forth in full.

Neuromyelitis optica spectrum disorders (NMOSD) include limited forms of Devic's disease, such as single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or transverse myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

Neuromyelitis optica (NMO or Devic's disease) is an inflammatory, demyelinating syndrome of the central nervous system that is characterized by severe attacks of optic neuritis and transverse myelitis, which, unlike the attacks in multiple sclerosis, commonly spare the brain in the early stages.

In developed nations, neuromyelitis optica disproportionately strikes non-white populations, in which multiple sclerosis is rare. Neuromyelitis optica presents with clinical, neuroimaging, and laboratory findings that distinguish it from multiple sclerosis. Moreover, the detection of neuromyelitis optica immunoglobulin G (NMO-IgG), an autoantibody, in the serum of patients with neuromyelitis optica, distinguishes neuromyelitis optica from other demyelinating disorders. NMO-IgG binds to aquaporin 4 which is the main channel that regulates water homoeostasis in the central nervous system. NMO-IgG is also detected in the serum of patients with disorders related to neuromyelitis optica, including Asian optic-spinal multiple sclerosis, recurrent transverse myelitis associated with longitudinally extensive spinal

cord lesions, recurrent isolated optic neuritis, and optic neuritis or transverse myelitis in the context of certain organ-specific and non-organ-specific autoimmune diseases.

NMO patients are currently treated using agents which reduce symptoms and reduce or prevent relapses. No cure for NMO or NMOSDs is currently available. Most individuals with NMO have an unpredictable, relapsing course of disease with attacks occurring months or years apart. Disability is cumulative, the result of each attack damaging new areas of myelin. Clearly, a need exists for improved treatments for this devastating disease which can limit the neurologic dysfunction that results from successive acute relapses of NMO.

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### Summary of the Invention

In accordance with the present invention, a method of treating or delaying the progression of a CNS disorder alleviated by inhibiting complement immune system activation in a patient in need of such treatment is disclosed. An exemplary method comprises administering, during an active CNS attack, a therapeutically effective amount of C1-esterase inhibitor (C1-INH) alone or in combination with one or more other agents or treatments useful for treatment of such CNS disorders. Also included are compositions comprising a C1-INH for use in a method of treating or delaying the progression of a CNS disorder alleviated by inhibiting complement immune system activation, wherein the method comprises administering the C1-INH during an active CNS attack. The treatment may involve administering C1-INH alone or in combination with one or more other agents or treatments useful for treatment of such CNS disorders. In a preferred embodiment, the disorder is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD). Such treatment can be during the acute phase of onset or soon thereafter and is preferably of short duration. In some embodiments, the C1-INH is administered at the onset of an active CNS attack.

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Also provided is a method of preventing or delaying the progression of a CNS disorder alleviated by inhibiting complement immune activation in a patient in need of such treatment, the method comprising administering, at the onset of an active CNS attack, a therapeutically effective amount of C1-INH. Further provided are compositions comprising a C1-INH for use in a method of preventing or delaying the progression of a CNS disorder alleviated by inhibiting complement immune activation, wherein the method comprises administering the C1-INH at the onset of an active CNS attack. The treatment may involve administering C1-INH alone or in

combination with one or more other agents useful for treatment of such CNS disorders. In a preferred embodiment, the disorder is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD).

The C1-esterase inhibitor (C1-INH) may be or may comprise a human plasma-derived C1-INH (hC1-INH), for example, CINRYZE®, or a recombinant C1-INH (rC1-INH).

The disorder may be selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with 10 lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

In one aspect, the C1-esterase inhibitor (C1-INH) comprises a human plasma-derived C1-INH (hC1-INH) or a recombinant C1-INH (rC1-INH) and the disorder is selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of 15 longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO. In a preferred embodiment, the disorder is NMO and said C1 esterase inhibitor is a human plasma-derived C1-INH (hC1-INH). In a particularly preferred embodiment, the disorder is NMO and said C1 esterase inhibitor is CINRYZE®.

The C1-INH may be administered in combination with another agent or treatment useful for treating NMO or NMOSD. Such agents/ treatments include without limitation, plasmapheresis and/or administration of intravenous immunoglobulin preparations, 25 administration of mycophenolate, rituximab and/or eculizumab. The agent or treatment may be an additional biologically active agent or treatment effective for treating or delaying the progression of a CNS disorder, such as neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD). For example, the additional biologically active agent may be a corticosteroid, an (intravenous) immunoglobulin preparation, or an anti-lymphocyte preparation, 30 mycophenolate, rituximab and/or eculizumab. In a preferred embodiment, the patient is or has also been treated with intravenous immune therapy (e.g. a corticosteroid, for example a

(synthetic) glucocorticoid, such as methylprednisolone). Accordingly, the additional biologically active agent may be a corticosteroid, for example a (synthetic) glucocorticoid, such as methylprednisolone. The additional biologically active agent may be administered intravenously. The agent/ treatment may alternatively, or in addition, involve plasmapheresis 5 (plasma exchange), for example in those patients who do not respond to IV steroids (e.g. where insufficient suppression of CNS inflammation is or has been observed following a course of IV steroid treatment). Thus, the patient may be a steroid-unresponsive patient and may optionally be receiving plasmapheresis. A non-responder with respect to a particular treatment may be defined as a patient not showing an improvement or showing some improvement but maintaining 10 a significant neurological deficit following said treatment. Relative improvements may, for example, be ascertained by comparing EDSS score on commencement of the treatment with EDSS score following commencement of treatment (e.g. at day 5, day 7, day 14 or day 30 post-commencement, or at discharge from hospital).

15 In certain approaches, the agents/ treatments are administered concurrently. In other approaches, they are administered sequentially.

The compositions and compositions for use as described herein may be formulated as a pharmaceutical composition. The pharmaceutical composition may comprise a C1-INH and a pharmaceutically acceptable carrier medium. The pharmaceutical composition may be for use in a method of treating or delaying the progression of a CNS disorder (e.g. NMO or NMOSD) as 20 described herein. The pharmaceutical composition may be administered in combination with (e.g. concurrently or sequentially with) an additional agent or treatment as defined herein.

Also provided is a kit comprising: (i) a C1-INH; and (ii) an additional biologically active agent as defined herein, wherein said components (i) and (ii) are packaged for concurrent or sequential administration to a patient.

25 Further provided is a C1-INH and an additional biologically active agent as defined herein as a combined preparation for concurrent or sequential use in a method of treatment according to the invention.

Also within the scope of the present invention is a pharmaceutical composition for treating or delaying the progression of a disorder caused by alleviated by inhibiting alternative 30 pathway complement immune system activation in a patient in need of such treatment, the composition comprising administration of an activation inhibiting amount of

a C1-esterase inhibitor (C1-INH); and optionally, a biologically active agent selected from the group consisting of, intravenous immune therapy, mycophenolate, rituximab and/or eculizumab or a combination thereof; and a pharmaceutically acceptable carrier medium.

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### **Brief Description of the Drawing**

Figure 1 is a photograph (Roemer et al. (2007) Brain 130:1194-1205) showing the classic complement deposition in NMO lesions in both the rim pattern (left) and rosette pattern. Staining is for C9neo.

### **Detailed Description of the Invention**

10 The present invention relates to the discovery that C1-esterase inhibitor (C1-INH) protein may be advantageously administered to NMO and NMOSD patients who present with relapsing autoimmune disease targeting the spinal cord and optic nerve leading to paralysis and blindness. It has been unexpectedly discovered that early short term treatment with C1-INH, as an adjunct to intravenous corticosteroid immunosuppressive therapy (such as IV methylprednisolone) and 15 plasmapheresis in those patients who do not respond to IV steroids (“standard-of-care”), can reduce the damage to the patients nervous system compared to “standard-of-care” alone. As a further advantage to this approach, the present inventors have discovered that early and/or short term duration treatment with C1-INH can produce a durable (longer term) reduction in disease burden post cessation of treatment. In a preferred embodiment of the invention, the C1-INH is 20 CINRYZE®. A preferred aspect of the invention is where the patients are treated with conventional intravenous immune therapy (e.g., a synthetic glucocorticoid, such as methylprednisolone). In an alternative embodiment, the IV immunotherapy includes other known therapies for treating NMO, for example, plasmapheresis and/or intravenous immunoglobulin preparations. Other approaches include off label uses of anti-lymphocyte 25 preparations, rituximab (antibody against CD20), mycophenolate and/or eculizumab (monoclonal antibody against terminal complement cascade protein C5).

Thus, a patient to be treated according to the present invention may present with relapsing autoimmune disease targeting the spinal cord and optic nerve and may optionally suffer from paralysis and blindness. The patient to be treated may have previously received, and/or 30 may be receiving a biologically active agent or treatment effective for treating or delaying the

progression of NMO or NMOSD, as defined herein. For example, the patient may have previously been treated with, and/or may be receiving (intravenous) immunotherapy. The (intravenous) immunotherapy may be selected from conventional intravenous immune therapy (e.g., a synthetic glucocorticoid, such as methylprednisolone) and/or plasmapheresis. The patient 5 may be a patient who does not respond to said previous or concurrent treatment (e.g. a patient who does not respond to IV steroid treatment, who may optionally be receiving or have received plasmapheresis). Alternatively, or in addition, the patient may be receiving (intravenous) immunoglobulin preparations or anti-lymphocyte preparations, rituximab, mycophenolate and/or eculizumab. The C1-INH may be administered at the onset of, and/or during, the early acute 10 phase of an active CNS attack. Alternatively, or in addition, the C1-INH may be administered to the patient for short term duration. Administering C1-INH early during an acute active CNS attack means that the inhibitor is administered when complement damage is at its peak and administering for a short duration minimizes the exposure to this medication and minimises the cost of care.

15 C1 esterase inhibitor (C1-INH) is an endogenous plasma protein (or a functional analog thereof) in the family of serine protease inhibitors (SERPINs) and has broad inhibitor activity in the complement, contact, and coagulation pathways. C1-INH inhibits the classical pathway of the complement system by binding C1r and C1s and inhibits the mannose-binding lectin-associated serine proteases in the lectin pathway. A nanofiltered plasma derived C1-INH 20 (Cinryze®; Viropharma) is FDA approved for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE), a disease characterized by constitutional deficiency or dysfunction of endogenous C1 esterase inhibitor.

25 Cinryze® is known to be well tolerated in humans via the experience in patients with HAE studied in randomized trials as well as in an extension trial. The most frequent adverse events reported at the doses used for HAE were headaches and nasopharyngitis. In more than four years of post-marketing surveillance, there have been no safety concerns for infectious events that could be attributed to Cinryze®. Moreover, plasma derived formulations of C1-INH have been evaluated for their clinical use in pilot studies of sepsis, ischemia-reperfusion injury, and capillary leak in bone marrow transplantation. Thus, C1-INH is an ideal therapeutic, either 30 alone or as part of a combination therapy, for diseases that implicate, for example, the classical

complement pathway (e.g., antibody-mediated diseases) and of the lectin pathway (e.g., ischemia reperfusion injury).

With respect to the present invention, the C1-INH may be, for example, an isolated human plasma derived C1-INH (hC1-INH) or a recombinant C1-INH (rC1-INH). In a preferred aspect, the C1-INH is rC1-INH.

The rC1-INH may be conestat alfa; the recombinant analogue of the human C1 esterase inhibitor (rhC1-INH) (which is produced by recombinant DNA technology in the milk of transgenic rabbits). The C1-INH used in the present invention may be nanofiltered.

The following definitions are provided to facilitate an understanding of the present invention.

“Neuromyelitis optica spectrum disorders (NMOSD), include, for example, neuromyelitis optica (NMO) or Devic’s disease, limited forms of Devic’s disease, such as single or recurrent events of longitudinally extensive transverse myelitis, and bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

NMOSD and NMO include “clinically definite NMO”, which is defined by a history of optic neuritis and history of transverse myelitis with a non-MS brain MRI, longitudinally extensive myelitis lesions and/or presence of the NMO-IgG biomarker and “seronegative NMO”, in which patients have transverse myelitis and optic neuritis, longitudinally extensive myelitis and a brain MRI that is not typical for multiple sclerosis. Patients having “NMOSD” are identified as AQP4 antibody positive individuals with either optic neuritis or transverse myelitis. A patient to be treated according to the invention may be unresponsive to typical MS treatments. Alternatively, or in addition, the patient may be test positive for the anti-AQP4 antibody. The NMOSD may comprise the spatially limited syndromes of longitudinally extensive transverse myelitis (LETM), recurrent isolated optic neuritis (RION)/bilateral optic neuritis (BON), and Asian opticospinal multiple sclerosis (OSMS), as long as patients test positive for the anti-AQP4 antibody (also referred to herein as “NMO-IgG seropositive”).

As used herein, "administering" refers to a method of delivering a composition of the invention (e.g., Cinryze®) alone and in combination with agents and/or treatments known to be

useful for ameliorating NMO and NMOSD symptoms to the patient. Such methods are well known to those skilled in the art and include, but are not limited to, oral, nasal, intravenous, intramuscular, intraperitoneal, subcutaneous, intrathecal, intradermal, or topical administration. The route of administration can depend on a variety of factors, such as the therapeutic goals.

5 Compositions of the invention may be administered on a continuous or an intermittent basis. Methods for formulating and subsequently administering therapeutic compositions are well known to those skilled in the art. See, for example, Remington, 2000, *The Science and Practice of Pharmacy*, 20th Ed., Gennaro & Gennaro, eds., Lippincott, Williams & Wilkins. The dose administered will depend on many factors, including the mode of administration and the

10 formulation. Typically, the amount in a single dose is an amount that effectively reduces the level of NMO antigenic polypeptides or NMO-specific autoantibodies in an individual without exacerbating the disease symptoms. A preferred feature of the invention entails self administration of C1-INH via systemic (IV) or subcutaneous injection in appropriate dosage forms.

15 The C1-INH may be administered at a dose of about 500 to 4000 units per day, for example about 1000-3000 units per day, preferably about 1500-2500 units per day, more preferably about 1750-2250 units per day, more preferably about 2000 units per day. In some embodiments, the C1-INH may be provided in a 2000 Unit dose. The C1-INH may be administered by infusion (e.g. IV infusion). The C1-INH may be administered at a concentration

20 of 50-200 units/ml. For example, the C1-INH may be administered at a concentration of 80-170 units/ml, 90-160 units/ml, 95-155 units/ml, 90-110 units/ml (e.g. for human plasma derived hC1-INH), or 140-160 units/ml (e.g. for rhC1-INH). In some embodiments, the C1-INH is administered at a concentration of about 100 units/ml (e.g. for human plasma derived hC1-INH) or 150 units/ml (e.g. for rhC1-INH). The C1-INH may be administered to a patient at a dose

25 sufficient to achieve a serum concentration in the patient of at least about 1 unit/ml, at least about 2 units/ml or at least about 3 units/ml. The serum concentration to be achieved in the patient may be up to about 15 units/ml (e.g. 1-15 units/ml, 2-15 units/ml, 3-15 units/ml). In some embodiments, the serum concentration to be achieved in the patient may be about 3-9 units/ml, for example about 6 units/ml. The serum concentration may, for example, be as detected 1 hour

30 post-administration.

The term “effective amount,” as used herein, refers to the quantity of a compound or composition that achieves a beneficial clinical outcome when the compound or composition is administered to a patient. For example, when a composition of the invention is administered to a patient with, intravenous immune therapy (and possibly along with plasmapheresis), a

5 “beneficial clinical outcome” includes the reduction in the neurologic deficits caused by optic neuritis (visual loss/blindness), transverse myelitis (paralysis, sensory loss, loss of bowel/bladder function, potential brainstem dysfunction), and/or other medical sequelae that may result as a consequence of neurologic dysfunction from acute relapses of NMO/NMOSD which could negatively impact the longevity of the patient (e.g. as compared to a patient not receiving a

10 composition of the invention).

The term “early” as used herein regarding treatment, refers to the timing of treatment which may advantageously occur or be initiated immediately upon attack onset, or within 7 days from the onset of the CNS attack, more preferably within 5 days. A preferred timing is within 72 hours, more preferably within 24 hours, and most preferably within 8 hours of onset of an acute

15 CNS attack. An alternate feature of the invention is where “early” denotes the initiation of treatment of a patient within 24 hours of pro-drome of an acute CNS attack in said patient, more preferably within 8 hours, and more preferably within 4 hours. In some embodiments, the patient to be treated presents with acute transverse myelitis and/or acute optic neuritis. These symptoms may be present at the onset of acute CNS attack. In some embodiments, the C1-INH

20 (and optionally the additional biologically active agent) is administered on day 1 of hospitalization.

As used herein, “short term duration” with regard to treatment, refers to drug treatments which occur between 1 to 10 days, more preferably between 3 to 7 days and most preferably for 5 days. In some embodiments, for example, the C1-INH is only administered for between 1 to 10

25 days, more preferably between 3 to 7 days and more preferably for 3 to 5 days, most preferably 5 days. In some embodiments, the C1-INH is only administered for 3 days.

The patient being treated with C1-INH may also receive the additional biologically active agent (e.g. a steroid, such as methylprednisolone) at the same time and for the same duration, *e.g.* for the same 3 to 5 days, preferably the same 5 days. Alternatively, or in addition, the patient

30 may have received the additional biologically active agent (e.g. a steroid, such as methylprednisolone) before C1-INH treatment, *e.g.* for 3-5 days, before receiving C1-INH

treatment. Methylprednisolone may be administered (e.g. IV) at a dose of about 0.5-1.5 grams, for example about 0.8-1.2 grams per day, and preferably about 1 gram per day. In some embodiments, the methylprednisolone is administered orally at a dose of 500mg – 2g per day. The patient may also have commenced plasmapheresis before receiving C1-INH treatment, or 5 may commence plasmapheresis during or concurrently with C1-INH treatment.

An “additional biologically active agent or treatment useful for treating NMO or NMOSD” may, for example, be an immunosuppressive therapy such as a steroid, plasmapheresis, an immunoglobulin preparation or an anti-lymphocyte preparation, mycophenolate, rituximab and/or eculizumab. The steroid may be an immunosuppressive 10 steroid. The steroid may be a corticosteroid, for example a (synthetic) glucocorticoid, such as methylprednisolone. The steroid may be administered intravenously. In some embodiments, the additional biologically active agent or treatment may be effective for treating acute relapse of NMO. For example, the agent may be methylprednisolone, prednisolone, azathioprine, methotrexate, mycophenolate or eculizumab. Examples of anti-lymphocyte preparations include 15 rituximab and mitoxantrone.

As used herein, EDSS refers to “The Kurtzke Disability Status Scale (DSS)” which was developed by Dr. John Kurtzke in the 1950s to measure the disability status of people with multiple sclerosis. This scale was modified several times to more accurately reflect the levels of disabilities clinically observed. The scale was renamed the Kurtzke Expanded Disability Status 20 Scale (EDSS). The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = normal neurologic exam; to (5) = ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS. In addition, it also 25 provides eight subscale measurements called Functional System (FS) scores. This scale is also is also appropriate for scoring NMO and NMOSD patients.

The term “isolated,” as used herein in describing a material, for example, refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polypeptide (i.e., protein) present in a living 30 animal is not isolated, but the same polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated.

Moreover, the “polypeptides” or “proteins” used in practicing the present invention may be natural proteins, synthesized proteins, or may be preferably recombinant proteins. Further, the proteins described herein can be naturally purified products, or chemically synthesized products, or recombinant products from prokaryotic or eukaryotic hosts (e.g., bacteria, yeast, 5 higher plant, insect, or mammalian cell). Such proteins can be glycosylated or non-glycosylated according to the different hosts used.

Turning to the recombinant proteins used in practicing the invention, the recombinant C1-INH (rC1-INH) proteins can be expressed or produced by conventional recombinant DNA technology, using a polynucleotide sequence specific to C1-INH as known in the art. Generally, 10 such recombinant procedure comprises the following steps:

- (1) transfected or transforming the appropriate host cells with the polynucleotide or its variants encoding C1-INH protein of the invention or the vector containing the polynucleotide;
- (2) culturing the host cells in an appropriate medium; and
- (3) isolating or purifying the protein from the medium or cells.

15 Regarding the invention more generally, in methods of treating NMO/NMOSD diseases, as defined herein, C1-INH may be used in combination with an additional biologically active agent effective for treating acute relapse of NMO in order to limit the disability from individual attacks and, over time, reduce overall morbidity and disease burden that accrues from multiple attacks of NMO. Moreover, such biologically active agents may not provide complete treatments 20 for NMO disorders and may in fact provide merely a partial or incomplete treatment, such as in the case of eculizumab. Therefore, in certain preferred aspects of the methods, compositions, preparations and kits of the invention, a C1-INH may be administered to a patient in combination with one or more of the agents listed above (e.g., co-administration).

When applying the methods, compositions, preparations and kits of the invention by co- 25 administration, where separate dosage formulations are used, the C1-INH and biologically active agent can be administered concurrently, or separately at staggered times, i.e., sequentially. Compositions, preparations and kits of the invention may comprise a C1-INH and another biologically active agent as described herein (e.g. a steroid or a C5 inhibitor such as eculizumab) for concurrent or sequential use. In practice, the agents of the invention may be administered as 30 separate dosage units or formulated for administration together, according to procedures well known to those skilled in the art. See, for example, Remington: The Science and Practice of

Pharmacy, 20th ed., A. Genaro et al., Lippencot, Williams & Wilkins, Baltimore, MD (2000). Preferably, the C1-INH is administered concurrently with the biologically active agent. In other preferred co-administration strategies, the C1-INH may be administered, for example, before administration of the biologically active agent, after administration of the biologically active 5 agent, or concomitantly with the administration of the biologically active agent. Additionally, the C1-INH may be administered concurrently with the biologically active agent where the amount or concentration of the biologically active agent is decreased or tapered with respect to the C1-INH, wherein the amount or concentration of the C1-INH is increased, decreased, or fixed.

10 Concurrent administration may include administration of two or more agents, compositions or components of the invention (e.g. the components of the compositions, preparations and kits of the invention) simultaneously and/or within 12 hours of each other, within 6 hours, within 3 hours, within 2 hours or within 1 hour of each other, typically within the same visit to a clinical centre. Sequential administration may include administration of two or 15 more agents, compositions or components of the invention (e.g. the components of the compositions, preparations and kits of the invention) within 1 month, within 2 weeks (e.g. within 14 ± 2 days), within a week, within 3 days, within 2 days, or within 24 hours of each other.

20 Suitable methods of introduction of compositions of the invention to a patient include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, epidural, and oral routes. Moreover, compositions of the invention may be administered by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal, and intestinal mucosa, etc.). Administration may further be systemic or local. And administration can be daily, weekly, monthly, etc.

25 The orally administered dosage unit may be in the form of tablets, caplets, dragees, pills, semisolids, soft or hard gelatin capsules, aqueous or oily solutions, emulsions, suspensions or syrups. Representative examples of dosage forms for parenteral administration include injectable solutions or suspensions, suppositories, powder formulations, such as microcrystals or aerosol spray. The composition may also be incorporated into a conventional transdermal delivery system.

30 Additionally, in certain situations, compounds used in practicing the invention may be delivered as pharmaceutical compositions that include a pharmaceutically acceptable carrier

medium. For example, the invention includes a pharmaceutical composition for treating or delaying the progression of a NMO disorder alleviated by inhibition of C1 esterase activity, in a patient in need of such treatment, the composition comprising a C1-esterase inhibitor (C1-INH); an additional biologically active agent, such as intravenous immune therapy, mycophenolate, 5 rituximab and/or eculizumab, or a combination thereof; and a pharmaceutically acceptable carrier medium.

As used herein, the expression “pharmaceutically acceptable carrier medium” includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface agent agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, 10 fillers and the like as suited for the particular dosage form desired. Remington: The Science and Practice of Pharmacy, 20th edition, A.R. Genaro et al., Part 5, Pharmaceutical Manufacturing, pp. 669-1015 (Lippincott Williams & Wilkins, Baltimore, MD/Philadelphia, PA) (2000)) discloses various carriers used in formulating pharmaceutical compositions and known 15 techniques for the preparation thereof. Except insofar as any conventional pharmaceutical carrier medium is incompatible with the compositions described herein, such as by producing an undesirable biological effect or otherwise interacting in an deleterious manner with any other component(s) of a formulation comprising the active agent(s), its use is contemplated to be within the scope of this invention.

More specifically, in the production of solid dosage forms, the pharmaceutical 20 composition may be mixed with pharmaceutically inert, inorganic or organic excipients, such as lactose, sucrose, glucose, gelatine, malt, silica gel, starch or derivatives thereof, talc, stearic acid or its salts, dried skim milk, vegetable, petroleum, animal or synthetic oils, wax, fat, polyols, and the like. Liquid solutions, emulsions or suspensions or syrups one may use excipients such as water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerine, lipids, phospholipids, 25 cyclodextrins, vegetable, petroleum, animal or synthetic oils. Suppositories may include excipients, such as vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. Aerosol formulations may include compressed gases suitable for this purpose, such as oxygen, nitrogen and carbon dioxide. The pharmaceutical composition or formulation may also contain one or 30 more additives including, without limitation, preservatives, stabilizers, e.g., UV stabilizers, emulsifiers, sweeteners, salts to adjust the osmotic pressure, buffers, coating materials and antioxidants.

The present invention further provides controlled-release, sustained-release, or extended-release therapeutic dosage forms for the pharmaceutical composition, in which the composition is incorporated into a delivery system. This dosage form controls release of the active agent(s) in such a manner that an effective concentration of the active agent(s) in the bloodstream can be 5 maintained over an extended period of time, with the concentration in the blood remaining relatively constant, to improve therapeutic results and/or minimize side effects. Additionally, a controlled-release system would provide minimum peak to trough fluctuations in blood plasma levels of the active agent.

Additionally, various delivery systems are known and can be used to administer 10 compositions that comprise C1-INH, or C1-INH in combination with a biologically active agent, such as eculizumab. For example, such compositions may be encapsulated in liposomes, microparticles, and microcapsules, for example.

The methods of the present invention will normally include medical follow-up to determine the therapeutic or prophylactic effect brought about in the patient undergoing 15 treatment with the compound(s) and/or composition(s) described herein.

Turning to the use of C1-INH as a treatment for disease more specifically, C1-INH may be used for treatment of NMO and related neuromyelitis optica spectrum disorders (NMOSD) in vivo. The results of the experiments described in the following example demonstrate that commercially available plasma-derived C1-INH can limit the neurologic disability from 20 individual attacks and, over time, reduce the overall morbidity and disease burden that accrues from multiple attacks of NMO.

The following example is provided to describe the invention in further detail. This example is provided for illustrative purposes only and is not intended to limit the invention in any way.

25

### **Example I**

**CINRYZE® (C1 esterase inhibitor [human]) for the treatment of acute optic neuritis and/or transverse myelitis in neuromyelitis optica and neuromyelitis optica spectrum disorder**

NMO is a severe, demyelinating autoimmune disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Although historically considered a subtype of multiple sclerosis (MS) with overlapping symptoms, NMO is distinct radiologically and prognostically and has a pathophysiology unresponsive to typical MS treatments

5 (Weinshenker et al., ( 2007) Arch Neurol 64:899-901); Kimbrough, et al., (2012). In 2004, an antibody targeting the water channel protein, aquaporin-4, was found to be associated with NMO. Compared to MS, NMO exhibits an older age at onset, a poorer prognosis, and a rarity of cerebrospinal fluid oligoclonal IgG bands. NMO attacks typically produce moderate to severe disability that leads to accumulation of disability with each attack; between attacks, patients

10 generally remain neurologically stable without evidence of progressive deterioration. Therefore, it is crucial that aggressive treatment for each relapse is optimized to prevent disability.

NMO affects predominantly females, with a female to male ratio of 6.5:1. The relative frequency of NMO among demyelinating disorders is quite variable, being higher in Asian, Hispanic and African populations and lower among Caucasians. The few population-based

15 prevalence studies of NMO conducted provide prevalence rates of 0.32 to 3.1 per 100,000 in the non-white population (Nandhagopal, et al., (2010) Postgrad Med J 86:153-159).

Clinically definite NMO is defined by a history of optic neuritis and history of transverse myelitis with a non-MS brain MRI, longitudinally extensive myelitis lesions and/or presence of the NMO-IgG biomarker. Seronegative NMO patients with transverse myelitis and optic neuritis

20 must have longitudinally extensive myelitis and a brain MRI that is not typical for multiple sclerosis. Seronegative NMO is a group that has not been adequately characterized for widespread inclusion in clinical trials. A third group, NMOSD, is identified as AQP4 antibody positive individuals with either optic neuritis or transverse myelitis.

NMOSD comprise the spatially limited syndromes of longitudinally extensive transverse myelitis (LETM), recurrent isolated optic neuritis (RION)/bilateral optic neuritis (BON), and Asian opticospinal multiple sclerosis (OSMS), as long as patients test positive for the anti-AQP4 antibody (Sellner, et al., (2010) European J. Neurol 17:1019-1032). Bizzoco, et al., reported that 7 of 13 (56%) NMOSD patients from Tuscany developed clinically definite NMO after a follow-up time of at least 2 years with the other six (46%) remaining NMOSD (Bizzoco et al., (2009) J.

30 Neurol 256:1891-1898). Weinshenker et al., (*supra*) prospectively studied 29 patients with a first event of LETM. Within 1 year, 6 of the 11 seropositive (AQP4+) patients had a relapse of

myelitis (indicative of recurrent transverse myelitis) or developed optic neuritis (indicative of neuromyelitis optica). By contrast, no seronegative patients relapsed over 1–7 years follow-up. NMO and Asian OSMS have similar neuroimaging, serological, and immunopathological characteristics, and the difference is primarily one of classification as in Japan these individuals 5 are diagnosed with MS, but in North America and Europe, these patients are diagnosed with NMO (Matsuoka, et al., (2007) *Brain* 130:1206-23; Wingerchuk et al., (2007) *Lancet Neurol* 6:805-815).

The current standard of care for treatment of acute NMO attacks of both optic neuritis and transverse myelitis is a 5-day course of high dose methylprednisolone (1000 mg 10 daily)(Kimbrough, *supra* 2012). In some patients, this course of steroid treatment is sufficient to suppress CNS inflammation and reverse some neurologic dysfunction. Factors that may predict success with steroids alone include a small CNS lesion caught early in the process and concurrent preventive immunosuppression. In many patients, steroids are not sufficient to suppress CNS inflammation, and treatment escalation to plasma exchange is necessary. Five 15 cycles of 1.0 – 1.5 volume exchanges require an additional 2-week inpatient hospitalization and a central line catheter. Plasma exchange carries a 4-10% risk of line infection or thrombotic complications. Despite these risks, plasma exchange is standard of care in steroid-unresponsive patients because it is 50-70% effective in reducing active CNS inflammation and reducing inflammatory damage in this patient population (Szczepiorkowski et al., (2010) *J Clin Apher* 20 25(3):83-177). Ultimately, neurologic recovery after high dose steroids and plasma exchange can be stratified into three groups: a group that does not improve at all, a group that improves some but maintains a significant neurologic deficit and a group that improves well if not back to baseline.

The rationale for using C1-esterase inhibitor (CINRYZE®) in NMO is based on 25 pathology showing a prominent role for complement in active NMO lesions (Luchinetti et al. (2002) *Brain* 125:1450-1461; Misu et al. (2007) *Brain* 130:1224-1234; Roemer et al. (*supra*, 2007). NMO is not unique in involving complement, which may have a pathogenic role in other demyelinating diseases including multiple sclerosis (Prineas, 2012) . However, NMO is characterized by its complement involvement depositing in a rim or rosette pattern in all active 30 lesions (Figure 1). In vitro, complement is critical in mediating damage initiated by anti-AQP4 antibody binding to astrocytes (Hinson et al., (2007) *Neurology* 69:2221-2231;Kinoshita et al.,

(2008) NeuroReport 20(5):508-512). The effector of antibody triggered cell damage is the complement cascade (Malignier et al. (2010) Brain 133:2578-2591; Sabater et al. (2009) J. of Neuroimmunology 215:31-35) and blocking the complement cascade with C1-inhibitor prevents damage ex vivo (Saadoun et al. (2012) Annals of Neurology 71(3):323-333). Based on this 5 mounting evidence the consensus in the field is that prevention of the complement cascade in the CNS would ameliorate the damage caused in NMO inflammatory attacks. This was the basis of the first open label prospective trial in NMO using eculizumab (Soliris ®). Results from this trial are now publically available. In contrast to the eculizumab trial, which is a prevention trial, the inventive approach described herein provides for complement inhibition as acute treatment 10 during an active CNS attack. This approach is designed to administer the inhibitory drug when complement damage is at its peak. This approach minimizes the exposure to this medication and dramatically reduces cost of care compared to eculizumab therapy.

Patients with NMO do not lack natural C1-esterase inhibitor, but administering pd C1- 15 INH to increase endogenous levels appears to suppress the complement pathways. Notably, in patients with hyperactive complement activation, this approach has been shown to be beneficial in sepsis and myocardial infarction. In sepsis, complement activation is a contributing factor to end organ failure. Notwithstanding concerns that complement inhibition would prevent bacterial clearance, high dose C1-esterase inhibitor provided to sepsis patients reduced sepsis-induced mortality and all-cause mortality (Ignonin et al., (2012) Crit Care Med 40(3):770-777). In 20 myocardial infarction, complement activation participates in reperfusion injury and induction of inflammation, leading to reduced coronary perfusion. Several studies have shown a benefit of C1 esterase inhibitors in ameliorating the complement-mediated reperfusion injury (Buerke et al. (1995) Circulation 91:393-402; Shandelya et al. (1993) Circulation 88:2812-2826; Weisman et al.(1990) Science 24:146-151; Fattouch et al. (2007) Eur J Cardiothorac Surg 32(2):326-332) 25 after myocardial infarction. The rationale behind all of these studies is that in patients with otherwise normal complement function, tipping the balance toward complement inhibition can reduce end organ damage in certain disease conditions.

Complement-mediated damage is presumed to account for a significant component of the 30 pathological changes observed in patients with NMO and is supported by ex vivo studies of the role of complement in NMO. Similar to the studies in sepsis and myocardial infarction, the rationale for adding human C1-esterase inhibitor to the treatment for NMO acute exacerbations

is to tip the balance toward complement suppression in an effort to reduce complement-mediated neurologic damage.

We conducted an open-label phase 1b safety and proof-of-concept trial in 10 subjects with NMO-IgG seropositive NMO or NMO spectrum disease (NMOSD) who presented with acute transverse myelitis and/or optic neuritis. In addition to treating with 1 gram of daily intravenous methylprednisolone, we infused 2000 Units of C1-esterase inhibitor daily x3 days beginning on day 1 of hospitalization. The primary outcome measure was safety, and the secondary efficacy measure was change in Expanded Disability Scale Scores (EDSS).

10

## Results

Ten NMO-IgG seropositive subjects were enrolled, 7 of whom presented with acute transverse myelitis and 3 with acute optic neuritis. C1-esterase inhibitor (Cinryze®) proved safe in all 10 NMO subjects with no serious adverse events reported. One subject had a headache during the first infusion. There were no thromboembolic events or related lab abnormalities in any of the subjects. EDSS scores dropped from a median of 4.5 on admission to 4.0 on discharge and then down to 2.5 on 30-day follow up. See Table 1. All but one subject returned to pre-attack EDSS and only one subject required escalation to plasmapheresis.

Table I

Study measurement/timing	EDSS score (median)	EDSS score (mean)
Baseline (pre-acute NMO attack)		2.75
Admission (NMO acute attack)	4.5	5.45
Discharge (post hospitalization)	4.0	4.25
30-day follow-up	2.5	3.28

Paired non-parametric t testing was used to compare pretreatment EDSS scores to each post treatment EDSS score.

### Conclusions

5 C1-esterase inhibitor (Cinryze®) is a safe add-on therapy for NMO/NMOSD patients presenting with acute transverse myelitis and optic neuritis. The evidence provided herein shows a promising benefit with C1-esterase inhibitor in reducing neurologic disability and improving outcomes.

10 While certain of the preferred embodiments of the present invention have been described and specifically exemplified above, it is not intended that the invention be limited to such embodiments. Various modifications may be made thereto without departing from the scope and spirit of the present invention, as set forth in the following claims.

15

## Claims

1. A composition comprising a C1-esterase inhibitor (C1-INH) for use in:
  - (i) a method of treating or delaying the progression of a CNS disorder alleviated by inhibiting complement immune system activation, wherein the method comprises administering the C1-INH during an active CNS attack; or
  - (ii) a method of preventing or delaying the progression of a CNS disorder alleviated by inhibiting complement immune activation, wherein the method comprises administering the C1-INH at the onset of an active CNS attack,  
wherein said disorder of (i) or (ii) is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD).
2. The composition for use according to claim 1, wherein the C1-INH comprises a human plasma-derived C1-INH (hC1-INH) or a recombinant C1-INH (rC1-INH).
3. The composition for use according to any one of the preceding claims, wherein the disorder is selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.
4. The composition for use according to any one of the preceding claims, wherein said disorder is NMO and said C1 esterase inhibitor is CINRYZE®.
5. The composition for use according to any one of the preceding claims, wherein the method comprises administering an additional biologically active agent or treatment effective for treating or delaying the progression of a disorder selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

6. The composition for use according to claim 5, wherein said treatment is intravenous immune therapy and wherein said agent is optionally a glucocorticoid, such as methylprednisolone.
7. The composition for use according to claim 5, wherein said agent or treatment is plasmapheresis and/or administration of intravenous immunoglobulin preparations.
8. The composition for use according to claim 5 comprising administering mycophenolate, rituximab and/or eculizumab.
9. The composition for use according to any one of claims 5-8 wherein the C1-INH and the biologically active agent or treatment are administered concurrently.
10. The composition for use according to any one of claims 5-8 wherein the C1-INH and the biologically active agent or treatment are administered sequentially.
11. The composition for use according to any preceding claim wherein said administration is during the early acute phase.
12. The composition for use according to any preceding claim, wherein said administration is of short term duration.
13. A method of treating or delaying the progression of a CNS disorder alleviated by inhibiting complement immune system activation in a patient in need of such treatment, the method comprising administering during an active CNS attack, a therapeutically effective amount of C1-esterase inhibitor (C1-INH), wherein said disorder is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD).
14. The method according to claim 13, wherein the C1-esterase inhibitor (C1-INH) comprises a human plasma-derived C1-INH (hC1-INH) or a recombinant C1-INH (rC1-INH).
15. The method according to claim 13 or claim 14, wherein the disorder is selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus,

periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

16. The method according to any one of claims 13-15, wherein said disorder is NMO and said

5 C1 esterase inhibitor is CINRYZE®.

17. The method according to any one of claims 13-16, comprising administering an additional biologically active agent or treatment effective for treating or delaying the progression of a disorder selected from the group consisting of neuromyelitis optica (NMO) or Devic's disease, single or recurrent events of longitudinally extensive transverse myelitis, bilateral simultaneous or recurrent optic neuritis, asian optic-spinal multiple sclerosis, optic neuritis associated with systemic autoimmune disease, optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nucleus, and brainstem, and NMO-IgG negative NMO: AQP4 antibody-seronegative NMO.

15 18. The method according to claim 17, wherein said treatment is intravenous immune therapy and wherein said agent is optionally a glucocorticoid, such as methylprednisolone.

19. The method according to claim 17, wherein said treatment is plasmapheresis and/or administration of intravenous immunoglobulin preparations.

20 20. The method according to claim 17, comprising administering mycophenolate, rituximab and/or eculizumab.

21. The method according to any one of claims 17-20 wherein the C1-INH and the biologically active agent are administered concurrently.

22. The method according to any one of claims 17-20 wherein the C1-INH and the biologically active agent are administered sequentially.

25 23. A pharmaceutical composition for treating or delaying the progression of a disorder caused by complement immune system activation in a patient in need of such treatment, the composition comprising administration of an activation inhibiting amount of

a C1-esterase inhibitor (C1-INH);

and optionally, a biologically active agent selected from the group consisting of, intravenous immune therapy, mycophenolate, rituximab and/or eculizumab or a combination thereof; and a pharmaceutically acceptable carrier medium.

5 24. A method of preventing or delaying the progression of a CNS disorder alleviated by inhibiting complement immune activation in a patient in need of such treatment, the method comprising administration at the onset of an active CNS attack, a therapeutically effective amount of C1-esterase inhibitor (C1-INH), wherein said disorder is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD), optionally wherein the method is as  
10 defined in any one of claims 14-22.

25. A method as claimed in claim 13 or claim 24, wherein said administration is during the early acute phase.

26. A method as claimed in claim 13 or claim 24, wherein said administration is of short term duration.

15 27. The composition comprising a C1-esterase inhibitor (C1-INH) for use according to claim 1, wherein the method of treating or delaying the progression the CNS disorder is a method as defined in any one of claims 13-22, 25 or 26 or wherein the method of preventing or delaying the progression of the CNS disorder is a method as defined in any one of claims 24-26.

28. Use of a C1-esterase inhibitor (C1-INH) in the manufacture of a medicament for: (i) treating or delaying the progression the CNS disorder by a method as defined in any one of claims 13-22, 25 or 26 or (ii) preventing or delaying the progression of the CNS disorder by a method as defined in any one of claims 24-26.

29. A kit comprising:  
(i) a C1-esterase inhibitor (C1-INH); and  
25 (ii) an additional biologically active agent effective for treating or delaying the progression of neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD);

wherein said components (i) and (ii) are packaged for concurrent or sequential administration to a patient.

30. A C1-esterase inhibitor (C1-INH) and an additional biologically active agent as a  
5 combined preparation for concurrent or sequential use in:

(i) a method of treating or delaying the progression of a CNS disorder alleviated by inhibiting complement immune system activation, wherein the method comprises administering the C1-INH during an active CNS attack; or

10 (ii) a method of preventing or delaying the progression of a CNS disorder alleviated by inhibiting complement immune activation, wherein the method comprises administering the C1-INH at the onset of an active CNS attack,

15 wherein the disorder of (i) or (ii) is neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD) and wherein the biologically active agent is effective for treating or delaying the progression of neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD).

31. The kit according to claim 29 or the preparation for use according to claim 30 wherein the additional biologically active agent is selected from the group consisting of a glucocorticoid, such as methylprednisolone, an intravenous immunoglobulin preparation or an anti-lymphocyte  
20 preparation, mycophenolate, rituximab and/or eculizumab, or a combination thereof.

1/1

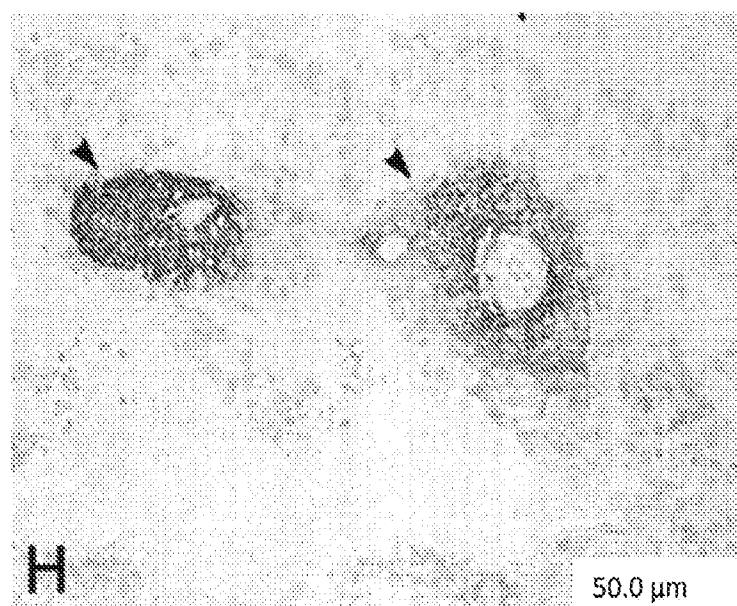


Figure 1

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/065180

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K38/55 A61K39/395 A61K35/16 A61P25/28  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>"C1-esterase Inhibitor (Cinryze) for Acute Treatment of Neuromyelitis Optica Exacerbation", clinicaltrials.gov</p> <p>, 28 January 2013 (2013-01-28), XP002734550, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT 01759602/2013_01_28 [retrieved on 2015-01-16]</p> <p>the whole document</p> <p>-----</p> <p>-/-</p>	1-7, 9-19, 21-31
Y		1-31

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

16 January 2015

06/02/2015

Name and mailing address of the ISA/

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Authorized officer

Fayos, Cécile

## INTERNATIONAL SEARCH REPORT

International application No PCT/US2014/065180
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	PHUAN PUAY-WAH ET AL: "C1q-targeted monoclonal antibody prevents complement-dependent cytotoxicity and neuropathology in in vitro and mouse models of neuromyelitis optica.", ACTA NEUROPATHOLOGICA JUN 2013, vol. 125, no. 6, June 2013 (2013-06), pages 829-840, XP002734552, ISSN: 1432-0533 the whole document -----	1-31
Y	EP 0 263 110 A1 (GRIEPENTROG HARTMUT [DE]; WEH HERBERT [DE]) 13 April 1988 (1988-04-13) the whole document claims 5, 15 -----	1-31
Y	COLLONGUES NICOLAS ET AL: "Current and future treatment approaches for neuromyelitis optica.", THERAPEUTIC ADVANCES IN NEUROLOGICAL DISORDERS MAR 2011, vol. 4, no. 2, March 2011 (2011-03), pages 111-121, XP002734553, ISSN: 1756-2864 the whole document -----	1-31
Y	KIM SU-HYUN ET AL: "Clinical efficacy of plasmapheresis in patients with neuromyelitis optica spectrum disorder and effects on circulating anti-aquaporin-4 antibody levels.", JOURNAL OF CLINICAL NEUROLOGY (SEOUL, KOREA) JAN 2013, vol. 9, no. 1, January 2013 (2013-01), pages 36-42, XP002734554, ISSN: 1738-6586 the whole document -----	1-31
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## INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/065180

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No

PCT/US2014/065180

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