

METHODS OF TREATING MULTIFOCAL MOTOR NEUROPATHY (MMN)

FIELD OF THE INVENTION

[0001] The present invention relates to methods and dosage regimens for treating multifocal motor neuropathy (MMN) using an antibody that binds specifically to the C2 protein in the complement cascade and induces unexpectedly beneficial effects in subjects suffering from MMN.

BACKGROUND OF THE INVENTION

[0002] Multifocal motor neuropathy (MMN) is a rare chronic immune-mediated neuropathy involving progressive muscle weakness of mainly the hands, forearms, and lower legs. It is clinically characterized by progressive asymmetric weakness involving 2 or more nerves and partial motor conduction block. The estimated prevalence of MMN is between 0.6 to 2 per 100,000 people and typically presents as an asymmetrical upper limb pure motor neuropathy. Unlike amyotrophic lateral sclerosis (ALS), which affects both upper and lower motor neuron pathways, MMN involves only the lower motor neuron pathway, specifically, the peripheral nerves emanating from the lower motor neurons. The hallmark of the disease is the presence of multifocal motor conduction blocks, i.e., impaired propagation of action potentials along the axon, and patients often show high serum levels of immunoglobulin M (IgM) antibodies against the ganglioside GM1 (monosialotetrahexosyl-ganglioside). GM1 is widely expressed in the nervous system by neurons, particularly around the nodes of Ranvier, and Schwann cells. The current prevailing view is that GM1 antibodies target the axolemma at the nodes of Ranvier. This is thought to interfere with axon-Schwann cell interactions, causing widening of the node, and direct damage to the axon.

[0003] The presence and titers of IgM anti-ganglioside GM1 (anti-GM1) antibodies (observed in about 40% of MMN patients) and their complement activating properties, correlate with clinical features such as weakness and axonal damage. Binding of these anti-GM1 antibodies to GM1 leads to activation of the classical complement pathway, and subsequent membrane attack complex (MAC) deposition. Consequently, this MAC deposition leads to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and the disturbance of membrane integrity at the (para)nodal regions resulting in demyelination. These findings suggest that complement plays an important role in the pathogenesis of MMN, and that the inhibition of complement activation may provide a new

therapeutic option in this disease. Despite this hypothesis, establishing safety and efficacy of a new therapeutic for treating MMN patients is highly unpredictable.

[0004] Currently, high dose IV immunoglobulin (IVIg) treatment is the only approved treatment for MMN. IVIg treatment often improves muscle strength, however the efficacy of IVIg in reducing MMN symptoms declines after several years and many patients report progressive neurological deficits. Despite treatment with IVIg, MMN related disabilities will continue to progress due to ongoing axonal degeneration.

[0005] Accordingly, there remains an unmet medical need for an efficacious treatment option for treating MMN.

SUMMARY OF INVENTION

[0006] The instant disclosure is directed to methods for treating MMN with a complement component 2 (C2) inhibitor. Also provided herein are particular dosage regimens for administering a C2 inhibitor that results in a rapid reduction of the free C2 level in the blood of a subject who has MMN. In an embodiment, the dosage regimen includes a loading regimen that rapidly reduces free C2 in the subject, followed by a maintenance regimen that maintains the reduced free C2 level in the subject.

[0007] In an aspect, provided herein is a method of treating multifocal motor neuropathy (MMN) in a subject in need thereof, the method comprising administering to the subject an effective amount of a C2 inhibitor.

[0008] More specifically, provided herein is a method of treating multifocal motor neuropathy (MMN) in a subject in need thereof, the method comprising administering to the subject an effective amount of a complement component 2 (C2) inhibitor, and wherein the C2 inhibitor is administered according to a dosage regimen comprising:

(i) a loading regimen comprising administration of a single initial dose of the C2 inhibitor followed by one or more subsequent doses of the C2 inhibitor, followed by

(ii) a maintenance regimen comprising administration of two or more subsequent doses of the C2 inhibitor, and wherein the dosing interval is longer in the maintenance regimen than in the loading regimen.

[0009] In an embodiment, following administration of the C2 inhibitor, the subject shows one or more of the following improved responses compared to baseline measurements: increased time until first retreatment with IVIg; improved patient report on the Patient Global Impression of Change (PGIC) 7-

point scale; improved scores in clinical endpoints selected from the group consisting of: modified Medical Research Counsel-10 (mMRC-10) sum score, modified Medical Research Counsel-14 (mMRC-14) sum score, grip strength three day moving average score in a most affected hand, grip strength three day moving average score in a less affected hand, MMN Rasch-built Overall Disability Scale for MMN (MMN-RODS), Chronic Acquired Polyneuropathy-Patient Reported Index (CAP-PR) score, and Fatigue Severity Scale (FSS) average score.

[0010] In an embodiment, the subsequent doses of the C2 inhibitor of the loading regimen and/or the maintenance regimen is/are each a lower dose than the single initial dose of the C2 inhibitor. In an embodiment, the subsequent doses of the C2 inhibitor of the loading regimen is/are each the same as the single initial dose of the C2 inhibitor, and the subsequent doses of the C2 inhibitor of the maintenance regimen is/are each lower than the single initial dose of the C2 inhibitor.

[0011] In an embodiment, the single initial dose of the loading regimen is 30 mg/kg or 15 mg/kg.

[0012] In an embodiment, the loading regimen comprises administration of two or more subsequent doses, each of 10 mg/kg and administered weekly. In an embodiment, the loading regimen comprises administration of two or more subsequent doses, each of 5 mg/kg and administered weekly. In an embodiment, the loading regimen comprises administration of one subsequent dose of 30 mg/kg. In an embodiment, the one or more subsequent doses of the loading regimen commence one week after the single initial dose.

[0013] In an embodiment, the two or more subsequent doses of the maintenance regimen are each 10 mg/kg, administered once every 2 weeks. In an embodiment, the two or more subsequent doses of the maintenance regimen are each 10 mg/kg, administered once every 4 weeks. In an embodiment, the two or more subsequent doses of the maintenance regimen are each 5 mg/kg, administered once every 4 weeks.

[0014] In an embodiment, (i) the loading regimen is a single initial dose of 30 mg/kg; and one or more subsequent doses, each of 10 mg/kg administered once weekly beginning one week after the single initial dose; and (ii) the maintenance regimen is a dose of 10 mg/kg administered once every two weeks. In an embodiment, (i) the loading regimen is a single initial dose of 30 mg/kg; and one or more subsequent doses, each of 30 mg/kg administered once weekly beginning one week after the single initial dose; and (ii) the maintenance regimen is a dose of 10 mg/kg administered once every four weeks.

[0015] In an embodiment, (i) the loading regimen is a single initial dose of 15 mg/kg; and one or more subsequent doses, each of 5 mg/kg administered once weekly beginning one week after the single initial dose; and (ii) the maintenance regimen is a dose of 5 mg/kg administered once every four weeks.

[0016] In an embodiment, the loading regimen consists of one subsequent dose. In an embodiment, the loading regimen consists of four or at least four subsequent doses.

[0017] In an embodiment, the maintenance regimen commences one week after the loading regimen.

[0018] In an embodiment, the loading regimen and the maintenance regimen are administered intravenously.

[0019] In an embodiment, the subject has been previously treated with IVIg. In an embodiment, the subject has been previously stabilized with IVIg. In an embodiment, the subject is dependent on IVIg. In an embodiment, the subject is not receiving concomitant IVIg at the time of commencing administration of the C2 inhibitor.

[0020] In an embodiment, the subject shows an increase in a modified Medical Research Council (mMRC) score following administration of the C2 inhibitor, compared to the subject's baseline mMRC score. In an embodiment, the mMRC score is an mMRC-10 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-10 sum score of 1 or more, compared to the subject's baseline mMRC-10 sum score. In an embodiment, the subject shows an increase in the mMRC-10 sum score of 1.5. In an embodiment, the subject shows an increase in the mMRC-10 sum score of at least 1.5. In an embodiment, the subject shows an increase in the mMRC-10 sum score of between 1.5 and 3. In an embodiment, the mMRC score is an mMRC-14 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-14 sum score of 1 or more, compared to the subject's baseline mMRC-14 sum score. In an embodiment, the subject shows an increase in the mMRC-10 sum score of 4. In an embodiment, the subject shows an increase in the mMRC-10 sum score of at least 4. In an embodiment, the subject shows an increase in the mMRC-10 sum score of between 4 and 7.

[0021] In an embodiment, the subject shows improved grip strength following administration of the C2 inhibitor, compared to the subject's baseline grip strength. In an embodiment, the subject shows improved grip strength in the most affected hand, in the less affected hand, or in both hands. In an embodiment, the subject shows improved grip strength in the most affected hand of greater than 10 kPa. In an embodiment, the subject shows improved grip strength in the most affected hand of 11.28 kPa. In an embodiment, the subject shows improved grip strength in the most affected hand of between 11.28 and 17.06 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of greater than 5 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand

of 6.5 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of between 6.5 and 9.94 kPa.

[0022] In an embodiment, the subject shows an increase in MMN Rasch-built Overall Disability Scale (MMN-RODS[®]) score following administration of the C2 inhibitor, compared to the subject's baseline MMN-RODS[®] score. In an embodiment, the subject shows an increase in MMN-RODS score of 5 or more, optionally 6 or more. In an embodiment, the subject shows an increase in MMN-RODS score of 6. In an embodiment, the subject shows an increase in MMN-RODS score of between 6 and 7.5.

[0023] In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in disease-specific quality of life, as measured using the Chronic Acquired Polyneuropathy – Patient Report Index (CAP-PRI), compared to the subject's score at baseline. In an embodiment, following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2 or more. In an embodiment, the subject shows an improved CAP-PRI score with a reduction of 2. In an embodiment, the subject shows an improved CAP-PRI score with a reduction between 2 and 2.5.

[0024] In an embodiment, following administration of the C2 inhibitor, the subject reports an improvement in the Patient Global Impression of Change (PGIC) 7-point scale, compared to the subject's baseline PGIC score. In an embodiment, a population of MMN subjects are treated, and 55.6% of subjects treated report their condition much improved or very much improved. In an embodiment, a population of MMN subjects are treated, and 94.4% of subjects treated report any improvement (minimally improved, much improved, or very much improved).

[0025] In an embodiment, following administration of the C2 inhibitor, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS), compared to the subject's baseline FSS score. In an embodiment, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS) comprising a reduction of 0.1 or more. In an embodiment, the reduction is 0.11. In an embodiment, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS) comprising a reduction of 0.4 or more. In an embodiment, the reduction is 0.444.

[0026] In an embodiment, the C2 inhibitor is an antibody that specifically binds to C2. In an embodiment, the C2 inhibitor is an antibody that specifically binds to C2b.

[0027] In an embodiment, the antibody comprises a heavy chain variable region (VH) comprising CDRH1 as represented by SEQ ID NO: 1, CDRH2 as represented by SEQ ID NO: 2 and CDRH3 as represented by SEQ ID NO: 3 and a light chain variable region (VL) comprising CDRL1 as represented by SEQ ID NO: 4, CDRL2 as represented by SEQ ID NO: 5 and CDRL3 as represented by SEQ ID NO:

6.

[0028] In an embodiment, the antibody comprises: a VH comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 7; and/or a VL comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 8.

[0029] In an embodiment, the antibody comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 7 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 8. In an embodiment, the amino acid sequence of the VH consists of the amino acid sequence set forth in SEQ ID NO: 7 and the amino acid sequence of VL consists of the amino acid sequence set forth in SEQ ID NO: 8.

[0030] In an embodiment, the antibody comprises a heavy chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 9 and/or a light chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 10.

[0031] In an embodiment, the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 9 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 10. In an embodiment, the amino acid sequence of the heavy chain consists of the amino acid sequence set forth in SEQ ID NO: 9 and the amino acid sequence of the light chain consists of the amino acid sequence set forth in SEQ ID NO: 10. In an embodiment, the antibody is empasiprubart.

[0032] In an aspect, provided herein is a C2 inhibitor for use in the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a method disclosed herein.

[0033] In an aspect, provided herein is a C2 inhibitor for use in the manufacture of a medicament for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a method disclosed herein.

[0034] In an aspect, provided herein is a use of a C2 inhibitor for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a method disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] **Figure 1** shows the study design of the Phase 2, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group, Multicenter Trial to Evaluate the Safety and Tolerability, Efficacy, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of ARGX-117 in Adults With Multifocal Motor Neuropathy – the ARGX-117-2002 study. ^a Patients could request IVIg retreatment with the investigator at any time during the treatment phase. ^b Patients who did not roll over into ARGX-117-2003 entered a 12-month safety follow up.

[0035] **Figure 2** shows a summary of participant disposition in the ARGX-117-2002 study.

[0037] **Figure 3** shows the baseline results for Cohort 1 and Cohort 2 participants of (A) grip strength for most affected hand, (B) grip strength for less affected hand, (C) MMN-RODS score, (D) CAP-PRI score, (E) FFS score (Cohort 1 only), (F) mMRC-10 score, (G) mMRC-14 score, and (H) average mMRC score for the two most important muscle groups for both treatment groups. Baseline is defined as the last value collected before the first dose of IMP (either empasiprubart or placebo).

[0037] **Figure 4** shows the results for “time to first retreatment with IVIg” and “time-to-relapse” for Cohort 1 and 2 participants. (A) is a Kaplan-Maier analysis showing the time to first retreatment with IVIg in ARGX-117 (empasiprubart/EMPA) and placebo treated groups of Cohort 1 participants. (B) is a Kaplan-Maier analysis showing the time to first retreatment compared to placebo of Cohort 2 participants. Time to first retreatment is defined as the time from last IVIg administration before randomization (including unscheduled visits) up to the first retreatment during the double-blind treatment period. (C) is a Kaplan-Maier analysis showing the time-to-relapse compared to placebo of Cohort 1 participants. (D) is a Kaplan-Maier analysis showing the time-to-relapse compared to placebo of Cohort 2 participants. Time-to-relapse is defined as the time from randomization up to the time the participant meets the threshold for clinical deterioration.

[0038] **Figure 5** provides graphical representations of the percentage of participants receiving ARGX-117 (empasiprubart/EMPA) and placebo that experienced relapse and/or retreatment with IVIg in Cohort 1. (A) Of the participants receiving ARGX-117, 11 experienced no relapse and were not retreated with IVIg; 4 experienced relapse but were not retreated with IVIg; and 3 experienced relapse and were retreated with IVIg. Of the participants receiving placebo, 1 experienced no relapse and was not retreated with IVIg; 1 experienced no relapse but was retreated with IVIg; 1 experienced relapse but was not retreated with IVIg; and 6 experienced relapse and were retreated with IVIg. (One of the placebo group participants who was not retreated with IVIg potentially received a dose of ARGX-117). (B) Of

the participants not retreated with IVIg, 4/15 (27%) in the ARGX-117-treated group met the endpoint for clinical deterioration, compared to 1/2 (50%) in the placebo-treated group.

[0039] **Figure 6** shows the improvement in mMRC-10 sum score compared to placebo. **(A)** Box plot of actual values by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 participants. **(B)** Box plot of change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 and 2 participants. **(C)** shows improvement in mMRC-14 sum score as a box plot of change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 and 2 participants.

[0040] **Figure 7** shows improvement in grip strength compared to placebo. **(A)** Box plot showing 3-day moving average (kPa) for each hand (most affected / less affected hand) as actual values by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 participants. **(B)** Box plot showing 3-day moving average (kPa) for most affected hand as change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 and 2 participants. **(C)** Box plot showing 3-day moving average (kPa) for least affected hand as change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) of Cohort 1 and 2 participants.

[0041] **Figure 8** shows improvement in MMN-RODS score compared to placebo. **(A)** Box plot of actual values by treatment group (ARGX-117-treated on left; Placebo-treated on right) for Cohort 1 participants. **(B)** Box plot of change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) for Cohort 1 and 2 participants.

[0042] **Figure 9** shows improvement in CAP-PRI score compared to placebo. **(A)** Box plot of actual values by treatment group (ARGX-117-treated on left; Placebo-treated on right) for Cohort 1 participants. **(B)** Box plot of change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) for Cohort 1 and 2 participants.

[0043] **Figure 10** is a bar chart showing improvement in Patient Global Impression of Change (PGIC) score compared to placebo for Cohort 1 and 2 participants. The numbers 1-7 in the bar chart correspond to the numbers 1-7 of the PGIC score.

[0044] **Figure 11** shows improvement in Fatigue Severity Scale (FSS) score compared to placebo. **(A)** Box plot of actual values by treatment group (ARGX-117-treated on left; Placebo-treated on right) for Cohort 1 participants. **(B)** Box plot of change from baseline by treatment group (ARGX-117-treated on left; Placebo-treated on right) for both Cohort 1 and Cohort 2 participants.

[0045] **Figure 12** shows the arithmetic mean ARGX-117-concentration ($\pm$ SD; linear) versus time during the DBTP for Cohort 1 and 2 participants.

[0046] **Figure 13** shows the median (IQR) free C2 ($\pm$ SE) serum concentration (semi-logarithmic) versus time during the DBTP for Cohort 1 and 2 participants. NB. At day 8, for pre and post-dose sample, unexpected high values for free C2 were observed for participant 0310013004 (treated with EMPA 15/5 mg/kg) although values close to 0 were expected.

[0047] **Figure 14 (A)** shows the mean percentage change from baseline of free C2 ($\pm$ SE) during the DBTP for Cohort 1 and 2 participants treated with EMPA. **(B)** shows the median (IQR) percentage change from baseline of free C2 ($\pm$ SE) during the treatment period for Cohort 1 and 2 participants treated with EMPA.

[0048] **Figure 15** shows the median (IQR) ($\pm$ SE) CH50 serum concentration (Linear) versus time during the DBTP for Cohort 1 and 2 participants.

[0049] **Figure 16** shows the median (IQR) percentage change from baseline of CH50 ($\pm$ SE) during the DBTP for Cohort 1 and 2 participants treated with EMPA.

[0050] **Figure 17** shows the median (IQR) of total C2 ($\pm$ SE) serum concentration (Linear) versus time during the DBTP for Cohort 1 and 2 participants.

DETAILED DESCRIPTION

[0052] The instant disclosure is directed to methods for treating MMN with a C2 inhibitor (e.g., an anti-C2 antibody). Also provided herein are particular dosage regimens for administering a C2 inhibitor that results in a rapid reduction of the free C2 level in the blood of a subject who has MMN. In an embodiment, the dosage regimen includes a loading regimen that rapidly reduces free C2 in the subject, followed by a maintenance regimen that maintains the reduced free C2 level in the subject.

Definitions

[0053] As used herein, the terms “antibody” and “antibodies” include full-length antibodies, antigen-binding fragments of full-length antibodies, and molecules comprising antibody CDRs, VH regions, and/or VL regions. Examples of antibodies include, without limitation, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including

bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affibodies, Fab fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-anti-Id antibodies), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, or IgY), any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2), or any subclass (e.g., IgG2a or IgG2b) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (e.g., human IgG1 or IgG4) or subclass thereof. In an embodiment, the antibody is a humanized monoclonal antibody. In an embodiment, the antibody is a human monoclonal antibody.

[0054] As used herein, the term “CDR” or “complementarity determining region” means the noncontiguous antigen combining sites found within the variable regions of heavy and light chain polypeptides. These particular regions have been described by, for example, Kabat et al., *J. Biol. Chem.* 252, 6609-6616 (1977) and Kabat et al., *Sequences of Proteins of Immunological Interest*. (1991), by Chothia et al., *J. Mol. Biol.* 196:901-917 (1987), and by MacCallum et al., *J. Mol. Biol.* 262:732-745 (1996), all of which are herein incorporated by reference in their entireties, where the definitions include overlapping or subsets of amino acid residues when compared against each other (see **Table 1** below). In certain embodiments, the term “CDR” is a CDR as defined by MacCallum et al., *J. Mol. Biol.* 262:732-745 (1996) and Martin A. “Protein Sequence and Structure Analysis of Antibody Variable Domains,” in *Antibody Engineering*, Kontermann and Dübeler, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In certain embodiments, the term “CDR” is a CDR as defined by Kabat et al., *J. Biol. Chem.* 252, 6609-6616 (1977) and Kabat et al., *Sequences of Proteins of Immunological Interest*. (1991). In certain embodiments, heavy chain CDRs and light chain CDRs of an antibody are defined using different conventions. In certain embodiments, heavy chain CDRs and/or light chain CDRs are defined by performing structural analysis of an antibody and identifying residues in the variable region(s) predicted to make contact with an epitope region of a target molecule (e.g., human C2). CDRH1, CDRH2, and CDRH3 denote the heavy chain CDRs, and CDRL1, CDRL2, and CDRL3 denote the light chain CDRs.

Table 1: CDR definitions

	CDR Definitions		
	Kabat	Chothia	MacCallum
VH CDR1	31-35	26-32	30-35
VH CDR2	50-65	53-55	47-58
VH CDR3	95-102	96-101	93-101
VL CDR1	24-34	26-32	30-36
VL CDR2	50-56	50-52	46-55
VL CDR3	89-97	91-96	89-96

[0055] As used herein, the terms “variable region” and “variable domain” are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable region are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In an embodiment, the variable region is a primate (e.g., non-human primate) variable region. In an embodiment, the variable region comprises rodent or murine CDRs and primate (e.g., non-human primate) framework regions (FRs).

[0056] As used herein, the terms “VH” and “VL” refer to antibody heavy and light chain variable regions, respectively, as described in Kabat et al., (1991) Sequences of Proteins of Immunological Interest (NIH Publication No. 91-3242, Bethesda), which is herein incorporated by reference in its entirety.

[0057] As used herein, the term “constant region” is common in the art. The constant region is an antibody portion, e.g., a carboxyl terminal portion of a light and/or heavy chain, which is not directly involved in binding of an antibody to antigen, but which can exhibit various effector functions, such as interaction with an Fc receptor (e.g., Fc gamma receptor).

[0058] As used herein, the term “heavy chain” when used in reference to an antibody can refer to any distinct type, e.g., alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ), based on the amino acid sequence of the constant region, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, e.g., IgG1, IgG2, IgG3, and IgG4.

[0059] As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, e.g., kappa (κ) or lambda (λ), based on the amino acid sequence of the constant region. Light chain amino acid sequences are well known in the art. In an embodiment, the light chain is a human light chain.

[0060] As used herein, the terms “specifically binds,” “specifically recognizes,” “immunospecifically binds,” and “immunospecifically recognizes” are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (e.g., epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen can bind to other peptides or polypeptides, generally with lower affinity as determined by, e.g., immunoassays, BIAcore®, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In an embodiment, molecules that specifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs (e.g., factors of 10), 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind non-specifically to another antigen.

[0061] As used herein, the term “EU numbering system” refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman G.M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health and Human Services, 5th edition, 1991, each of which is herein incorporated by reference in its entirety.

[0062] As used herein, the term “subject” includes any human or non-human animal. In an embodiment, the subject is a human.

[0063] As used herein, the term “baseline” refers to a measurement (e.g., free C2 level) in a subject, e.g., in a subject’s blood, prior to the first administration (e.g., intravenous, or subcutaneous administration) of a treatment (e.g., a C2 inhibitor).

[0064] As used herein, the term “effective amount” in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect.

[0065] As used herein, the term “IVIg retreatment” refers to administering IVIg therapy to a subject who has previously been treated with IVIg. In an embodiment, the subject is given IVIg retreatment based on clinical deterioration. In an embodiment, the clinical deterioration is defined as a

>30% decline in grip strength of either hand observed at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score compared to the day of randomization.

[0066] As used herein, the terms “IVIg dependent” or “dependent on IVIg” refer to a subject who shows clinical deterioration if IVIg therapy is discontinued or a subject who shows clinical improvement if IVIg therapy is initiated. In an embodiment, the subject is considered IVIg dependent if the subject was stabilized to IVIg for longer than 3 months and a clinically meaningful deterioration is established. In an embodiment, the subject is considered IVIg dependent if the subject is stabilized to IVIg for less than 3 months and demonstrates a clinical improvement following the initiation of IVIg therapy.

[0067] As used herein, the term “about” when referring to a measurable value, such as a dosage, encompasses variations of $\pm 20\%$, $\pm 15\%$, $\pm 10\%$, $\pm 5\%$, $\pm 1\%$, or $\pm 0.1\%$ of a given value or range, as are appropriate to perform the methods disclosed herein.

[0068] As used herein, the terms “empasiprubar”, “EMPA” and ARGX-117” are used interchangeably.

Multifocal Motor Neuropathy (MMN)

Diagnosis of MMN

[0069] The diagnosis of MMN depends on demonstrating that a patient has a purely motor disorder affecting individual nerves, that there are no upper motor neuron (UMN) signs, that there are only minor or no sensory deficits, and that there is evidence of conduction block. These criteria are designed to differentiate the disorder from ALS (purely motor but with UMN signs), the Lewis-Sumner Syndrome variant of chronic inflammatory demyelinating polyneuropathy (CIDP) (similar to MMN but usually with significant sensory loss), and “vasculitis” (a type of multiple mononeuropathy syndrome caused by inflammatory damage to the blood vessels in nerves that also causes sensory and motor symptoms).

[0070] A neurologist is usually needed to determine the diagnosis, which is based on the history and physical examination along with an electrodiagnostic study, which includes nerve conduction studies (NCS) and needle electromyography (EMG). The NCS usually demonstrate conduction block. This can be done by showing that the nerve signal cannot conduct past a “lesion” at some point along the nerve. For example, if the nerve is blocked in the forearm, an electrical impulse can easily get from the wrist to the hand if the stimulus is placed at the wrist. However, the signal will be blocked from reaching the

hand if the stimulus is applied at the elbow. In MMN, sensory conduction along the same path should be normal. The EMG portion of the test looks for signals in the way muscles fire. In MMN it will most likely reveal abnormalities suggesting that some percentage of the motor axons has been damaged. Laboratory testing for GM1 antibodies is frequently done and can be very helpful if they are abnormal. However, since only a third of patients with MMN have these antibodies, a negative test does not rule out the disorder. Spinal fluid examination is not usually helpful.

Standard-of-Care Treatment

[0071] In 2012, the U.S. Food and Drug Administration (FDA) approved Gammagard Liquid 10% for the treatment of MMN. This medication is an intravenous immunoglobulin (IVIg) and most affected individuals respond to treatment with IVIg. There is usually a rapid improvement in muscle weakness when treatment is started. The effects of IVIg treatment eventually wear off and affected individuals need to take the medication again every 2-6 weeks (maintenance therapy). Sometimes, affected individuals become less responsive to the medication and will require higher doses or more frequent maintenance therapy. If affected individuals do not respond to treatment with IVIg or stop responding to this therapy, then other medications can be tried. Various other medications have been tested for treating MMN, including cyclophosphamide, rituximab, beta-interferon, mycophenolate mofetil, cyclosporine, azathioprine, and infliximab.

C2 Inhibitors

[0072] C2 inhibitors that are useful in the methods and uses provided herein include but are not limited to any anti-C2 antibody, including antigen-binding fragments thereof.

[0073] In an embodiment, the C2 inhibitor is an antibody that specifically binds to the C2b part of C2 in a pH- and Ca^{2+} -dependent manner. In an embodiment, the C2 inhibitor is an anti-C2b antibody. As used herein, C2b refers to the smaller 30 kDa fragment of complement protein C2. In an embodiment, the antibody inhibits the function of C2 and blocks downstream complement activation.

[0074] In an embodiment, the antibody comprises: a heavy chain variable region (VH) comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in SEQ ID NO: 7, or a variant thereof comprising 1-5 amino acid changes in any one of the CDRH1, CDRH2, or CDRH3 amino acid sequences; and/or a light chain variable region (VL) comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in SEQ ID

NO: 8, or a variant thereof comprising 1-5 amino acid changes in any one of the CDRL1, CDRL2, or CDRL3 amino acid sequences.

[0075] In an embodiment, (a) the VH comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of: SEQ ID NO: 1, or a variant thereof comprising 1-5 amino acid changes, SEQ ID NO: 2, or a variant thereof comprising 1-5 amino acid changes, and SEQ ID NO: 3, or a variant thereof comprising 1-5 amino acid changes; and/or (b) the VL comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of SEQ ID NO: 4, or a variant thereof comprising 1-5 amino acid changes, SEQ ID NO: 5, or a variant thereof comprising 1-5 amino acid changes, and SEQ ID NO: 6, or a variant thereof comprising 1-5 amino acid changes.

[0076] In an embodiment, the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 1, 2, 3, 4, 5, and 6, respectively.

[0077] In an embodiment, the antibody comprises: a VH comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 7; and/or a VL comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 8.

[0078] In an embodiment, the antibody comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 7 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 8. In an embodiment, the amino acid sequence of the VH consists of the amino acid sequence set forth in SEQ ID NO: 7 and the amino acid sequence of VL consists of the amino acid sequence set forth in SEQ ID NO: 8.

[0079] In an embodiment, the antibody comprises a heavy chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 9 and/or a light chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 10.

[0080] In an embodiment, the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 9 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 10. In an embodiment, the amino acid sequence of the heavy chain consists of the amino acid sequence set forth in SEQ ID NO: 9 and the amino acid sequence of the light chain consists of the amino acid sequence set forth in SEQ ID NO: 10.

[0081] In an embodiment the antibody is ARGX-117 (empasiprubart, also referred to herein as

“EMPA”), the sequences of which are provided in **Table 2** below.

Table 2: Amino acid sequences of ARGX-117 (empasiprubart or EMPA)

Description	SEQ ID NO:	Amino acid sequence
CDRH1	1	DYNMD
CDRH2	2	DINPNYESTGYNQKFKG
CDRH3	3	EDDHDAFAY
CDRL1	4	RASKSVRTSGYNYMH
CDRL2	5	LASNLS
CDRL3	6	QHSRELPYT
VH	7	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMDWVRQATGQ GLEWIGDINPNYESTGYNQKFKGRATMTVDKSISTAYMELSSLRSE DTAVYYCAREDDHDAFAYWGQGLTVTVSS
VL	8	DNVLTQSPDSLAVSLGERATISCRASKSVRTSGYNYMHWYQQKPG QPPKLLIYLASNLSKSGVPDRFSGSGSGTDFTLTISSLQAEDAATYYC QHSRELPYTFGQGTKEIK
Heavy chain	9	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMDWVRQA TGQGLEWIGDINPNYESTGYNQKFKGRATMTVDKSISTAYM ELSSLRSEDTAVYYCAREDDHDAFAYWGQGLTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGFFLYSKLTVD KSRWQQGNVFSCSVMHEALKFHYTQKSLSLSPG
Light chain	10	DNVLTQSPDSLAVSLGERATISCRASKSVRTSGYNYMHWYQQKPG QPPKLLIYLASNLSKSGVPDRFSGSGSGTDFTLTISSLQAEDAATYYC QHSRELPYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLT LSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

[0082] ARGX-117 binds human and cynomolgus monkey C2 in a pH- and Ca²⁺-dependent manner with affinity to human C2 ranging from 0.109 nM to 2.02 nM and affinity to cynomolgus monkey C2 from 0.056 nM to 0.13 nM, respectively. In an embodiment of any one of the methods disclosed herein, the C2 inhibitor binds human and cynomolgus monkey C2 in a pH- and Ca²⁺-dependent manner with affinity to human C2 ranging from 0.109 nM to 2.02 nM and affinity to cynomolgus monkey C2 from 0.056 nM to 0.13 nM, respectively. ARGX-117 is not cross-reactive to C2 from rat, rabbit, hamster, mouse, and guinea pig. Epitope mapping revealed that ARGX-117 binds predominantly the sushi 2

domain of C2. In an embodiment of any one of the methods disclosed herein, the C2 inhibitor binds the sushi 2 domain of C2.

[0083] ARGX-117 inhibits the classical and lectin pathway of the complement system but does not affect the alternative pathway. In an embodiment of any one of the methods disclosed herein, the C2 inhibitor inhibits the classical and lectin pathways of the complement system. In an embodiment of any one of the methods disclosed herein, the C2 inhibitor does not inhibit the alternative pathway.

Methods and Dosage Regimens

[0084] The instant disclosure demonstrates that C2 inhibitors are highly effective in treating multifocal motor neuropathy (MMN). Accordingly, the instant disclosure is broadly directed to methods for treating MMN with a C2 inhibitor. Also provided herein are particular dosage regimens for administering a C2 inhibitor that results in a rapid reduction of the free C2 level in the blood of a subject who has MMN.

[0085] In an aspect, provided herein is a method of treating multifocal motor neuropathy (MMN) in a subject in need thereof, the method comprising administering to the subject an effective amount of a C2 inhibitor.

[0086] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg.

[0087] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg. In an embodiment,

the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[0088] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[0089] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[0090] In an embodiment, the C2 inhibitor is administered intravenously or subcutaneously. In an embodiment, the C2 inhibitor is administered intravenously. In an embodiment, the C2 inhibitor is administered subcutaneously.

[0091] In an embodiment, the C2 inhibitor is administered once weekly. In an embodiment, the C2 inhibitor is administered once every 2 weeks. In an embodiment, the C2 inhibitor is administered once every 4 weeks. In an embodiment, the C2 inhibitor is administered once every 5 weeks. In an embodiment, the C2 inhibitor is administered once every 6 weeks. In an embodiment, the C2 inhibitor is administered once every 7 weeks. In an embodiment, the C2 inhibitor is administered once every 8 weeks.

[0092] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once weekly. In an embodiment, the C2 inhibitor is

administered at a dose of about 15 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once weekly.

[0093] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once weekly. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once weekly.

[0094] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once weekly. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once weekly.

[0095] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once weekly. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once weekly.

[0096] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 2 weeks. In an

embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 2 weeks.

[0097] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 2 weeks.

[0098] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 2 weeks.

[0099] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 2 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 2 weeks.

[00100] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 3 weeks.

weeks.

[00101] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 3 weeks.

[00102] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 3 weeks.

[00103] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 3 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 3 weeks.

[00104] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 4 mg/kg to 60 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 4 weeks.

[00105] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 4 weeks.

[00106] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 4 weeks.

[00107] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 4 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 4 weeks.

[00108] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 10 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 15 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 30 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 60 weeks.

[00109] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg

once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 5 weeks.

[00110] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 5 weeks.

[00111] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 5 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 5 weeks.

[00112] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 6 weeks.

[00113] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5mg/kg to 60 mg/kg

once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 6 weeks.

[00114] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 6 weeks.

[00115] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 6 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 6 weeks.

[00116] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 7 weeks.

[00117] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5

mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 7 weeks.

[00118] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 7 weeks.

[00119] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 7 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 7 weeks.

[00120] In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg to 100 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg to 60 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 5 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 10 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 15 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 30 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of about 60 mg/kg once every 8 weeks.

[00121] In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg,

40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg once every 8 weeks.

[00122] In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg to 1500 mg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 8 weeks.

[00123] In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg once every 8 weeks. In an embodiment, the C2 inhibitor is administered at a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg once every 8 weeks.

[00124] In an embodiment, the C2 inhibitor is administered intravenously at a dose of 10 mg/kg once weekly or every 2 weeks. In an embodiment, the C2 inhibitor is administered intravenously at a dose of 30 mg/kg once weekly or every 2 weeks. In an embodiment, the C2 inhibitor is administered intravenously at a dose of 60 mg/kg once weekly or every 2 weeks. In an embodiment, the C2 inhibitor is administered intravenously at a dose of 15 mg/kg once weekly or every 2 weeks. In an embodiment, the C2 inhibitor is administered intravenously at a dose of 5 mg/kg once weekly, every 2 weeks or every 4 weeks.

[00125] In an embodiment, the C2 inhibitor is administered according to a loading regimen, preferably a loading regimen that reduces the level of free C2 in the blood of the subject to or below a threshold level.

[00126] In an embodiment, the method further comprises a maintenance regimen following the loading regimen, preferably wherein the maintenance regimen comprises administration of the C2 inhibitor according to a regimen that maintains the level of free C2 in the blood of the subject at or below the threshold level.

[00127] In an embodiment, the threshold level is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, or 0.8 µg/mL. In an embodiment, the threshold level is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% of the subject's baseline level of free C2. In an embodiment, the threshold level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, or 0.8 µg/mL. In an embodiment, the threshold level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9,

1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% of the subject's baseline level of free C2. As used herein, "baseline level of free C2" refers to the level or concentration of circulating (serum or plasma) C2 in the subject prior to first administration of the C2 inhibitor (e.g. ARGX-117). The C2 level can be measured using any suitable technique. See, for example, Tange CE et al., Clin Chem Lab Med 2018; 56(9): 1498-1506.

[00128] In an embodiment, the loading regimen is a single initial dose followed by one or more subsequent doses. In an embodiment, the one or more subsequent doses are each a lower amount than the single initial dose. In an embodiment, the one or more subsequent doses are each a greater amount than the single initial dose. In an embodiment, the one or more subsequent doses are each equal to the amount of the single initial dose.

[00129] In an embodiment, the single initial dose is followed by 1, 2, 3, 4, 5, or 6 subsequent doses. In an embodiment, the subsequent doses are administered once weekly or every 2 weeks. In an embodiment, the single initial dose is followed by 1, 2, 3, 4, 5, or 6 subsequent doses, administered once weekly. In an embodiment, the single initial dose is followed by 1, 2, 3, 4, 5, or 6 subsequent doses, administered once every 2 weeks. In an embodiment, the single initial dose is followed by 4 subsequent doses, administered once weekly.

[00130] In an embodiment, the first subsequent dose is administered one week after the single initial dose. In an embodiment, the first subsequent dose is administered 10 days after the single initial dose. In an embodiment, the first subsequent dose is administered two weeks after the single initial dose.

[00131] In an embodiment, the single initial dose is a dose of about 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of about 10 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of about 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the single initial dose is a dose of about 15 mg/kg. In an embodiment, the single initial dose is a dose of about 30 mg/kg. In an embodiment, the single initial dose is a dose of about 60 mg/kg.

[00132] In an embodiment, the single initial dose is a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20

mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00133] In an embodiment, the single initial dose is a fixed dose of about 500 mg to 1500 mg. In an embodiment, the single initial dose is a fixed dose of about 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00134] In an embodiment, the single initial dose is a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00135] In an embodiment, the subsequent doses are each a dose of about 0.1 mg/kg to 100 mg/kg. In an embodiment, the subsequent doses are each a dose of about 5 mg/kg to 60 mg/kg. In an embodiment, the subsequent doses are each a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the subsequent doses are each a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the subsequent doses are each a dose of about 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the subsequent doses are each a dose of about 5 mg/kg. In an embodiment, the subsequent doses are each a dose of about 10 mg/kg. In an embodiment, the subsequent doses are each a dose of about 30 mg/kg.

[00136] In an embodiment, the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg.

[00137] In an embodiment, the subsequent doses are each a fixed dose of about 500 mg to 1500 mg. In an embodiment, the subsequent doses are each a fixed dose of about 500 mg, 600 mg, 700 mg,

800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00138] In an embodiment, the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00139] In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 15 mg/kg, 10 mg/kg, 30 mg/kg, or 60 mg/kg.

[00140] In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 0.1 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00141] In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00142] In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 0.5 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00143] In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00144] In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 2.5 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00145] In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00146] In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 10 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00147] In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5

mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a dose of 5 mg/kg.

[00148] In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 15 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00149] In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a dose of 10 mg/kg.

[00150] In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 30 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00151] In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5

mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a dose of 30 mg/kg.

[00152] In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 60 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00153] In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00154] In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a dose of 80 mg/kg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00155] In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a dose of 0.1 mg/kg to 100 mg/kg. In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a dose of 5 mg/kg to 60 mg/kg. In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg,

85 mg/kg, 90 mg/kg, 95 mg/kg, or 100 mg/kg. In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg. In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.

[00156] In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a fixed dose of 500 mg to 1500 mg. In an embodiment, the single initial dose is a fixed dose of 1200 mg and the subsequent doses are each a fixed dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg.

[00157] In an embodiment, the single initial dose is 30 mg/kg and the subsequent doses are each 10 mg/kg. In an embodiment, the single initial dose is 30 mg/kg and the subsequent dose or doses is/are each 30 mg/kg. In an embodiment, the single initial dose is 60 mg/kg and the subsequent doses are each 30 mg/kg. In an embodiment, the single initial dose is 15 mg/kg and the subsequent doses are each 5 mg/kg.

[00158] In an embodiment, the loading regimen is administered intravenously or subcutaneously. In an embodiment, the loading regimen is administered intravenously. In an embodiment, the loading regimen is administered subcutaneously. In an embodiment, the single initial dose is administered intravenously and the subsequent dose are administered subcutaneously. In an embodiment, the single initial dose is administered subcutaneously and the subsequent dose are administered intravenously. In an embodiment, the single initial dose and the subsequent dose are both administered intravenously. In an embodiment, the single initial dose and the subsequent dose are both administered subcutaneously.

[00159] In an embodiment, the loading regimen reduces the level of free C2 to or below the threshold level in about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days. In an embodiment, the loading regimen reduces the level of free C2 to or below the threshold level in 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days. In an embodiment, the loading regimen reduces the level of free C2 to or below the threshold level in about 1, 2, 3, 4, 5, 6, 7, or 8 weeks. In an embodiment, the loading regimen reduces the level of free C2 to or below the threshold level in 1, 2, 3, 4, 5, 6, 7, or 8 weeks.

[00160] In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, or every 8 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, or every 8 weeks.

[00161] In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once weekly. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 2 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 3 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 5 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 6 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 7 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1-100 mg/kg administered once every 8 weeks.

[00162] In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once weekly. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 2 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 3 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 5 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 6 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 7 weeks. In an embodiment, the maintenance regimen is a dose of 0.1-100 mg/kg administered once every 8 weeks.

[00163] In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once weekly. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 2 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 3 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 5 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 6 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10

mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 7 weeks. In an embodiment, the maintenance regimen is a dose of about 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 8 weeks.

[00164] In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once weekly. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 2 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 3 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 5 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 6 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 7 weeks. In an embodiment, the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 8 weeks.

[00165] In an embodiment, the maintenance regimen is a dose of about 5 mg/kg, administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of about 5 mg/kg, administered once every 8 weeks. In an embodiment, the maintenance regimen is a dose of about 10 mg/kg, administered once every 2 weeks. In an embodiment, the maintenance regimen is a dose of about 10 mg/kg, administered once every 4 weeks. In an embodiment, the maintenance regimen is a dose of about 10 mg/kg, administered once every 8 weeks. In an embodiment, the maintenance regimen is a dose of about 30 mg/kg, administered once every 2 weeks.

[00166] In an embodiment, the maintenance regimen is a fixed dose of about 500 mg to 1500 mg, administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks. In an embodiment, the maintenance regimen is a fixed dose of about 1200 mg administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks.

[00167] In an embodiment, the maintenance regimen is a fixed dose of 500 mg to 1500 mg,

administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks. In an embodiment, the maintenance regimen is a fixed dose of 1200 mg administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks.

[00168] In an embodiment, the maintenance regimen is administered 1, 2, 3, 4, 5, 6, 7, or 8 weeks after the loading regimen. In an embodiment, the maintenance regimen is administered if the level of free C2 in the blood of the subject is above a threshold level.

[00169] In an embodiment, the threshold level is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 µg/mL. In an embodiment, the threshold level is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% of the subject's baseline level of free C2. In an embodiment, the threshold level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 µg/mL. In an embodiment, the threshold level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% of the subject's baseline level of free C2.

[00170] In an embodiment, the maintenance regimen is administered intravenously or subcutaneously. In an embodiment, the maintenance regimen is administered intravenously. In an embodiment, the maintenance regimen is administered subcutaneously.

[00171] In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once weekly. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 2 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 3 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 4 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 5 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 6 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 0.1 mg/kg, administered once every 7 weeks. In an embodiment, the

dose of 60 mg/kg, administered once every 3 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 60 mg/kg, administered once every 4 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 60 mg/kg, administered once every 5 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 60 mg/kg, administered once every 6 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 60 mg/kg, administered once every 7 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 60 mg/kg, administered once every 8 weeks.

[00178] In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once weekly. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 2 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 3 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 4 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 5 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 6 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 7 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a dose of 80 mg/kg, administered once every 8 weeks.

[00179] In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once weekly. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 2 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 3 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200

mg, administered once every 4 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 5 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 6 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 7 weeks. In an embodiment, the loading regimen is any one of the loading regimens described herein, and the maintenance regimen is a fixed dose of 1200 mg, administered once every 8 weeks.

[00180] In an embodiment, the loading regimen is: a single initial dose of 0.1 mg/kg to 100 mg/kg; and four subsequent doses, each of 0.1 mg/kg to 100 mg/kg administered once weekly or every 2 weeks beginning one week after the single initial dose; and the maintenance regimen is: a dose of 0.1 mg/kg to 100 mg/kg administered once every two weeks, or once every 4 weeks. In an embodiment, the loading regimen is: a single initial dose of 0.1 mg/kg to 100 mg/kg; and one subsequent dose of 0.1 mg/kg to 100 mg/kg administered one week after the single initial dose; and the maintenance regimen is: a dose of 0.1 mg/kg to 100 mg/kg administered once every two weeks, or once every 4 weeks.

[00181] In an embodiment, the loading regimen is: a single initial fixed dose of 500 mg to 1500 mg; and four subsequent doses, each of 500 mg to 1500 mg administered once weekly or every 2 weeks beginning one week after the single initial dose; and the maintenance regimen is: a dose of 500 mg to 1500 mg administered once every two weeks, or once every 4 weeks.

[00182] In an embodiment, the loading regimen is: a single initial dose of 60 mg/kg; and at least four, preferably four subsequent doses, each of 30 mg/kg administered once weekly beginning one week after the single initial dose; and the maintenance regimen is: a dose of 30 mg/kg administered once every two weeks.

[00183] In an embodiment, the loading regimen is: a single initial dose of 30 mg/kg; and one or more subsequent doses, each of 10 mg/kg administered once weekly beginning one week after the single initial dose; and the maintenance regimen is two or more doses of 10 mg/kg administered once every two weeks. In an embodiment, the loading regimen is: a single initial dose of 30 mg/kg; and one or more subsequent doses, each of 10 mg/kg or 30 mg/kg administered once weekly beginning one week after the single initial dose; and the maintenance regimen is two or more doses of 10 mg/kg administered once every two or four weeks.

[00184] In an embodiment, the loading regimen is: a single initial dose of 30 mg/kg; and at least four, preferably four subsequent doses, each of 10 mg/kg administered once weekly beginning one week

after the single initial dose; and the maintenance regimen is: two or more doses of 10 mg/kg administered once every two weeks. In an embodiment, the loading regimen is: a single initial dose of 30 mg/kg; and one subsequent dose of 30 mg/kg administered one week after the single initial dose; and the maintenance regimen is two or more doses of 10 mg/kg administered once every four weeks.

[00185] In an embodiment, the loading regimen is: a single initial dose of 15 mg/kg; and one or more subsequent doses, each of 5 mg/kg administered once weekly beginning one week after the single initial dose; and the maintenance regimen is two or more doses of 5 mg/kg administered once every four weeks.

[00186] In an embodiment, the loading regimen is: a single initial dose of 15 mg/kg; and at least four, preferably four, subsequent doses, each of 5 mg/kg administered once weekly beginning one week after the single initial dose; and the maintenance regimen is: two or more doses of 5 mg/kg administered once every four weeks.

[00187] In an embodiment, the frequency of dosing in the maintenance regimen is increased if the subject shows signs of clinical deterioration. In an embodiment, the frequency of dosing in the maintenance regimen is increased from administration once every 8 weeks to administration once every 4 weeks if the subject shows signs of clinical deterioration. The frequency of dosing in the maintenance regimen may be decreased again if the subject shows signs of clinical improvement. For example, the frequency of dosing in the maintenance regimen may be decreased from once every 4 weeks to once every 8 weeks if the subject shows signs of clinical improvement.

[00188] In an embodiment, the frequency of dosing in the maintenance regimen is decreased if the subject shows signs of clinical improvement. In an embodiment, the frequency of dosing in the maintenance regimen is decreased from administration once every 4 weeks to administration once every 8 weeks if the subject shows signs of clinical improvement. The frequency of dosing in the maintenance regimen may be increased again if the subject shows signs of clinical deterioration. For example, the frequency of dosing in the maintenance regimen may be increased from once every 8 weeks to once every 4 weeks if the subject shows signs of clinical deterioration.

[00189] In an embodiment, the maintenance regimen begins 1 week after the last subsequent dose of the loading regimen. In an embodiment, the maintenance regimen begins 10 days after the last subsequent dose of the loading regimen. In an embodiment, the maintenance regimen begins 2 weeks after the last subsequent dose of the loading regimen. In an embodiment, the maintenance regimen begins 3 weeks after the last subsequent dose of the loading regimen. In an embodiment, the maintenance regimen begins 4 weeks after the last subsequent dose of the loading regimen.

[00190] In an embodiment, the loading regimen is administered intravenously and the maintenance regimen is administered subcutaneously. In an embodiment, the loading regimen is administered subcutaneously and the maintenance regimen is administered intravenously. In an embodiment, the loading regimen and the maintenance regimen are both administered intravenously. In an embodiment, the loading regimen and the maintenance regimen are both administered subcutaneously.

[00191] In an embodiment, the subject's motor strength and/or the subject's sensory symptoms are improved compared to the subject's motor strength and/or the subject's sensory symptoms achieved with standard-of-care treatment using intravenous immunoglobulin (IVIg). Sensory symptoms include paresthesia (a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body), hypesthesia (impaired or decreased tactile sensibility) or a combination of both.

[00192] In an embodiment, the subject shows a reduction in the level of free C2 in the blood of the subject following administration of the C2 inhibitor, compared to a baseline level of free C2 in the blood of the subject. In an embodiment, the level of free C2 in the blood of the subject is reduced by at least about 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % compared to a baseline level of free C2 in the blood of the subject. It is surprising that a reduction of at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % reduction of free C2 level in the subject compared to baseline level of free C2 is sufficient to treat MMN patients efficiently, as the complement system is a cascade system which can go out of balance in MMN patients (unbalanced complement system or overactivation of the complement system can result in inflammation and subsequent tissue (e.g. motor nerve) damage in MMN patients). It was not commonly known which amount of free C2 level can still be present in the subject whereby the complement system can be brought back in balance in MMN patients in response to the treatment with a C2 inhibitor (e.g. ARGX-117), thereby effectively treating the MMN patient.

[00193] In an embodiment, the method further comprises administering an additional therapeutic agent to the subject. In an embodiment, the additional therapeutic agent is IVIg. In an embodiment, the additional therapeutic is rituximab, eculizumab, cyclophosphamide, or mycophenolate mofetil.

[00194] In an embodiment, the IVIg is administered to the subject once every two weeks, once every three weeks, once every four weeks, or once every five weeks.

[00195] In an embodiment, the subject has a detectable baseline serum level of an anti-ganglioside IgM antibody. In an embodiment, the anti-ganglioside IgM antibody is an anti-GM1 antibody. In an embodiment, the anti-ganglioside IgM antibody is an anti-GM2 antibody.

[00196] In an embodiment, the subject shows a reduction in a serum level of a cytokine following administration of the C2 inhibitor, compared to a baseline serum level of the cytokine. In an embodiment, the cytokine is TNF- α , IFN- γ , IL-2, IL-6, IL-8, or IL-10.

[00197] In an embodiment, the subject has been previously treated with IVIg. In an embodiment, the subject has been previously stabilized with IVIg. In an embodiment, the subject is dependent on IVIg.

[00198] In an embodiment, the subject is not receiving concomitant IVIg at the time of commencing administration of the C2 inhibitor.

[00199] In an embodiment, the subject shows an increase in a modified Medical Research Council (mMRC) score following administration of the C2 inhibitor, compared to the subject's baseline mMRC score. In an embodiment, the mMRC score is an mMRC-10 sum score or an mMRC-14 sum score. In an embodiment, the mMRC score is an mMRC-10 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-10 sum score of 1 or more, compared to the subject's baseline mMRC-10 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-10 sum score of 1.5, compared to the subject's baseline mMRC-10 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-10 sum score of at least 1.5, compared to the subject's baseline mMRC-10 sum score. In an embodiment, the mMRC score is an mMRC-14 sum score. In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in the mMRC-14 sum score of 1 or more, compared to the subject's baseline mMRC-14 sum score. In an embodiment, the subject shows an increase in the mMRC-10 sum score of 4. In an embodiment, the subject shows an increase in the mMRC-10 sum score of at least 4.

[00200] In an embodiment, the subject shows improved grip strength following administration of the C2 inhibitor, compared to the subject's baseline grip strength. In an embodiment, the subject shows improved grip strength in the most affected hand, in the less affected hand, or in both hands. In an embodiment, the subject shows improved grip strength in the most affected hand of greater than 10 kPa. In an embodiment, the subject shows improved grip strength in the most affected hand of 11.28 kPa. In an embodiment, the subject shows improved grip strength in the most affected hand of 17.06 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of greater than 5 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of greater than 6.5 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of 6.5 kPa. In an embodiment, the subject shows improved grip strength in the less affected hand of 8.78 kPa.

[00201] In an embodiment, the subject shows an increase in MMN Rasch-built Overall Disability Scale (MMN-RODS©) score following administration of the C2 inhibitor, compared to the subject's baseline MMN-RODS© score. In an embodiment, the subject shows an increase in MMN-RODS score of 5 or more, optionally 6 or more. In an embodiment, the subject shows an increase in MMN-RODS score of 6. In an embodiment, the subject shows an increase in MMN-RODS score of 7.5.

[00202] In an embodiment, following administration of the C2 inhibitor, the subject shows an increase in disease-specific quality of life, as measured using the Chronic Acquired Polyneuropathy – Patient Report Index (CAP-PRI), compared to the subject's score at baseline. In an embodiment, following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2 or more. In an embodiment, following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2. In an embodiment, following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2.5.

[00203] In an embodiment, following administration of the C2 inhibitor, the subject reports an improvement in the Patient Global Impression of Change (PGIC) 7-point scale. In an embodiment, a population of MMN subjects are treated, and 55.6% of subjects treated report their condition much improved or very much improved. In an embodiment, a population of MMN subjects are treated, and 94.4% of subjects treated report any improvement (minimally improved, much improved, or very much improved).

[00204] In an embodiment, following administration of the C2 inhibitor, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS). In an embodiment, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS) comprising a reduction of 0.1 or more. In an embodiment, the reduction is 0.11. In an embodiment, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS) comprising a reduction of 0.4 or more. In an embodiment, the reduction is 0.444.

[00205] In an embodiment, the C2 inhibitor is administered subcutaneously and the C2 inhibitor is administered with hyaluronidase. In an embodiment, the C2 inhibitor is administered subcutaneously and the C2 inhibitor is co-formulated with hyaluronidase. In an embodiment, the hyaluronidase is recombinant human hyaluronidase PH20 (rHuPH20).

[00206] In an aspect, provided herein is a C2 inhibitor for use in the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a method disclosed herein.

[00207] In an aspect, provided herein is a C2 inhibitor for use in the manufacture of a medicament for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a

method disclosed herein.

[00208] In an aspect, provided herein is a use of a C2 inhibitor for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to a method disclosed herein.

EXAMPLES

Example 1 – Investigation of efficacy and safety of ARGX-117 (empasiprubart) in adults with multifocal motor neuropathy (MMN)

[00209] This example describes a randomized, double-blinded, placebo-controlled, parallel-group, multicenter trial carried out to evaluate the safety and tolerability, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of dosage regimens of ARGX-117 (a therapeutic complement-inhibiting antibody that targets complement factor 2 (C2)) in adults with multifocal motor neuropathy (MMN) (ARGX-117-2002). Despite the thoughtful study design, it is well established that less than 10% of clinical trials are successful and meet the endpoints included in the study design.

[00210] Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. MMN is considered a chronic immune-mediated neuropathy driven by the classical complement pathway related to the presence of auto-antibodies, e.g. can be the presence of anti-ganglioside GM1 (monosialotetrahexosylganglioside [anti-GM1]), anti-GM2 (and other gangliosides) immunoglobulin M (IgM) antibodies produced by a limited number of B cell clones. These antibodies activate the complement system's classical pathway and subsequently yield membrane attack complex (MAC) deposition leading to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and disturbance of membrane integrity at the (para)nodal regions that result in demyelination and motor nerve conduction block.

[00211] Patients with MMN initially respond to the standard of care, intravenous immunoglobulin (IVIg); however, the disease will continue to progress despite treatment. The objective of the trial described in this example is to evaluate the safety and efficacy of ARGX-117 treatment patients with MMN who have been previously stabilized with IVIg.

A. Study design

Overall design

[00212] This is a phase 2, randomized, stratified, double-blinded, placebo-controlled, parallel-group, multicenter trial of ARGX-117 in adults with MMN. The total trial duration was a minimum 25 weeks for all participants. The order and duration of study periods was as follows for both cohort 1 and cohort 2:

- Screening period: Up to 28 days;
- IVIg dependency period (IVDP) (if applicable): only participants whose IVIg dependency was uncertain at the end of the screening period entered the IVDP;
- IVIg monitoring period (IVMP): the length of the IVMP depended on the participant's IVIg dose frequency;
- Double-blinded treatment period (DBTP): 16-weeks;
- Safety follow-up period: participants who did not enrol into the long-term extension study (LTE) entered the 15-month safety follow-up period after completing the DBTP.

[00213] Two treatment cohorts were enrolled, referred to as cohort 1 and cohort 2. Data collected from the first 9 participants in cohort 1 who completed or discontinued early from the 16-week DBTP were evaluated by an independent data monitoring committee (IDMC). The IDMC made recommendations informing the unblinded executive data review team (EDRT) on the decision to begin the enrollment of cohort 2.

[00214] The diagnosis of MMN and IVIg dependency was assessed by the MMN Confirmation Committee (MCC) during the screening period. Participants whose IVIg dependency was uncertain entered the IVDP to assess the impact of delayed IVIg administration on grip strength (GS) and/or motor function. The IDMC monitored accumulating safety data throughout the trial.

Screening period

[00215] The screening period was used to determine an individual's eligibility to participate in the trial. Assessments were taken as described in the schedule of activities (SoA), see **Table 3**.

[00216] The screening period lasted up to 28 days and was possibly extended by an additional 14 days to a total of 42 days with the written approval of the medical monitor. An additional extension of the screening period to align a participant's subsequent IDV1 or IMV1 with their IVIg dosing schedule did not lead to screen failure.

IVIg dependency period (IVDP)

[00217] The IVDP was used to determine the IVIg dependency of participants whose IVIg dependency was uncertain based on the description provided to the MCC summarized in the participant profile during screening.

[00218] The IVDP lasted up to 15 weeks (105 days) depending on the IVIg dose frequency. A participant's IVIg administration was delayed during the IVDP. Assessments were taken at the time points described in the SoA, see **Table 3**.

[00219] Participants received IVIg following a delayed administration compared to their stable IVIg regimen interval, as follows:

- Participants receiving IVIg every 2 weeks extended the interval to 4 weeks;
- Participants receiving IVIg every 3 weeks extended the interval to 6 weeks;
- Participants receiving IVIg every 4 weeks extended the interval to 8 weeks; and
- Participants receiving IVIg every 5 weeks extended the interval to 10 weeks.

[00220] Participants had an earlier visit than planned during the IVDP if they demonstrated a clinically meaningful deterioration between the scheduled visits of the IVDP. Clinically meaningful deterioration was defined as a >30% decline in the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) since the peak post-IVIg GS after IDV1 and/or a decline of at least 2 points on the mMRC-10 sum score from IDV1 to IDV2.

IVIg monitoring period (IVMP)

[00221] The IVMP began after the participant completed the screening period and the IVDP, if applicable, and consisted of multiple administration cycles of IVIg (see **Table 3**).

[00222] This period established baseline values for all clinical endpoints assessed during the DBTP.

- Participants received IVIg at the frequency, duration, and dose described in their medical history.
- The IVMP included 3 IVIg treatment cycles
- The length of the IVMP depended on an individual's IVIg dose frequency, as follows:
 - o Dosed every 2 weeks: 35 days
 - o Dosed every 3 weeks: 49 days
 - o Dosed every 4 weeks: 63 days

- Dosed every 5 weeks: 77 days

[00223] The length of the IVMP may have been greater if a participant received IVIg over the course of several days. Assessments were done at the time points described in **Table 3**.

Table 3: IVIg dependency and IVIg monitoring period schedule of activities through day 7

	IVIg Dosing Frequency	SCN ^a	IVIg Dependency ^b		IVIg Monitoring ^c		
Visit (Days)		Up to 28 days	IDV1 ^d	IDV2 ^e	IMV1 ^f	IMV2	IMV3
	Q 2 weeks		1	29	1	15	29
	Q 3 weeks		1	43	1	22	43
	Q 4 weeks		1	57	1	29	57
	Q 5 weeks		1	71	1	36	71
Visit Window (Days)				±7	±3	±3	±3
Activity							
Informed consent		X					
Inclusion/exclusion criteria check		X			X		
MCC confirmation		X			X		
Medical history		X					
Demography		X					
Pregnancy test ^g		X			X		
FSH level ^h		X					
Physical examination ⁱ		X	X	X	X	X	X
Vital sign measurements ^j		X	X	X	X	X	X
12-lead ECGs ^k		X				X	X
SIB risk and monitoring ^l		X	X	X	X	X	X
Samples for safety laboratory tests		X	X	X	X	X	X
Samples for SLE panel ^m		X					
Samples for urinalysis		X					X
Samples for pharmacodynamics ⁿ			X	X	X	X	X
Samples for immunogenicity ^o		X					
Biomarkers ^p					X	X	X

Table 3 (Continued)

	IVIg Dosing Frequency	SCN ^a	IVIg Dependency ^b		IVIg Monitoring ^c		
Visit (Days)		Up to 28 days	IDV1	IDV2	IMV1	IMV2	IMV3
	Q 2 weeks		1	29	1	15	29
	Q 3 weeks		1	43	1	22	43
	Q 4 weeks		1	57	1	29	57
	Q 5 weeks		1	71	1	36	71
Visit Window (Days)				±7	±3	±3	±3
Activity							
Virology screen		X					
Pharmacogenetic sample		X ^q					
Samples for NfL ^f					X	X	X
Samples for autoantibodies (anti-GM1 and others) titer ^f					X		
Research sample ^f					X ^s	X ^s	X ^s
IVIg administration ^l			X	X	X	X	X
Grip strength ^u		X	Continuous monitoring				
MMN-RODS©		X	X	X	X	X	X
mMRC		X	X	X	X	X	X
9-HPT		X	X	X	X	X	X
HRPQ					X	X	X
EQ-5D-5L					X	X	X
CAP-PRI					X	X	X
FSS					X	X	X
14-item TSQM					X	X	X
Concomitant medication/procedures ^v		Continuous monitoring					
Adverse events ^v		Continuous monitoring					

9-HPT=nine-Hole Peg Test; ANA=anti-nuclear antibody; BMI=body mass index; CAP-PRI=Chronic Acquired Polyneuropathy Patient-Reported Index; C-SSRS=Columbia-suicide severity rating scale; DBTP=double-blinded treatment period; dsDNA=double stranded DNA; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; EQ-5D-5L=Euro-Quality of Life 5 Dimensions 5 Levels; FSH=follicle-stimulating hormone; FSS=Fatigue Severity Scale; GM1=monosialotetrahexosylganglioside; HRPQ=Health-Related Productivity Questionnaire; IDV=IVIg dependency visit; IMP=investigational medicinal product; IMV=IVIg monitoring visit; INR=international normalized ratio; IVDP=IVIg

dependency period; IVMP=IVIg monitoring period; IVIg=intravenous immunoglobulin; MCC=MMN Confirmation Committee; MMN=multifocal motor neuropathy; MMN-RODS©=Rasch- built Overall Disability Scale for MMN; mMRC=modified Medical Research Council; NAbs=neutralizing antibodies; NfL=neurofilament light protein; PD=pharmacodynamic(s); PE=physical examination; PHQ-9=patient health questionnaire 9 depression questionnaire; Q=every; SCN=screening period; SIB=suicidal ideation and behavior; SLE=systemic lupus erythematosus; SNP=single nucleotide polymorphism; TSQM=Treatment Satisfaction 14-item Questionnaire for Medication.

^a The screening period was 1 to 28 days before the IVIg monitoring period or the IVIg dependency period. The scheduled time of visit was variable based on the participant's IVIg dose regimen retrieved from their medical record (inclusion criterion 5.a) and if the IVIg dependency period is necessary. The screening period could be extended by an additional 14 days to a total of 42 days with the written approval of the medical monitor.

^b The IVIg dependency period, if applicable, occurred up to 15 weeks (105 days) before the IVIg monitoring period.

^c The IVIg monitoring period occurred up to 11 weeks before trial day 1.

^d IDV1 coincided with the participant's regularly scheduled IVIg administration.

^e Participants had an earlier visit than planned if they demonstrated a clinically meaningful deterioration between the scheduled visits of the IVDP. This visit was considered IDV2.

^f IMV1 coincided with the participant's regularly scheduled IVIg administration and would be the participant's next regularly scheduled IVIg visit after IDV2 if they entered the IVDP. The visit window for IMV1 was not applicable if the participant did not enter the IVDP.

^g Female participants had a serum pregnancy test performed at screening. A urine pregnancy test was performed at IMV1 for women of childbearing potential.

^h FSH levels were measured at screening for all female participants.

ⁱ The PE included, at a minimum, assessments of the skin, lymph nodes, and musculoskeletal extremities.

^j Vital signs included temperature, pulse rate, respiratory rate, and blood pressure. Weight, height, and BMI calculation were performed at screening. Weight was also measured at IMV3 and used to calculate the dose for all IMP administrations.

^k Triplicate 12-lead ECGs were performed during screening and at V1. A single 12-lead ECG was performed at all other scheduled timepoints.

^l The C-SSRS was used to assess the risk of suicidal ideation at screening. SIB risk monitoring was based on question 9 of the PHQ-9 at all other scheduled time points.

^m An ANA test was performed at screening, the titer and staining pattern was reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) were evaluated from the blood samples collected. The presence of ENA autoantibodies were only be reported if ANA $\geq$ 1:100.

ⁿ Detailed schedules for collecting blood samples for PD analyses are provided. Samples were collected before IVIg is administered

^o Immunogenicity assessments were performed predose of IVIg administration.

^p Blood samples were collected to evaluate the impact of C2 inhibition on C1q, C3, C4, and C5. Samples were collected before IVIg is administered.

^q A blood sample for SNP analysis was collected at this time point.

^r Samples were collected before IVIg is administered.

^s A research sample was collected during the IVIg monitoring period (visits IMV1-IMV3). This sample was collected predose and postdose of the IVIg administration. This sample was collected immediately after the end of the IVIg administration, regardless of the duration (after the last hour or day) of the administration.

^t IVIg was administered during the IVIg dependency and IVIg monitoring period at the time points scheduled. IVIg was administered over several days according to the local standard of care. All IVIg administrations must occur within the specified visit windows.

^u Grip strength was measured on-site at all trial visits and monitored daily starting from the IVDP or IVMP.

^v Adverse events and concomitant medications/procedures was monitored continuously from receipt of informed consent signature until the last trial-related activity. All available vaccination history was recorded.

Double-blinded treatment period

[00224] The dosing of the Investigational Medicinal Product (IMP) began on the first visit (V1) and continued throughout the DBTP as described in the schedule of activities (SoA, **Table 5**). The DBTP

began 7 days after the final IVIg administration of the IVMP (i.e., V1 will be 7 days after the final IVIg administration). Participants were randomized at V1 of the DBTP to ARGX-117 or placebo in a 2:1 ratio or a 2:2:1:1 ratio, as discussed below. Randomization was stratified based on an individual's IVIg dose frequency.

[00225] Two dose regimens were investigated in this trial (see **Table 4** below):

Cohort 1:

❖ Dose regimen 1

A single dose of 30 mg/kg ARGX-117 or placebo on day 1 followed by 4 weekly doses of 10 mg/kg ARGX-117 or placebo on day 8, 15, 22 and 29 (4 infusions in total) and a dose of 10 mg/kg ARGX-117 or placebo every 2 weeks until the end of the DBTP, starting from day 43 (5 infusions in total). Participants were randomized at V1 of the DBTP to ARGX-117 or placebo in a 2:1 ratio.

Cohort 2:-

Three options were contemplated as the dose regimen for cohort 2, of which 1 was assessed per the decision of the EDRT:

❖ Option 1 (Dose regimen 2)

A single dose of 60 mg/kg ARGX-117 or placebo on day 1 followed by 4 weekly doses of 30 mg/kg ARGX-117 or placebo on day 8, 15, 22 and 29 (4 infusions in total) and a dose of 30 mg/kg ARGX-117 or placebo every 2 weeks until the end of the DBTP, starting from day 43 (5 infusions in total). Participants randomized at V1 of the DBTP to ARGX-117 or placebo in a 2:1 ratio.

❖ Option 2 (Dose regimen 3)

A single dose of 15 mg/kg ARGX-117 or placebo on day 1 followed by 4 weekly doses of 5 mg/kg ARGX-117 or placebo on day 8, 15, 22 and 29 (4 infusions in total) and a dose of 5 mg/kg ARGX-117 or placebo every 4 weeks on days 57 and 85 until the end of the DBTP (2 infusions in total). Additionally, placebo will be given every 4 weeks, on days 43, 71 and 99. Participants randomized at V1 of the DBTP to ARGX-117 or placebo in a 2:1 ratio.

❖ Option 3 (Dose regimen 2 and 3)

Participants randomized at V1 of the DBTP to ARGX-117 (high dose/dose regimen 2), ARGX-117 (lower dose/dose regimen 3), placebo (high dose/dose regimen 2) or placebo (lower dose/dose regimen 3) in a 2:2:1:1 ratio.

[00226] The relationship between free C2 concentrations and functional complement activity (CH50) following ARGX-117 administration indicated that a small amount of free C2 is capable of

triggering the complement cascade reflected in CH50 activity. Therefore, different free C2 thresholds were selected to target 99%, 98%, or 96% reduction in free C2 levels. As the relationship between the PD effect of ARGX-117 and the (time to) clinical response in patients with MMN is currently unknown, to explore the dose/exposure response relationship of ARGX-117, the chosen dose regimens in this study span a broad PD effect range, from near-complete C2 and functional complement inhibition at the higher-dose regimen (dose regimen 2), to 2 levels of submaximal inhibition at the 2 lower-dose regimens (dose regimen 1 and dose regimen 3)..

- Dose regimen 1 targets a submaximal PD effect of ARGX-117: A free C2 threshold of 0.4 µg/mL was chosen, i.e., an inhibition of 98% of baseline free C2 concentrations (20 µg/mL) is predicted, together with a mean predicted reduction of CH50 activity to approximately 35% of normal levels.
- Dose regimen 2 (option 1; high dose) targets a maximal PD effect of ARGX-117: A free C2 threshold of 0.2 µg/mL, i.e., an inhibition of 99% of baseline free C2 concentrations (20 µg/mL) is predicted, together with a mean predicted reduction of CH50 activity to approximately 15% of normal levels.
- Dose regimen 3 (option 2; lower dose) targets a submaximal PD effect of ARGX-117: A free C2 threshold of 0.8 µg/mL, i.e., an inhibition of 96% of baseline free C2 concentrations (20 µg/mL) is predicted, together with a mean predicted reduction of CH50 activity to approximately 70% of normal levels.

[00227] For both dose regimens, a rapid PD effect of ARGX-117 that translates into a clinical response is targeted to avoid clinical deterioration and subsequent IVIg retreatment. To achieve a rapid PD effect, dose regimens that consist of an induction or loading phase followed by a maintenance phase with a lower dosing frequency have been selected. This concept of rapid and sustained reduction of complement activity achieved by an induction or loading dose and sustained by maintenance doses is also applied for eculizumab and ravulizumab, C5 targeting monoclonal antibodies approved for various indications.

Table 4: Study arms

Cohort 1 was treated in accordance with the protocol of dosage regimen 1, and cohort 2 was treated in accordance with the protocol of dosage regimen 3.

Arm title	Cohort 1	Cohort 2	Placebo
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Arm type	Experimental	Experimental	Placebo
Arm description ^a	<u>Dose regimen 1</u> Participants will receive a dose of 30 mg/kg on day 1, a dose of 10 mg/kg every 7 days for 4 weeks, and a dose of 10 mg/kg every 14 days until the end of the DBTP. The total dose per IMP infusion is capped at 3600 and 1200 mg for participants with body weight ≥ 120 kg for the 30 and 10 mg/kg dose, respectively.	<u>Dose regimen 3</u> Participants will receive a dose of 15 mg/kg on day 1, a dose of 5 mg/kg every 7 days for 4 weeks, and a dose of 5 mg/kg every 28 days until the end of the DBTP. The total dose per IMP infusion is capped at 1800 and 600 mg for participants with body weight ≥ 120 kg for the 15 and 5 mg/kg dose, respectively.	Participants will receive placebo on day 1, every 7 days for 4 weeks, and every 14 days until the end of the DBTP.
Associated intervention labels	ARGX-117 IV LD	ARGX-117 IV LLD	Placebo

DBTP=double-blind treatment period; LD=low dose; LLD=low low dose; IV=intravenous

^aThe dose level and/or administration frequency in cohort 2 could be lowered based on emerging data from cohort 1 reviewed by IDMC and EDRT (this includes a dose level and/or frequency lower than the dose level and administration frequency assessed in cohort 1). Substantial changes of the clinical trial protocol will be submitted for review and approval by the health authority, EC/IRB in accordance with local requirements.

[00228] Participants were retreated with IVIg during the DBTP if there was a clinically meaningful deterioration in muscle strength and/or motor function. A clinically meaningful deterioration is defined as a >30% decline in grip strength (GS) of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score since randomization.

[00229] Administration of IMP was not paused/stopped when IVIg retreatment was initiated. Based on their clinical judgment, the investigator chose to not re-treat the participant with IVIg in the event of a clinically meaningful deterioration. All trial participants could request IVIg retreatment with the investigator anytime during the DBTP.

Table 5: IMP administration period schedule of activities, day 1 through day 113

	Trial Day															
Visit (Days)	V1	V2 ^a	V3	V4	V5	V6	V7	V8	V9	V10 ^a	V11	V12	V13 ^a	V14/ ED ^b	UNS IVIG ^c	UNS ^d
	1	4	8	15	22	29	43	57	71	78	85	99	102	113		
Visit Window (Days)		+1	±2			±3			±4			+1	±3			
Activity																
Inclusion/exclusion criteria check	X															
Pregnancy test ^e	X					X		X			X	X		X		X
Physical examination ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs ^h	X							X						X		X
SIB risk and monitoring ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for safety laboratory tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for SLE panel ^j	X													X		X
Samples for urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for pharmacokinetics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for pharmacodynamics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5 (Continued)

	Trial Day																
Visit (Days)	V1	V2 ^a	V3	V4	V5	V6	V7	V8	V9	V10 ^a	V11	V12	V13 ^a	V14/ ED ^b	UNS IVI ^c	UNS ^d	
	1	4	8	15	22	29	43	57	71	78	85	99	102	113			
Visit Window (Days)		+1	±2				±3				±4		+1	±3			
Activity																	
Samples for cytokines ^l	X		X			X											
Samples for immunogenicity ^m	X			X		X		X			X			X	X	X	
Samples for biomarkers ⁿ	X		X	X	X	X	X	X			X			X	X	X	
Pharmacogenetic sample ^o	X																
Samples for NfLP	X			X		X		X			X			X		X	
Samples for autoantibodies (anti-GM1 and others) titer ^p	X													X		X	
Research sample ^p				X		X								X		X	
Randomization	X																
Eligibility confirmation and decision to roll over into the LTE														X			
IVIg retreatment ^q	X																
Administration of IMP ^r	X		X	X	X	X	X	X	X		X	X					

Table 5 (Continued)

	Trial Day															
Visit (Days)	V1	V2 ^a	V3	V4	V5	V6	V7	V8	V9	V10 ^a	V11	V12	V13 ^a	V14/ ED ^b	UNS IV Ig ^c	UNS ^d
	1	4	8	15	22	29	43	57	71	78	85	99	102	113		
Visit Window (Days)		+1	±2				±3				±4		+1	±3		
Activity																
Grip strength ^s	Continuous monitoring															
MMN-RODS [©]	X		X	X	X	X	X	X	X		X	X		X	X	X
mMRC	X		X	X	X	X	X	X	X		X	X		X	X	X
9-HPT	X		X	X	X	X	X	X	X		X	X		X	X	X
HRPQ	X			X		X		X			X			X	X	X
EQ-5D-5L	X			X		X		X			X			X	X	X
CAP-PRI	X			X		X		X			X			X	X	X
FSS	X			X		X	X	X	X		X	X		X	X	X
14-item TSQM	X			X		X	X	X	X		X	X		X	X	X
PGIC	X			X		X	X	X	X		X	X		X	X	X
Concomitant medication/ procedures ^t	Continuous monitoring															
Adverse events ^t	Continuous monitoring															

Continuous monitoring

Continuous monitoring

Continuous monitoring

9-HPT=nine-Hole Peg Test; ANA=anti-nuclear antibody; BMI=body mass index; CAP-PRI=Chronic Acquired Polynuropathy Patient-Reported Index; C-SSRS=Columbia-suicide severity rating scale; dsDNA=double stranded DNA; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; ED=early discontinuation; EQ-5D-5L= Euro-Quality of Life 5 Dimensions 5 Levels; FSS=Fatigue Severity Scale; HRPQ=Health-Related Productivity Questionnaire; IMP=investigational medicinal product; INR=international normalized ratio; IV=intravenous; IVIg=intravenous immunoglobulin; LTE=long- term extension; MMN=multifocal motor neuropathy; MMN-RODS[©]=Rasch-built Overall Disability Scale for MMN; mMRC=modified Medical Research Council;

NABs=neutralizing antibodies; PD=pharmacodynamic(s); PE=physical examination; PGIC=patient global impression change; PHQ-9=patient health questionnaire 9 depression questionnaire; PK=pharmacokinetic(s); SIB=suicidal ideation and behavior; SLE=systemic lupus erythematosus; TSQM=Treatment Satisfaction 14-item Questionnaire for Medication; UNS=unscheduled; V=visit
 Note: Participants who do not elect to enroll in the long-term extension study will have additional follow-up visits.

^a V2 (day 4), V10 (day 78), and V13 (day 102) were not mandatory and were considered optional visits.

^b The assessments in this visit was for participants who completed the DBTP and participants who discontinued the trial prematurely after randomization (i.e., ED visit).

^c Participants who demonstrated a clinical deterioration during the DBTP were retreated with IVIg. A UNS IVIg visit was performed at the participant's first occurrence of clinical deterioration necessitating retreatment with IVIg. If the timing for subsequent IVIg retreatment did not coincide with a regularly scheduled visit day of the DBTP, a UNS visit was done for the participant to receive IVIg.

^d A UNS visit occurred at the request of the investigator and additional assessments were performed at the discretion of investigator.

^e Female participants had a serum pregnancy test performed at screening. A urine pregnancy test was performed IMV1, V1, V6, V8, V11, V12, V14/ED and at any UNS visits for women of childbearing potential.

^f The PE included, at a minimum, assessments of the skin, lymph nodes, and musculoskeletal extremities.

^g Vital signs included temperature, pulse rate, respiratory rate, and blood pressure. Weight, height, and BMI calculation was performed at screening. Weight was measured at IMV3 and was used to calculate the dose for all IMP administrations.

^h Triplicate 12-lead ECGs were performed during screening and at V1. A single 12-lead ECG would be performed at all other scheduled timepoints.

ⁱ The C-SSRS was used to assess the risk of suicidal ideation at screening. SIB risk monitoring was based on question 9 of the PHQ-9 at all other scheduled time points.

^j An ANA test was performed at the specified timepoints, the titer and staining pattern will be reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) was evaluated from the blood samples collected. The presence of ENA autoantibodies will only be reported if ANA $\geq$ 1:100.

^k PK and PD assessments on day 1 was performed predose, 2 hours and 6 hours postdose of the IMP infusion. Detailed schedules for collecting blood samples for PK and PD analyses are provided.

^l A detailed schedule for collecting blood samples for cytokine analyses is provided.

^m Immunogenicity assessments will be performed predose of IMP administration.

ⁿ Blood samples were collected to evaluate the impact of C2 inhibition on C1q, C3, C4, and C5.

^o Sample collection was optional.

^p Samples were collected predose on days when IMP or IVIg are administered.

^q IVIg was administered to participants demonstrating a meaningful clinical deterioration as described.

^r IMP was administered as an IV infusion over approximately 2 hours at V1. IMP was administered over approximately 1 hour at all other scheduled time points. Participants were monitored for at least 1 hour after the end of the infusion. Further information on study interventions and IMP are provided. Details regarding temporary interruption of IMP are provided.

^s Grip strength was measured on-site at all trial visits and monitored daily.

^t Adverse events and concomitant medications/procedures were monitored continuously from receipt of informed consent signature until the last trial-related activity. All available vaccination history was recorded as part of the participant's prior medication for vaccination received in the past, or as concomitant medication for vaccinations received during the trial.

Follow-up period

[00230] The safety follow-up period characterized safety, PK, and PD during the elimination of ARGX-117, and included only participants that did not roll over into the LTE. The safety follow-up period began after the DBTP and occurred over 15 months. Assessments were carried out at the time points described in **Table 6**.

Table 6: Schedule of activities, follow-up period

	Follow-up period					
Visit	FUV1	FUV2	FUV3	FUV4	FUV5	EOT/FUV6
Time of Visit (Weeks)	W4	W12	W24	W36	W52	W64
Visit Window (Weeks)	±1					±2
Pregnancy test ^a	X	X	X	X	X	X
Physical examination ^b	X	X	X	X	X	X
Vital signs ^c	X	X	X	X	X	X
12-lead ECGs ^d		X		X		X
Samples for safety laboratory tests	X	X	X	X	X	X
Samples for SLE panel ^e						X
Samples for urinalysis	X	X	X	X	X	X
Samples for pharmacokinetics ^e	X	X	X	X	X	X
Samples for pharmacodynamics ^e	X	X	X	X	X	X
Samples for immunogenicity		X		X		X
Samples for NFL		X	X	X	X	X
Samples for autoantibodies (anti-GM1 and others) titer		X	X		X	X

Research sample		X	X	X	X	X
Concomitant medication/ procedures ^f	Continuous monitoring					
Adverse events ^f	Continuous monitoring					

ANA=antinuclear antibody; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; EOT=end of trial; INR=international normalized ratio; SLE=systemic lupus erythematosus; FUV=follow-up visit; IVIg=intravenous immunoglobulin; W=week Note: The follow-up period is not applicable for participants who roll over into the LTE. Note: FUV1 will be 4 weeks after the final visit of the double-blinded treatment period.

^a Female participants had a serum pregnancy test performed at the scheduled time points.

^b The PE included, at a minimum, assessments of the skin, lymph nodes, and musculoskeletal extremities.

^c Vital signs included temperature, pulse rate, respiratory rate, and blood pressure.

^d 12-lead ECGs were performed.

^e An ANA test were performed at the specified timepoints, the titer and staining pattern will be reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) will be evaluated from the blood samples collected. The presence of ENA autoantibodies will only be reported if ANA $\geq 1:100$. Detailed schedules for collecting blood samples for PK and PD analyses are provided.

^f Adverse events, and concomitant medications/procedures were monitored continuously from receipt of informed consent signature until the last trial-related activity. IVIg administered throughout the safety follow-up period were monitored as a concomitant medication. All available vaccination history was recorded as part of the participant's prior medication for vaccination received in the past, or as concomitant medication for vaccinations received during the trial.

End of trial definition

[00231] A participant was considered to have completed the trial if he/she completed the last visit of the DBTP period and rolled over into the LTE or the last visit of the follow-up period described in the SoA (see **Table 6**).

B. Study population

Inclusion criteria

[00232] Participants were eligible to be included in the trial only if all of the following criteria applied:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Male/female at least 18 years of age at the time the ICF is signed.
3. Probable or definite MMN according to the EFNS/PNS 2010 guidelines at screening confirmed by the MCC (see clinical criteria and guidelines in **Tables 7-10** below).
4. Receiving a stable IVIg regimen before screening and both of the following:
 - a. IVIg treatment interval of 2 to 5 weeks, and
 - b. IVIg dose of 0.4 to 2.0 grams per kg body weight and infusion.
5. IVIg treatment dependency confirmation by the MCC at screening or at IVIg monitoring visit 1 (IMV1), based on one of the following:
 - a. Recently initiated IVIg treatment (less than 3 months):
 - Clinical improvement following IVIg initiation documented in the participant's medical record.
 - b. Maintenance therapy with IVIg (longer than 3 months), based on one of the following:
 - Clinical deterioration following IVIg withdrawal, IVIg dose reduction, or IVIg delayed administration within 12 months prior to screening (documented in the participant's medical record), or
 - Clinical deterioration following IVIg delayed administration during the IVDP.
6. Immunization with the first meningococcal vaccine and pneumococcal vaccine, and the single Haemophilus influenza type B vaccine must be performed at least 14 days before IMP administration at V1 according to local country-specific immunization schedules. A documented history of vaccination against Neisseria meningitidis, Haemophilus influenza type B, and streptococcus pneumonia will be permitted.
7. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
 - a. Male participants must agree to not donate sperm from the time the ICF is signed until 12 months after the last IMP administration.
 - b. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before IMP can be administered.

Table 7: Clinical criteria for MMN

Core criteria (both must be present)	
1.	Slowly progressive or stepwise progressive, focal, asymmetric ^a limb weakness, that is, motor involvement in the motor nerve distribution of at least 2 nerves, for more than 1 month. ^b If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made (see Table 6)
2.	No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs ^c
Supportive clinical criteria	
3.	Predominant upper limb involvement ^d
4.	Decreased or absent tendon reflexes in the affected limb ^e
5.	Absence of cranial nerve involvement ^f
6.	Cramps and fasciculations in the affected limb
7.	Response in terms of disability or muscle strength to immunomodulatory treatment
Exclusion criteria	
8.	Upper motor neuron signs
9.	Marked bulbar involvement
10.	Sensory impairment more marked than minor vibration loss in the lower limbs
11.	Diffuse symmetric weakness during the initial weeks

Source: Joint Task Force of the EFNS and the PNS, *J Peripher Nerv Syst.* 2010;15(4):295-301.

MMN=multifocal motor neuropathy; mMRC=modified Medical Research Council

^a Asymmetric=a difference of 1 mMRC grade if strength is mMRC >3 and 2 mMRC grades if strength is MRC ≤ 3.

^b Usually more than 6 months.

^c Sensory signs and symptoms may develop over the course of MMN.

^d At onset, predominantly lower limb involvement account for nearly 10% of cases.

^e Slightly increased tendon reflexes, in particular in the affected arm, have been reported and do not exclude the diagnosis of MMN provided criterion 8 is met.

^f Twelfth nerve palsy has been reported.

Table 8: Electrophysiological criteria for conduction block (CB)

1.	Definite motor CB ^a
	Negative peak CMAP area reduction on proximal vs. distal stimulation of at least 50% whatever the nerve segment length (median, ulnar, and peroneal). Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20% of the lower limit of normal and >1 mV and increase of proximal to distal negative peak CMAP duration must be ≤30%
2.	Probable motor CB ^a
	Negative peak CMAP area reduction of at least 30% over a long segment (e.g., wrist to elbow or elbow to axilla) of an upper limb nerve with increase of proximal to distal negative peak CMAP duration ≤30% OR Negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration >30%
3.	Normal sensory nerve conduction in upper limb segments with CB (see exclusion criteria)

Source: Joint Task Force of the EFNS and the PNS, *J Peripher Nerv Syst.* 2010;15(4):295-301.

CB=conduction block; CMAP=compound muscle action potential.

^a Evidence for CB must be found at sites distinct from common entrapment or compression syndromes.

Table 9: Supportive criteria

1.	Elevated IgM anti-ganglioside GM1 antibodies
2.	Laboratory: increased CSF protein (<1 g/L)
3.	Magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with a diffuse nerve swelling of the brachial plexus
4.	Objective clinical improvement following IVIg treatment

Source: Joint Task Force of the EFNS and the PNS, *J Peripher Nerv Syst.* 2010;15(4):295-301.

Table 10: Diagnostic categories for MMN

Definite MMN
Clinical criteria 1, 2, and 8–11 (Table 7) AND electrophysiological criteria 1 and 3 (Table 8) in 1 nerve
Probable MMN
Clinical criteria 1, 2, and 8–11 (Table 7) AND electrophysiological criteria 2 and 3 (Table 8) in two nerves
Clinical criteria 1, 2, and 8–11 (Table 7) AND electrophysiological criteria 2 and 3 (Table 8) in 1 nerve AND at least 2 supportive criteria 1–4 (Table 9)
Possible MMN
Clinical criteria 1, 2, and 8–11 (Table 7) AND normal sensory nerve conduction studies AND supportive criteria 4 (Table 9)
Clinical criteria 1 (Table 7) with clinical signs present in only 1 nerve, clinical criteria 2, and 8–11 (Table 7) AND electrophysiological criteria 1 or criteria 2 and 3 (Table 8) in 1 nerve

Source: Joint Task Force of the EFNS and the PNS, *J Peripher Nerv Syst.* 2010;15(4):295-301.

Exclusion criteria

[00233] Participants were excluded from the trial if any of the following criteria applied:

1. Any coexisting condition which may interfere with the outcome assessments (e.g., diabetic neuropathy, CIDP, inflammatory arthritis, or osteoarthritis affecting the hand).
2. Clinical signs or symptoms suggestive for neuropathies other than MMN such as motor neuron disease (e.g., bulbar signs or brisk reflexes) or other inflammatory neuropathies (e.g., sensory neuropathy).
3. Severe psychiatric disorder (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the participant or could affect adherence with the trial protocol.

4. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection during the screening and/or IVMP.
5. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of MMN or put the participant at undue risk (e.g., SLE).
6. History of malignancy unless resolved by adequate treatment with no evidence of recurrence for ≥ 3 years before the first administration of the IMP. Participants with the following carcinomas will be eligible:
 - a. Adequately treated basal cell or squamous cell skin cancer;
 - b. Carcinoma in situ of the cervix;
 - c. Carcinoma in situ of the breast; or
 - d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b).
7. Clinical evidence of other significant serious diseases, have had a recent major surgery, or who have any other condition in the opinion of the investigator, that could confound the results of the trial or put the participant at undue risk.
8. Prior/concomitant therapy:
 - a. Cyclophosphamide and/or rituximab and/or eculizumab and/or mycophenolate mofetil within 3 months prior to screening; and/or
 - b. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of the IMP.
9. Positive serum test at screening for an active viral infection with any of the following conditions:
 - a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection;
 - b. Hepatitis C virus (HCV) based on HCV antibody assay; or
 - c. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count < 200 cells/mm³.
10. Current or history of (i.e., within 12 months of screening) alcohol, drug, or medication abuse.
11. Known hypersensitivity reaction to one of the components of the IMP or any of its excipients.

12. Female participants with a positive serum or urine pregnancy test, lactating females, and those who intend to become pregnant during the trial or within 15 months after last dose of the IMP.
13. ALT or AST $\geq 2 \times$ upper limit of normal and total bilirubin $\geq 1.5 \times$ upper limit of normal of the central laboratory reference range, or any other clinically significant laboratory abnormality.
14. An estimated glomerular filtration rate of ≤ 60 mL/min/1.73m² calculated by the central laboratory using the 4-variable Modification of Diet in the Renal-Disease equation.

C. Study assessments and procedures

[00234] Trial procedures and their timing are summarized in the schedule of activities in **Tables 3, 5, and 6** above.

[00235] For calculation of changes from baseline, the last value collected before the first dose of IMP was used as baseline.

Efficacy assessments

[00236] It was preferred that efficacy assessments were performed before IMP and IVIg administration and in this preferred order:

- GS
- mMRC-14 sum score
- Participant reported outcome measures, including: MMN-RODS©, EQ-5D-5L, CAP-PRI, PGIC, FSS, HRPQ, and TSQM
- 9-HPT

[00237] It was preferred that IMP was administered before IVIg if IVIg and IMP were administered on the same day.

Time to retreatment with IVIg

[00238] The criterion for retreatment with IVIg was based on clinical deterioration, defined as a >30% decline in GS of either hand observed at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score compared to the day of randomization. Both GS and mMRC-10 sum score are standard and clinically

relevant instruments used to measure clinical efficacy in clinical trials in MMN. By using these measures as criteria for retreatment with IVIg, the time to retreatment is thus directly related to clinically meaningful outcomes. Both outcomes were assessed separately as secondary endpoints, to support the results of the time to retreatment with IVIg endpoint. The respective thresholds for deterioration are set to represent clinically significant declines in disease activity.

[00239] The time that a participant reached this threshold was considered the time-to-relapse. The date and time that IVIg retreatment is administered was considered the time to retreatment with IVIg. Both the time-to-relapse and the time to retreatment with IVIg was recorded.

[00240] All trial participants could request IVIg retreatment with the investigator anytime during the DBTP. The investigator contacted the medical monitor if the participant does not meet the criteria for a clinically meaningful deterioration but requests retreatment with IVIg.

mMRC-14 and mMRC-10 sum score

[00241] The mMRC sum score evaluates motor strength/weakness from predetermined muscle groups (upper and lower limbs). It was recommended that a participant is scored on the mMRC sum score by the same evaluator during trial visits.

[00242] The scoring system of the mMRC sum score and the muscle groups tested for each mMRC sum score is provided in **Table 11** and **Table 12**, respectively.

Table 11: Scoring of the mMRC sum score

mMRC Scale	
0	Complete paralysis
1	Minimal contraction
2	Active movement with gravity eliminated
3	Weak contraction against gravity
4	Active movement against gravity and resistance
5	Normal strength

Table 12: Muscle groups tested for each mMRC sum score

Muscle Groups Tested on Both Sides	mMRC 10-Sum Score	mMRC 14-Sum Score
Upper limbs		
Shoulder abductors	X	X
Elbow flexors	X	X

Elbow extensors	X	X
Wrist extensors	X	X
Wrist flexors	X	X
Finger flexors		X
Finger extensors at metacarpophalangeal joints		X
Thumb abductor		X
Index finger abductor		X
Lower limbs		
Hip flexors	X	X
Knee flexors	X	X
Knee extensors	X	X
Foot dorsal flexors	X	X
Foot plantar flexors	X	X
Total score ^a	0-100	0-140

Source: Leger et al. *J Peripher Nerv Syst.* 2019;24(1):56-63.

mMRC=modified Medical Research Council

^a Each muscle group is scored from 0 (paralysis) to 5 (normal strength). A higher value indicates better muscle strength. The total score is based on the sum of both the left and right side of the body.

Grip strength

[00243] The Martin vigorimeter was used for daily measurement of grip strength during the screening period, IVDP (if applicable), IVMP, and DBTP, respectively. During these periods, grip strength was measured in a standardized manner on a daily basis.

[00244] Each daily grip strength measurement consisted of 3 repeated contractions with the participant's maximal effort. The duration of each contraction was 3 seconds. It was recommended for each test to begin with the participant gripping with the right hand followed by the left. The tests were performed in the following recommended order: 3 repetitions executed consecutively by the right hand followed by 3 repetitions of the left hand. There was a 30-second rest period between each of the 3 repetitions and a 2-minute rest period between each hand.

[00245] The participants performed all grip strength tests in a seated position: participants were comfortably seated in a chair without arm rests, with feet fully resting on the floor, hips as far back in the chair as possible, and the hips and knees positioned at approximately 90°. The shoulder of the tested extremity were adducted and neutrally rotated, the elbow flexed at 90°, the forearm in neutral position and the wrist between 0° and 30° of dorsiflexion and between 0° and 15° of ulnar deviation. Participants were instructed to maintain their position during the grip strength test.

[00246] Measurements were assessed and reported by the trial physician during on-site trial visits. It was recommended that a participant was assessed by the same evaluator during on-site visits. Grip strength will be measured daily throughout the IVDP, IVMP, and DBTP by the participant. The time of day and results were recorded electronically when performed by the participant.

[00247] Measurements were recommended to be performed at similar times (preferably in the morning) of the day at each assessment.

[00248] The 3 daily measurements of GS from the left hand and the 3 daily measurements of GS from the right hand were recorded and the daily average for the left hand and right hand was calculated, respectively. A 3-day moving average was generated based on the average of the obtained averages for each hand. The daily moving average consisted of day -2, day -1, and day 0.

Rasch-built Overall Disability Scale (RODS)

[00249] The MMN-RODS© is a disease-specific PRO instrument constructed specifically to capture activity limitations in patients with MMN. It consists of 25 items that are scored 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty) for each item yielding a total score from 0 to 50. The 25-item MMN-RODS© is provided in **Table 13**.

Table 13: 25-Item Rasch-built Overall Disability Scale for MMN (MMN-RODS©)

Question	Are you able to:	Unable to perform 0	Able to perform but with difficulty 1	Able to perform without difficulty 2
1	Read a book?			
2	Make a telephone call?			
3	Eat?			
4	Open and close a door?			
5	Dress your upper body?			
6	Brush your teeth?			
7	Drink out of a mug/glass?			
8	Turn a key in a lock?			
9	Use a knife/fork/spoon?			
10	Clean after toilet?			
11	Fill in a form/write?			
12	Zip your trousers?			
13	Get money from a cash			

	point?			
14	Do your own cooking?			
15	Pick up a small object?			
16	Work on a computer?			
17	Do the bed?			
18	Fold laundry?			
19	Throw an object (e.g., ball)?			
20	Slice vegetables?			
21	Peel an apple/orange?			
22	Handle small objects (e.g., coin)?			
23	Tie your laces?			
24	Clip your fingernails?			
25	Button your shirt/blouse?			

Source: Vanhoute et al. *J Peripher Nerv Syst.* 2015;20(3):296-305.

9-Hole Peg Test

[00250] The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. Both the dominant and non-dominant hands were tested twice (2 consecutive trials of the dominant hand, followed immediately by 2 consecutive trials of the non-dominant hand). All participants received training in assessing the 9-HPT before the start of the trial, to exclude any training effect. It was recommended that a participant is assessed by the same evaluator during on-site visits.

Euro-Quality of Life 5 Dimensions 5 Levels

[00251] Quality of life was assessed through the EQ-5D-5L, which allows responses recording based on 5 levels of severity. It is a standardized instrument for use as a measure of health for clinical and economical appraisal. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores for each dimension include 5 levels: no problem, slight problem, moderate problem, severe problem, and extreme problem. Participants marked their health status from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Chronic Acquired Polyneuropathy Patient-Reported Index

[00252] Next to general QOL, disease specific QOL was assessed through the CAP-PRI. This instrument includes the assessment of 15 items. Items will be scored 0 (not at all), 1 (a little bit), or 2 (a lot) yielding a total score that ranges from 0 to 30.

Patient Global Impression Change

[00253] The PGIC is a patient-reported outcome, which was published in 1976 by the National Institute of Mental Health (U.S.). The self-report measure PGIC reflects a patient's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement.

Fatigue Severity Scale

[00254] The FSS is a 9-item self-reported questionnaire scale developed in 1989 and designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS consists of answering a short questionnaire that requires the participant to rate his or her own level of fatigue on 9 items and rated from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement. The scoring is done by calculating the average response to the questions (adding all answers and dividing by 9).

Health-Related Productivity Questionnaire

[00255] The HRPQ was originally developed in patients with Parkinson's disease to provide data related to missed hours at work or educational activities and reduced effectiveness during any attempted work. These criteria form an important portion of work related productivity and will be used to assess health-related and work related productivity in this trial.

14-Item Questionnaire for Medication

[00256] The original version (version 1.4) of the TSQM questionnaire was developed in 2004 to measure patients' satisfaction with their medication using 4 scales (side effects, effectiveness, convenience, and global satisfaction) and was used in this trial.

D. Pharmacokinetics

[00257] The concentrations of ARGX-117 in serum were determined using a validated enzyme-linked immunosorbent assay. Concentrations were calculated by interpolation from a calibration curve. Quality control samples were analyzed throughout the trial. Their measured concentrations were used to determine between-run, overall precision, and accuracy of the analyses.

[00258] The serum PK parameters for ARGX-117 were derived by non-compartmental analysis of the serum concentration-time profiles using the actual collection times. The PK parameters, definitions, and the methods of calculation are as follows:

AUC_{0-t}	AUC from time zero to time t of the last measured quantifiable concentration calculated using the linear-up/logarithmic-down trapezoidal method
AUC_{0-xh}	AUC from time zero to x hours after IMP administration, calculated using the linear-up/logarithmic-down trapezoidal method
AUC_{∞}	AUC from time zero to infinity, calculated form $AUC_{0-t} + (C_t/\lambda_z)$, where C_t is the last observed quantifiable concentration and λ_z is the terminal elimination rate constant
C_{max}	maximum observed serum concentration
C_{xh}	concentration at x hours post dose
t_{max}	time to reach C_{max}
$t_{1/2}$	apparent terminal half-life
$V_z(F)$	(apparent) volume of distribution
$Cl(F)$	(apparent) total clearance

[00259] Dose-normalized parameters, including C_{max}/dose and $AUCs/\text{dose}$, were assessed.

E. Pharmacodynamics

[00260] Blood samples were collected for the determination of free C2 concentrations, total C2 concentrations, and functional complement activity (CH50) as indicated in the schedule of assessments. Visit 2 (day 4), visit 10 (day 78), and visit 13 (day 102) were not mandatory and were considered optional. A minimum of 14 participants per cohort were targeted to attend the optional visits.

[00261] Blood was collected according to the specialty lab standard procedures. Information on equipment and further details on the procedures on sample collection are documented in the separate laboratory manual.

[00262] These PD markers was determined using assays which are validated for their intended use.

F. Genetics

[00263] A blood sample for DNA isolation was collected from participants who have consented to participate in the genetic analysis component of the trial. Participation was optional. Participants who did not wish to participate in the genetic research may still participate in the trial.

[00264] DNA will be isolated from blood samples for single nucleotide polymorphism (SNP) analysis, including complement regulatory proteins. Samples were collected according to the schedule described in the SoA.

G. Biomarkers

[00265] Blood samples were collected to assess the impact of ARGX-117 treatment on components of the complement cascade. Biomarkers included C1q, C3, C4, and C5. Samples were be collected according to the schedule described in the SoA.

H. Exploratory endpoints

[00266] The following exploratory endpoints were reported in the clinical trial report. Blood samples for cytokine measurement were collected. At a minimum, the following cytokines were assessed: TNF- α , IFN- γ , IL-2, IL-6, IL-8, and IL-10. Blood samples for biomarkers were collected to assess the impact of ARGX-117 treatment on components of the complement cascade.

[00267] The following exploratory endpoints were reported separately from the main clinical trial report. Blood samples were collected to assess the impact of ARGX-117 on a marker of neurological damage, NfL.

[00268] Blood samples were collected to assess the impact of ARGX-117 treatment on autoantibody titers against gangliosides, including but not limited to anti-GM1 and anti-GM2.

[00269] Blood samples were also collected for SNP analysis

[00270] Research samples were also collected; additional markers could be measured in the samples that will be stored for future analysis.

[00271] The sponsor may store samples for up to 15 years after the end of the trial. Additionally, with participants' consent, samples may be used for further research by the sponsor or others such as universities or other companies to address any scientific questions related to ARGX-117, complement biology, MMN, or other diseases, the development of related or new treatments, or research methods. In addition, blood samples may be used to validate methods used to measure ARGX-117, antibodies, and biomarkers.

I. Immunogenicity assessments

Assessments of anti-ARGX-117 antibodies

[00272] Blood samples were collected at the time points specified in the schedule of activities to evaluate serum levels of ADA against ARGX-117. These samples were tested by the sponsor or sponsor's designee.

[00273] Serum samples were screened and confirmed for ADA against ARGX-117 and the titer of confirmed positive samples will be reported. Other analyses could be performed to further characterize the immunogenicity of ARGX-117.

[00274] Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ARGX-117.

Anti-ARGX-117 neutralizing antibodies

[00275] Neutralizing antibodies to ARGX-117 can be evaluated in the collected serum samples and banked from all participants according to the schedule of activities.

[00276] Samples will be stored for future use for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ARGX-117.

J. Objectives and endpoints**Table 14: Objectives and endpoints**

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARGX-117 compared to placebo in adult participants previously stabilized with IVIg	Safety outcomes based on adverse event (AE) monitoring and other safety assessments
Secondary	
To evaluate the efficacy of ARGX-117 compared to placebo on muscle strength and/or motor function in adult participants previously stabilized with IVIg	- Time to the first retreatment with IVIg^a since the final IVIg treatment of the IVIg monitoring period - Time-to-relapse modified Medical Research Council (mMRC) - AUC of the change from baseline in mMRC-10 sum score - Change from baseline in the average score of the 2 most important muscle groups as assessed by the mMRC-14 sum score - Value and change from baseline in the mMRC-14 sum score - Proportion of participants showing a deterioration of 1 or more points in at least 2 muscle groups as assessed by the mMRC-14 sum score - Proportion of participants with no deterioration in 2 or more muscle groups as assessed by mMRC-14 sum score Grip strength (GS) - AUC of the change from baseline in GS - Proportion of participants with a GS decrease of 8 kilopascal (kPa) or more over 3 consecutive days - Values, change, and percent change from baseline in GS
To evaluate the efficacy of ARGX-117 on functional ability, arm and hand function, quality of life, and fatigue in adult participants with MMN	- Values and change from baseline in the Rasch-built Overall Disability Scale for MMN (MMN-RODS[®]) - Values and change from baseline in upper extremity (arm and hand) function (9-Hole Peg Test [9-HPT], or timed Peg Board Test) - Proportion of participants by level of severity on each dimension of the Euro-Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L) scale - Values and change from baseline in EQ-5D-5Lvisual analog scale (VAS) - Values and change from baseline in the Chronic Acquired Polyneuropathy Patient-Reported Index (CAP-

Objectives	Endpoints
	PRI • Values of the Patient Global Impression Change (PGIC) scale • Values and change from baseline in the 9-item Fatigue Severity Scale (FSS)
To evaluate the effect of ARGX-117 on health-related productivity and work productivity	Values for work-related and household chore activities of the Health-Related Productivity Questionnaire (HRPQ) at each visit: - Hours lost because of absenteeism - Hours lost because of presenteeism - Total hours lost (absenteeism + presenteeism) - Percentage of scheduled hours lost because of absenteeism - Percentage of scheduled hours lost because of presenteeism - Percentage of scheduled hours lost in total (absenteeism + presenteeism)
To evaluate medication treatment satisfaction	Effectiveness, side effects, convenience, and overall satisfaction scores as assessed by the Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM)
To assess the PK, PD, and immunogenicity of ARGX-117	Serum concentrations and PK parameters for ARGX-117 Values and change from baseline in free C2, total C2, functional complement activity (CH50) Incidence and prevalence of ADA against ARGX-117
Exploratory	
To assess the impact of ARGX-117 treatment on complement factors	Values and change from baseline in complement factors 1q, 3, 4, and 5 (C1q, C3, C4, and C5)
To assess the impact of ARGX-117 treatment on biomarkers of neuro-inflammation	Serum concentration of neurofilament light protein (NfL)
To assess the impact of ARGX-117 treatment on biomarkers of MMN	Serum titers of anti-GM1 IgM and other autoantibodies
To assess the impact of ARGX-117 on cytokines	Values and change from baseline for cytokines TNF- α , IFN- γ , IL-2, IL-6, IL-8, and IL-10

^a The threshold for retreatment with IVIg is defined as a clinical deterioration of >30% in muscle strength (>30% decline in GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a deterioration of at least 2 points based on the mMRC-10 sum score compared to the day of randomization.

[00277] To determine the effectiveness of ARGX-117 compared to placebo in adult participants with MMN previously stabilized with IVIg, median time to first retreatment with IVIg was estimated by treatment group using the Kaplan-Meier product limit method, and comparison between treatment arms was performed using the stratified log-rank test. Participants who discontinued the trial for any reason or who complete the DBTP before retreatment with IVIg was censored at the last visit of contact date.

[00278] A sensitivity analysis for time-to-relapse was also performed. Time-to-relapse is defined as the time until a participant meets the threshold for clinical deterioration.

[00279] To correct for differences in trial durations, the endpoints based on AUC is standardized to an average AUC per week (7 days).

[00280] For continuous endpoints, ANCOVA model was used, including factors for treatment and stratification variables and baseline (mMRC-10 score or GS) as covariate. For proportions, the stratified Cochran-Mantel-Haenszel test was used, controlled for stratification variables.

Example 2 - Results for Cohort 1 and 2 participants from the ARGX-117-2002 study

[00281] This example describes an analysis of the efficacy of dosage regimens of ARGX-117 (empasiprubart) in adults with multifocal motor neuropathy (MMN) as assessed in the ARGX-117-2002 study described in Example 1. Participants in Cohorts 1 and 2 underwent an initial screening and monitoring period followed by a 16-week double blind treatment period (DBTP) as described above.

[00282] Two cohorts were enrolled sequentially. In each cohort, 27 participants were randomized at first visit (V1) of the DBTP in a 2:1 ratio to receive either ARGX-117 (18 participants) or placebo (9 participants).

- ❖ **Cohort 1 (Dosage regimen 1):** A single dose of 30 mg/kg ARGX-117 or placebo on day 1 followed by 4 weekly doses of 10 mg/kg ARGX-117 or placebo on day 8, 15, 22 and 29 (4 infusions in total) and a dose of 10 mg/kg ARGX-117 or placebo every 2 weeks until the end of the DBTP, starting from day 43 (5 infusions in total).
- ❖ **Cohort 2 (Dosage regimen 3):** A single dose of 15 mg/kg ARGX-117 or placebo on day 1 followed by 4 weekly doses of 5 mg/kg ARGX-117 or placebo on days 8, 15, 22,

and 29 (4 infusions in total), and a dose of 5 mg/kg ARGX-117 or placebo every 4 weeks until the end of the DBTP, on days 57 and 85 (2 infusions in total).

SUMMARY

[00283] A clear signal of efficacy was observed for each dosing regimen of empasiprubart assessed:

- Time to first retreatment with IVIg for empasiprubart IV compared to placebo:
 - Cohort 1: HR (95% CI) = 0.09 (0.02; 0.44)
 - Cohort 2: HR (95% CI) = 0.16 (0.02; 1.54)
- Similar median efficacy was observed for both dose regimens of empasiprubart, with consistent improvement across all efficacy parameters. For most end-points, more variability was observed in outcome measures for participants in Cohort 2 than participants in Cohort 1.
- Based on PGIC, 10 (55.6%) participants in Cohort 1 and 12 (66.7%) participants in Cohort 2 who received empasiprubart had their condition improved much or very much, compared to 1 (11.1%) participant in Cohort 1 and 2 (22.2%) participants in Cohort 2 who received placebo had their condition improve much or very much.

[00284] The empasiprubart PK profiles for the loading dose, induction (or loading) regimen, and maintenance regimen were favourable for both cohorts. Cohort 1 and 2 dosing regimens reduced free C2 levels to the predefined thresholds (i.e., 0.4 mg/L and 0.8 mg/L, respectively). CH50 levels were reduced, and total C2 levels increased by approximately 4-fold after empasiprubart administration.

[00285] The safety profile of both empasiprubart dosing regimens was favorable based on the assessment of AEs; no differences in AEs were observed between the dose regimens.

[00286] For Cohorts 1 and 2, improvement was observed in all measured end-points for participants who received empasiprubart IV. Improvement at the end of the DBTP was measured compared to the baseline that occurred 7 days after last IVIg administration, which approximately corresponds to IVIg peak-of-effect for most participants.

[00287] In Cohort 1, the Kaplan-Meier analysis for the time to first IVIg retreatment indicates that participants in the empasiprubart IV 30/10 mg/kg arm had a lower retreatment rate

than participants in the placebo arm. The median (95% CI) time to first IVIg retreatment with IVIg was NE (NE-NE) in the empasiprubarb IV 30/10 mg/kg arm and 37.0 (16.0-NE) days in the placebo arm. A total of 3 (16.7%) participants in the empasiprubarb IV 30/10 mg/kg arm and 7 (77.8%) in the placebo arm were retreated with IVIg during the 16-week DBTP.

[00288] In Cohort 2, the Kaplan-Meier analysis for the time to the first IVIg retreatment indicates that the participants in the empasiprubarb IV 15/5 mg/kg arm had a lower rate of retreatment than the participants in the placebo arm. The median (95% CI) time to first retreatment with IVIg was NE (NE-NE) in the empasiprubarb IV 15/5 mg/kg arm and NE (35.0-NE) days in the placebo arm. One (5.6%) participant in the empasiprubarb IV 15/5 mg/kg arm and 3 (33.3%) participants in the placebo arm were retreated with IVIg during the 16-week DBTP.

[00289] Descriptive analyses of the change from baseline for MMN-RODS, CAP-PRI, GS 3-day moving average, mMRC-10 sum score, mMRC-14 sum score, and average mMRC-14 sum score for the 2 most important muscle groups showed consistent improvement at the last assessment during DBTP for both dose regimens of empasiprubarb. In contrast, placebo-treated subjects showed no change or worsening at the last assessment during the DBTP.

RESULTS

[00290] A schematic of the trial design is shown in **Figure 1**.

Disposition and Participant Population

[00291] A summary of the participants' disposition is presented in **Figure 2**.

[00292] Overall, 78 participants were screened: 31 entered the IVDP, and 27 directly entered the IVMP. For 30 of the 31 participants who entered the IVDP, the dependency on IVIg was confirmed, and they entered the IVMP, for a total of 57 participants in the IVMP. At the end of the IVMP, 54 participants completed the period: 27 entered Cohort 1, and 27 entered Cohort 2.

[00293] In Cohort 1, participants were randomized 2:1 to empasiprubarb or placebo. Eighteen participants received empasiprubarb IV 30/10 mg/kg, and 9 received placebo. A total of

25 (92.6%) participants completed the 16-week DBTP (empasiprubart IV 30/10 mg/kg, 94.4%; placebo, 88.9%), of which 24 were rolled over to the long-term extension (LTE) study ARGX-117-2003. Two participants discontinued IMP: 1 in the empasiprubart IV 30/10 mg/kg arm (due to an AE) and 1 in the placebo arm (withdrawal by participant). One participant was ongoing in the 15-month safety follow-up period at the data cut-off date.

[00294] In Cohort 2, participants were randomized 2:1 to empasiprubart or placebo. Eighteen participants received empasiprubart IV 15/5 mg/kg, and 9 received placebo. At the data cut-off date, 24 participants had completed the 16-week DBTP and were rolled over to the LTE. Three participants were ongoing in DBTP at the data cut-off date (2 in the empasiprubart IV 15/5 mg/kg arm and 1 in the placebo arm). No participants discontinued IMP.

Demographic Characteristics

[00295] Demographics of the participants of Cohort 1 and 2 are indicated in **Table 15** below.

Table 15: Demographics of enrolled participants of cohort 1 and 2

Category or statistic	<u>Cohort 1</u>			<u>Cohort 2</u>			<u>Total</u> <u>(N=54)</u>
	<u>EMPA</u>			<u>EMPA</u>			
	<u>IV</u>			<u>IV</u>			
	<u>30/10</u>	<u>PBO</u>		<u>15/5</u>	<u>PBO</u>		
	<u>mg/kg</u>	<u>IV</u>	<u>Total</u>	<u>mg/kg</u>	<u>IV</u>	<u>Total</u>	
	<u>(N=18)</u>	<u>(N=9)</u>	<u>(N=27)</u>	<u>(N=18)</u>	<u>(N=9)</u>	<u>(N=27)</u>	
<u>Age (years)</u>							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	54.5 (47.0, 61.0)	44.0 (42.0, 54.0)	49.0 (44.0, 61.0)	55.5 (50.0, 59.0)	58.0 (55.0, 61.0)	56.0 (50.0, 60.0)	55.0 (47.0, 61.0)
<u>Age category, n (%)</u>							
n	18	9	27	18	9	27	54
18 to <65 years	16 (88.9)	7 (77.8)	23 (85.2)	16 (88.9)	7 (77.8)	23 (85.2)	46 (85.2)
≥65 years	2 (11.1)	2 (22.2)	4 (14.8)	2 (11.1)	2 (22.2)	4 (14.8)	8 (14.8)

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA	PBO	Total	EMPA	PBO	Total	
	IV			IV			
	30/10			15/5			
	mg/kg			mg/kg			
	(N=18)			(N=9)			
Sex at birth, n (%)							
n	18	9	27	18	9	27	54
Female	7 (38.9)	4 (44.4)	11 (40.7)	6 (33.3)	4 (44.4)	10 (37.0)	21 (38.9)
Male	11 (61.1)	5 (55.6)	16 (59.3)	12 (66.7)	5 (55.6)	17 (63.0)	33 (61.1)
Race, n (%)							
n	18	9	27	18	9	27	54
White	17 (94.4)	7 (77.8)	24 (88.9)	17 (94.4)	8 (88.9)	25 (92.6)	49 (90.7)
Not reported	0 (0.0)	1 (11.1)	1 (3.7)	1 (5.6)	1 (11.1)	2 (7.4)	3 (5.6)
Other	1 (5.6)	1 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.7)
Ethnicity, n (%)							
n	18	9	27	18	9	27	54
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (3.7)	1 (1.9)
Not Hispanic or Latino	17 (94.4)	8 (88.9)	25 (92.6)	16 (88.9)	7 (77.8)	23 (85.2)	48 (88.9)
Not reported	1 (5.6)	0 (0.0)	1 (3.7)	1 (5.6)	2 (22.2)	3 (11.1)	4 (7.4)
Unknown	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Weight (kg)							
n	18	9	27	17	9	26	53
Median (Q1, Q3)	77.10 (58.00, 93.10)	75.60 (65.50, 81.00)	75.60 (60.00, 93.10)	81.00 (75.00, 88.00)	81.50 (62.00, 98.43)	81.25 (68.00, 91.50)	78.40 (65.18, 91.50)
BMI (kg/m²)							
n	18	9	27	17	9	26	53
Median (Q1, Q3)	25.050 (19.610, 29.860)	24.960 (23.150, 29.990)	24.960 (19.840, 29.990)	25.520 (23.530, 28.410)	25.490 (23.410, 31.210)	25.505 (23.460, 28.700)	25.490 (23.040, 29.860)

BMI=body mass index; EMPA=empasiprubart; IV=intravenous(ly); PBO=placebo; n (for continuous data)=number of participants with data; N=number of participants per treatment arm; n (%) (for categorical data)=number of participants for whom the observation was reported; Q1=quartile 1; Q3=quartile 3

Note: The denominator for the percentage calculations is the total number of participants per treatment arm in the safety set, excluding missing values.

MMN Disease History

[00296] MMN disease history of the participants of Cohort 1 and 2 is indicated in **Table 16** below.

Table 16: MMN disease history of enrolled participants

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
Estimated duration of disease since diagnosis at randomization (years)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	8.10 (5.39, 11.28)	9.99 (4.77, 11.29)	8.56 (4.99, 11.29)	10.14 (5.99, 13.30)	15.63 (8.24, 23.17)	10.15 (5.99, 16.97)	9.53 (5.39, 14.23)
Most affected hand, n (%)							
n	18	9	27	18	9	27	54
Right hand	9 (50.0)	5 (55.6)	14 (51.9)	9 (50.0)	4 (44.4)	13 (48.1)	27 (50.0)
Left hand	9 (50.0)	4 (44.4)	13 (48.1)	9 (50.0)	5 (55.6)	14 (51.9)	27 (50.0)
Most affected hand is also dominant hand, n (%)							
n	18	9	27	18	9	27	54
Yes	10 (55.6)	5 (55.6)	15 (55.6)	11 (61.1)	5 (55.6)	16 (59.3)	31 (57.4)
No	8 (44.4)	4 (44.4)	12 (44.4)	7 (38.9)	4 (44.4)	11 (40.7)	23 (42.6)
One of the 2 most affected muscle groups, n(%)							
n	18	9	27	18	9	27	54

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
Shoulder abductors – Right side	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (11.1)	2 (7.4)	2 (3.7)
Shoulder abductors – Left side	2 (11.1)	0 (0.0)	2 (7.4)	2 (11.1)	0 (0.0)	2 (7.4)	4 (7.4)
Elbow flexor muscles – Left side	1 (5.6)	0 (0.0)	1 (3.7)	2 (11.1)	0 (0.0)	2 (7.4)	3 (5.6)
Elbow extensor muscles - Left side	1 (5.6)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Wrist joint extensor tendons - Right side	3 (16.7)	1 (11.1)	4 (14.8)	3 (16.7)	0 (0.0)	3 (11.1)	7 (13.0)
Wrist joint extensor tendons - Left side	1 (5.6)	1 (11.1)	2 (7.4)	3 (16.7)	2 (22.2)	5 (18.5)	7 (13.0)
Wrist joint flexor tendons - Right side	0 (0.0)	2 (22.2)	2 (7.4)	1 (5.6)	0 (0.0)	1 (3.7)	3 (5.6)
Wrist joint flexor tendons - Left side	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Finger flexor muscles - Right side	1 (5.6)	1 (11.1)	2 (7.4)	0 (0.0)	3 (33.3)	3 (11.1)	5 (9.3)
Finger flexor muscles - Left side	2 (11.1)	1 (11.1)	3 (11.1)	2 (11.1)	1 (11.1)	3 (11.1)	6 (11.1)

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
Finger extensor muscles - Right side	3 (16.7)	1 (11.1)	4 (14.8)	4 (22.2)	1 (11.1)	5 (18.5)	9 (16.7)
Finger extensor muscles - Left side	6 (33.3)	2 (22.2)	8 (29.6)	4 (22.2)	1 (11.1)	5 (18.5)	13 (24.1)
Thumb abductor - Right side	2 (11.1)	1 (11.1)	3 (11.1)	2 (11.1)	2 (22.2)	4 (14.8)	7 (13.0)
Thumb abductor - Left side	3 (16.7)	0 (0.0)	3 (11.1)	5 (27.8)	3 (33.3)	8 (29.6)	11 (20.4)
Index finger abductor - Right side	2 (11.1)	1 (11.1)	3 (11.1)	3 (16.7)	1 (11.1)	4 (14.8)	7 (13.0)
Index finger abductor - Left side	2 (11.1)	0 (0.0)	2 (7.4)	3 (16.7)	2 (22.2)	5 (18.5)	7 (13.0)
Hip flexors - Left side	1 (5.6)	1 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.7)
Knee flexors - Right side	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Knee extensors - Right side	0 (0.0)	1 (11.1)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Foot dorsal flexors - Right side	2 (11.1)	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.7)
Foot dorsal flexors - Left side	3 (16.7)	3 (33.3)	6 (22.2)	1 (5.6)	0 (0.0)	1 (3.7)	7 (13.0)
Foot plantar flexors - Right side	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (3.7)	1 (1.9)

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
Foot plantar flexors - Left side	1 (5.6)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)

EMPA=empasiprubarb; PBO=placebo; IV=intravenous(ly); Q1=quartile 1; Q3=quartile 3Note: The denominator for the percentage calculations is the total number of participants per treatment arm in the safety set, excluding missing values.

IVIg History

[00297] The IVIg history of the participants of Cohort 1 and 2 is indicated in **Table 17** below.

Table 17: IVIg history of the enrolled participants

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
Time from first IVIg administration (years)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	3.706 (1.229, 7.302)	3.211 (0.635, 9.161)	3.444 (1.098, 9.161)	3.849 (2.133, 7.992)	7.567 (5.306, 9.990)	5.481 (2.133, 9.692)	4.192 (1.229, 9.161)
IVIg administration ongoing at screening							
>IVIg duration (years)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	2.634 (0.764, 5.426)	1.892 (0.274, 3.211)	2.470 (0.405, 5.109)	0.498 (0.271, 3.047)	1.802 (0.235, 9.990)	0.745 (0.246, 4.077)	1.517 (0.290, 4.077)
>IVIg Frequency issued from eCRF, n(%)							

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
n	18	9	27	18	9	27	54
Every 2 or 3 weeks	10 (55.6)	5 (55.6)	15 (55.6)	10 (55.6)	5 (55.6)	15 (55.6)	30 (55.6)
Every 4 or 5 weeks	8 (44.4)	4 (44.4)	12 (44.4)	8 (44.4)	4 (44.4)	12 (44.4)	24 (44.4)
>IVIg dose (g/kg)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	1.550 (1.000, 2.000)	1.300 (0.800, 1.500)	1.500 (0.860, 1.940)	1.000 (0.800, 1.210)	1.000 (0.620, 1.000)	1.000 (0.700, 1.210)	1.000 (0.800, 1.600)

eCRF=electronic Case Report Form; EMPA=empasiprubart; IVIg=Intravenous Immunoglobulin; IV=intravenous(ly); IWRS=Interactive Web Response System; n (for continuous data)=number of participants with data; N=number of participants per treatment arm; n (%) (for categorical data)=number of participants for whom the observation was reported; PBO=placebo; Q1=quartile 1; Q3=quartile 3

Notes: The denominator for the percentage calculations is the total number of participants per treatment arm in the safety set, excluding missing values. The duration of IVIg ongoing as screening (in days) is defined as follows: screening date – starting date of last IVIg administration stable before screening +1.

IMP Exposure and Compliance

[00298] An overview of IMP administration during the 16-week DBTP is presented in **Table 18**. All participants received the planned administrations, except:

- 1 participant in the empasiprubart IV 30/10 mg/kg arm withdrew IMP following an AE (*Acute coronary syndrome*) and received 8 administrations of empasiprubart.
- 1 participant in the placebo arm of cohort 1 discontinued IMP and withdrew from the study (after 6 administrations) after being retreated with IVIg at day 43.
- 1 participant in the placebo arm of cohort 1 did not receive IMP at day 57 due to an AE (*Gastrointestinal infection*).

In Cohort 2, 3 participants were ongoing and have received all IMP as planned.

Table 18: IMP Exposure and Compliance

Category or statistic	Cohort 1		Cohort 2	
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)
Duration of treatment (weeks)				
n	18	9	18	9
Median (Q1, Q3)	14.1 (14.1, 14.3)	14.1 (13.9, 14.4)	14.1 (14.0, 14.1)	14.1 (14.1, 14.1)
Number of infusions				
n	18	9	18	9
Median (Min, Max)	10.0 (8, 10)	10.0 (6, 10)	10.0 (6, 10)	10.0 (5, 10)
Cumulative dose (mg/kg)				
n	18	9	18	9
Median (Min, Max)	119.797 (100.76, 121.26)	0.000 (0.00, 0.00)	60.174 (41.44, 60.75)	0.000 (0.00, 0.00)
Compliance (%)				
n	18	9	18	9
Median (Q1, Q3)	100.000 (100.000, 100.000)	100.000 (100.000, 100.000)	100.000 (100.000, 100.000)	100.000 (100.000, 100.000)

EMPA=empasiprubarb; IMP=investigational medicinal product; IV=intravenous(ly); max=maximum; min=minimum; N=number of participants per treatment arm; n (for continuous data)=number of participants with data; PBO=placebo; Q1=quartile 1; Q3=quartile 3

Notes: Treatment duration was defined as (last administration day – first administration day + 1)/7. Dose (mg) is calculated as the volume of IMP (collected in eCRF) multiplied by strength (120 mg/ml). Dose (mg/kg) is calculated by dose divided by weight in kg at baseline.

Efficacy Parameters at Baseline of Treatment Period

[00299] Baseline values were established for all clinical endpoints assessed during the DBTP. Baseline scores of the enrolled participants for Cohort 1 and Cohort 2 are depicted in **Figure 3**. Baseline scores were established for grip strength (both most affected and less affected hand), mMRC-10 sum score, mMRC-14 sum score, average mMRC-14 sum score for the 2 most important muscle groups, MMN-RODS score, FSS score (Cohort 1 only), and CAP-PRI score. These are indicated in **Table 19** below for both Cohort 1 and 2.

Table 19: Summary of Baseline Scores for Efficacy Endpoints

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
mMRC-10 sum score							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	96.0 (87.0, 98.0)	95.0 (88.0, 96.0)	96.0 (87.0, 97.0)	93.5 (91.0, 95.0)	98.0 (89.0, 99.0)	94.0 (89.0, 97.0)	94.5 (87.0, 97.0)
mMRC-14 sum score							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	124.5 (107.0, 133.0)	130.0 (114.0, 134.0)	125.0 (111.0, 134.0)	124.0 (109.0, 130.0)	133.0 (109.0, 134.0)	125.0 (109.0, 133.0)	125.0 (109.0, 133.0)
Average mMRC-14 sum score for the 2 most important muscle groups							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	3.25 (2.50, 4.50)	3.00 (1.50, 4.50)	3.00 (2.00, 4.50)	3.25 (2.00, 4.00)	4.00 (2.00, 4.50)	3.50 (2.00, 4.50)	3.25 (2.00, 4.50)
GS 3-day moving average for the most affected hand (kPa)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	33.500 (14.444, 61.778)	40.000 (23.111, 54.667)	34.778 (18.556, 61.778)	31.111 (6.667, 52.556)	47.333 (40.778, 61.111)	39.333 (11.889, 57.444)	36.389 (15.111, 57.444)
GS 3-day moving average for the less affected hand (kPa)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	56.917 (37.778, 74.000)	64.000 (41.000, 69.000)	57.500 (37.778, 74.000)	56.972 (22.000, 87.444)	57.778 (55.333, 74.889)	57.778 (27.222, 87.444)	57.639 (35.222, 75.667)
MMN-RODS total score (centile metric)							
n	18	9	27	18	9	27	54
Median (Q1, Q3)	59.0 (53.0, 67.0)	70.0 (60.0, 82.0)	62.0 (54.0, 76.0)	63.0 (58.0, 76.0)	66.0 (66.0, 76.0)	66.0 (58.0, 76.0)	64.0 (58.0, 76.0)
CAP-PRI total score							

Category or statistic	Cohort 1			Cohort 2			Total (N=54)
	EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Total (N=27)	
n	18	9	27	18	9	27	54
Median (Q1, Q3)	13.0 (10.0, 19.0)	8.0 (6.0, 10.0)	10.0 (8.0, 15.0)	10.5 (5.0, 15.0)	12.0 (8.0, 12.0)	11.0 (5.0, 13.0)	10.0 (7.0, 15.0)

CAP-PRI=chronic acquired polyneuropathy patient-reported index; EMPA=empasiprubart; IV=intravenous(ly); GS=grip strength; kPa=kilopascal; MMN-RODS=Rasch-built overall disability scale for MMN; mMRC=Modified Medical Research Counsel; N=number of participants per treatment arm; n (for continuous data)=number of participants with data; PBO=placebo; Q1=quartile 1; Q3=quartile 3

[00300] In Cohort 1, 25 participants completed the 16-week treatment period. In Cohort 2, 24 participants completed the 16-week DBTP.

Efficacy Results

[00301] To evaluate the efficacy of ARGX-117 compared to placebo in adult participants with MMN previously stabilized with IVIg, the following clinical endpoints were assessed: time to retreatment with IVIg/time-to-relapse; change in mMRC-10 or mMRC-14 sum score from baseline; change in grip strength from baseline; change in MMN-RODS score from baseline; change in CAP-PRI score from baseline; patient reported values using the Patient Global Impression Change (PGIC) scale; and change in FSS score from baseline.

Time to Retreatment with IVIg / Time-to-Relapse

[00302] As mentioned above, a typical threshold for retreatment with IVIg is defined as:

- >30% decline in Grip Strength of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations); or
- A decrease of at least 2 points on the mMRC-10 sum score compared to baseline.

[00303] Both the date the threshold was reached (i.e. the time-to-relapse) and the date that IVIg retreatment was administered (i.e. time to retreatment) were recorded. Time-to-relapse was defined as the time from randomization up to the time the participant met the threshold for clinical deterioration. Time to first retreatment with IVIg was defined as the time from last IVIg

administration before randomization (including unscheduled visits) up to the first IVIg retreatment during DBTP.

[00304] The hazard ratio (HR) for time to first retreatment with IVIg comparing the dose regimens of empasiprubart versus placebo was estimated from a Cox proportional hazards model stratified by IVIg dose frequency. These data are presented in **Table 20**.

Table 20: Retreatment with IVIg During DBTP

Cohort 1			Cohort 2		
EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	Comparison of EMPA IV 30/10 mg/kg with PBO IV	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)	Comparison of EMPA IV 15/5 mg/kg with PBO IV
n (%)	n (%)	HR (95% CI)	n (%)	n (%)	HR (95% CI)
3 (16.7)	7 (77.8)	0.09 (0.02; 0.44)	1 (5.6)	3 (33.3)	0.16 (0.02; 1.54)

EMPA=empasiprubart; DBTP=double-blinded treatment period; HR=hazard ratio; IV=intravenous(ly); IVIg=Intravenous Immunoglobulin; N=number of participants per treatment arm in the safety set; n (%)=number and percentage of participants with events of retreatment with IVIg per treatment arm; PBO=placebo
Note: The HR was obtained from a Cox proportional hazards model with treatment as fixed effect; the model was stratified by IVIg dose frequency.

[00305] During the double blind treatment period, empasiprubart demonstrated a 91% reduction in Cohort 1 (HR: 0.09 95% CI (0.02; 0.44)) and 84% reduction in Cohort 2 (HR: 0.16 95% CI (0.02;1.54)) in the risk for IVIg retreatment compared to placebo.

[00306] The results are also shown in **Figure 4** as the percentage probability of being retreated with IVIg (Cohort 1; **Fig 4A** and Cohort 2; **Fig 4B**) and percentage probability of experiencing relapse (Cohort 1; **Fig 4C** and Cohort 2; **Fig 4D**).

[00307] A summary of IVIg retreatments during the DBTP for Cohorts 1 and 2 is presented in **Table 21** below and graphically represented for Cohort 1 in **Figure 5**.

[00308] For Cohort 1, the data shows that of the 18 participants receiving ARGX-117 treatment, just 3 participants required retreatment with IVIg over the course of the study, 2 of whom required a single retreatment, and 1 who required two retreatments. In contrast, of the 9 participants receiving placebo, 7 participants had to be retreated with IVIg, 6 of whom required more than two retreatments. Accordingly, ~78% placebo participants required IVIg retreatment

compared to ~17% empasiprubarb-treated patients.

[00309] For Cohort 2, the data shows that of the 18 participants receiving ARGX-117 treatment, just 1 participant required retreatment with IVIg over the course of the study, whom required more than 2 retreatments. In contrast, of the 9 participants receiving placebo, 3 participants had to be retreated with IVIg, 2 of whom required two retreatments and 1 who required more than two retreatments. Accordingly, ~33% placebo participants required IVIg retreatment compared to ~6% empasiprubarb-treated patients.

Table 21: Number of retreatments with IVIg

IVIg dose frequency subgroup		EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)
All	Participants retreated with IVIg, n (%)	3 (16.7)	7 (77.8)	1 (5.6)	3 (33.3)
	Participants not retreated with IVIg, n (%)	15 (83.3)	2 (22.2)	17 (94.4)	6 (66.7)
	Number of times retreated with IVIg, n (%)				
	1	2 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
	2	1 (5.6)	0 (0.0)	0 (0.0)	2 (22.2)
	> 2	0 (0.0)	6 (66.7)	1 (5.6)	1 (11.1)
	Total number of IVIg retreatments	4	27	6	7
IVIg dose frequency every 2 or 3 weeks	Number of times retreated with IVIg, n (%)				
	1	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
	> 2	0 (0.0)	5 (100.0)	1 (10.0)	1 (20.0)
	Total number of IVIg retreatments	1	23	6	5
IVIg dose frequency every 4 or 5 weeks	Number of times retreated with IVIg, n (%)				
	1	1 (12.5)	1 (25.0)	0 (0.0)	0 (0.0)
	2	1 (12.5)	0 (0.0)	0 (0.0)	1 (25.0)
	> 2	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)

IVIg dose frequency subgroup		EMPA IV 30/10 mg/kg (N=18)	PBO IV (N=9)	EMPA IV 15/5 mg/kg (N=18)	PBO IV (N=9)
	Total number of IVIg retreatments	3	4	0	2

[00310] For the 10 participants of Cohort 1 (3 from the treatment group; 7 from the placebo group) that were retreated, the time to first retreatment with IVIg (recorded as number of days) together with details of any clinical observations are shown in **Table 22** below. The average time to retreatment for the participants receiving ARGX-117 was 63.3 days (~9 weeks), whereas the average time to retreatment for the participants receiving placebo was 37 days (~5 weeks).

Table 22: Time to retreatment with IVIg

Treatment group (subject ID)	Time to first retreatment (days)	Number of retreatments	IVIg frequency	Clinical relapse	Comments
ARGX-117 (0010013002)	35	1	4/5	Y	Dysphagia started before IVIg retreatment, pneumonia, pyrexia and headache just after
ARGX-117 (0010143001)	104	1	2/3	Y	Covid-19 right before infection
ARGX-117 (0340044001)	54	2	4/5	Y	Headache at time of IVIg, Urinary tract infection earlier
Placebo (0010019001)	54	4	2/3	Y	Several AE's overlapping with 1st retreatment (amnesia, insomnia, oedema peripheral), arthralgia right after IVIg
Placebo (0010066002)	31	6	2/3	N	Upper respiratory tract infection, Chest discomfort
Placebo (0010071002)	49	1	4/5	Y	Discontinued just after IVIg retreatment
Placebo (0330042001)	37	3	4/5	Y	No AE
Placebo (0340043001)	35	5	2/3	Y	Oropharyngeal pain, Headache & Myalgia, Hypersensitivity, Skin abrasion
Placebo (0340056004)	37	5	2/3	Y	No AE
Placebo (0440034002)	16	3	2/3	Y	Candida infection, Animal bit, Pain in extremity

[00311] For the 14 participants of Cohort 1 that experienced clinical relapse (7 from the treatment group; 7 from the placebo group), details of the endpoint leading to relapse are reported in **Table 23** below. For the majority of participants, clinical relapse was triggered by a decrease of at least 2 points on the mMRC-10 sum score.

Table 23: Clinical relapse

Treatment group (subject ID)	Time to first relapse (days)	Endpoint leading to relapse	Grip strength deterioration?	Clinical relapse	IVIg frequency
ARGX-117 (0010013002)	22	mMRC-10		Y	4/5
ARGX-117 (0010143001)	7	mMRC-10		Y	2/3
ARGX-117 (0320027001)	86	mMRC-10		N	4/5
ARGX-117 (0330039002)	17	mMRC-10		N	2/3
ARGX-117 (0340044001)	6	mMRC-10	Yes (both hands)	Y	4/5
ARGX-117 (0340056001)	10	mMRC-10		N	4/5
ARGX-117 (0430012001)	17	mMRC-10		N	2/3
Placebo (0010019001)	46	mMRC-10	Yes (both hands)	Y	2/3
Placebo (0010071002)	15	mMRC-10		Y	4/5
Placebo (0330042001)	32	mMRC-10		Y	4/5
Placebo (0340043001)	26	mMRC-10	Yes (less affected hand)	Y	2/3
Placebo (0340056004)	15	mMRC-10		Y	2/3
Placebo (0390057001*)	22	mMRC-10		N	4/5
Placebo (0440034002)	7	mMRC-10	Yes	Y	2/3

*Subject randomized to placebo potentially received EMPA IV 30/10 mg/kg at day 21

mMRC-14 and mMRC-10 sum score

[00312] As described above, the mMRC sum score evaluates motor strength/weakness

from predetermined muscle groups (upper and lower limbs). Each muscle group is scored from 0 (paralysis) to 5 (normal strength). A higher value indicates better muscle strength. The total score is based on the sum of both the left and right side of the body. The mMRC-10 results are depicted in **Figure 6**. A box plot of actual values by treatment group at IVMP baseline, DBTP baseline, Last Assessment before IVIg and Last Assessment during treatment period for Cohort 1 is shown in **Fig 6A**. A box plot showing change from baseline by treatment group for each cohort at Last Assessment before IVIg and Last Assessment during treatment period is depicted in **Fig 6B**. The last assessment in DBTP before IVIg retreatment is the last assessment before or on the day of IVIg retreatment for retreated participants and the last assessment in the DBTP for not retreated participants. This provides a “pure” comparison of empasiprubart IV to placebo. The last assessment in DBTP considers assessments after IVIg retreatment and provides a comparison of empasiprubart IV with or without IVIg versus placebo with or without IVIg.

[00313] The data show that treatment with ARGX-117 results in improvement in mMRC-10 sum score, i.e. an improvement in motor strength. In contrast, participants receiving placebo experienced a deterioration in score compared to baseline values. **Table 24** below provides an analysis of covariance with change from baseline as response variable, the treatment group and the stratification factor (IVIg frequency) and baseline as covariates for Cohort 1. A positive difference is in favour of ARGX-117 IV 30/10 mg/kg.

Table 24: Analysis of covariance

	mMRC-10 sum score change from DBTP baseline Last assessment before IVIg	Comparison ARGX-117 IV 30/10 mg/kg versus Placebo IV at day 113	
	Least Square Mean (SE)	Least Square Mean Difference with Placebo (SE)	95% CI
ARGX-117 IV 30/10 mg/kg (n=18)	3.7 (1.46)	6.1 (2.52)	0.8 ; 11.3
Placebo IV (n=9)	-2.4 (2.06)		

[00314] The mMRC-14 results are depicted in **Fig 6C**. A box plot showing change from baseline by treatment group for each cohort at Last Assessment before IVIg and Last Assessment

during treatment period is depicted.

[00315] The data show that treatment with ARGX-117 results in improvement in mMRC-14 sum score, i.e. an improvement in motor strength. In contrast, participants receiving placebo experienced no improvement or deterioration in score compared to baseline values.

Grip Strength

[00316] As described above, the Martin vigorimeter was used for daily measurement of grip strength during the screening period, IVDP (if applicable), IVMP, and DBTP. Each daily grip strength measurement consisted of 3 repeated contractions with the participant's maximal effort. The duration of each contraction was 3 seconds. The 3 daily measurements of GS from the left hand and the 3 daily measurements of GS from the right hand were recorded and the daily average for the left hand and right hand was calculated, respectively. A 3-day moving average was generated based on the average of the obtained averages for each hand. The daily moving average consisted of day -2, day -1, and day 0. The results are depicted in **Figure 7**. A box plot showing grip strength measurements by treatment group at Last Assessment before IVIg and Last Assessment during treatment period is depicted in **Fig 7A** for Cohort 1. Box plots of change from baseline of GS 3-day moving average for each hand (most affected and less affected) by treatment arm for each cohort at the time of last assessment are presented in **Fig 7B** (most affected) and **Fig 7C** (less affected). The data show that treatment with ARGX-117 results in improvement in grip strength compared to placebo.

MMN-RODS

[00317] As described above, the MMN-RODS© is a disease-specific PRO instrument constructed specifically to capture activity limitations in patients with MMN. It consists of 25 items that are scored 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty) for each item yielding a total score from 0 to 50. The total score is further translated to a centile score. The results of the MMN-RODS centile score are depicted in **Figure 8**. A box plot of actual values by treatment group at IVMP baseline, DBTP baseline, Last Assessment before IVIg and Last Assessment during treatment period for Cohort 1 is shown in **Fig 8A**. A box plot showing change from baseline by treatment group at Last Assessment before IVIg and Last Assessment during treatment period is depicted in **Fig 8B**. The data show that

treatment with ARGX-117 results in improvement in MMN-RODS score compared to placebo. In contrast, participants receiving placebo experienced a deterioration in score compared to baseline values. **Table 25** below provides an analysis of covariance with change from baseline as response variable, the treatment group and the stratification factor (IVIg frequency) and baseline as covariates for Cohort 1. A positive difference is in favour of ARGX-117 IV 30/10 mg/kg.

Table 25: Analysis of covariance

	MMN-RODS score change from DBTP baseline Last assessment before IVIg	Comparison ARGX-117 IV 30/10 mg/kg versus Placebo IV at day 113	
	Least Square Mean (SE)	Least Square Mean Difference with Placebo (SE)	95% CI
ARGX-117 IV 30/10 mg/kg (n=18)	7.8 (2.97)	8.6 (5.44)	-2.6 ; 19.9
Placebo IV (n=9)	-0.8 (4.31)		

CAP-PRI

[00318] As described above, disease specific quality of life was assessed through the CAP-PRI. This instrument includes the assessment of 15 items. Items are scored 0 (not at all), 1 (a little bit), or 2 (a lot) yielding a total score that ranges from 0 to 30. Results are presented in **Figure 9**. A box plot of actual values by treatment group at IVMP baseline, DBTP baseline, Last Assessment before IVIg and Last Assessment during treatment period for Cohort 1 is shown in **Fig 9A**. A box plot showing change from baseline by treatment group at Last Assessment before IVIg and Last Assessment during treatment period is depicted in **Fig 9B**. The data show that treatment with ARGX-117 results in improvement in CAP-PRI score compared to placebo.

PGIC

[00319] As described above, the PGIC is a patient-reported outcome, which was published in 1976 by the National Institute of Mental Health (U.S.). The self-report measure PGIC reflects a patient's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. The participant must provide a response to the question "*How much has your condition (MMN) changed as compared to the time you received the first*

treatment in this trial?”, with answers ranging from 1: Very much improved to 7: Very much worse. Results are shown in **Figure 10**, which provides a bar chart of patient response by treatment group at DBTP, Last assessment before IVIg and Last Assessment during treatment period. At Last Assessment during treatment period, the 18 participants of Cohort 1 receiving ARGX-117 reported responses of “Very much Improved”, “Much improved”, and “Minimally improved”. Only one participant reported “Minimally worse”, although this subject was retreated twice with IVIg. In contrast, the 9 participants receiving placebo reported “No change”, “Minimally worse”, “Much worse” and “Very much worse”. The one participant in the placebo group who reported “Much improved” is the subject who potentially received a dose of ARGX-117 during the DBTP. In Cohort 2, at Last Assessment during treatment period 15 participants who received empasiprubart had “Very much Improved”, “Much Improved” and “Minimally Improved”. In contrast, 5 participants receiving placebo reported “No change” or “Minimally worse”.

[00320] Overall, the results show improvement in PGIC following treatment with ARGX-117 compared to placebo. 55.6% (10/18) of participants treated with empasiprubart had their condition much or very much improved. 94.4% (17/18) of participants in Cohort 1 and 83.3% (15/18) of participants in Cohort 2 treated with empasiprubart had any improvement (minimal, much and very much). 88.9% (8/9) and 55.6% (5/9) placebo participants had no change or worsened.

FSS

[00321] As described above, the FSS is a 9-item self-reported questionnaire scale developed in 1989 and designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS consists of answering a short questionnaire that requires the participant to rate his or her own level of fatigue on 9 items and rated from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement. The scoring is done by calculating the average response to the questions (adding all answers and dividing by 9). The results are shown in **Figure 11**. A box plot of actual values by treatment group at IVMP baseline, DBTP baseline, Last Assessment before IVIg and Last Assessment during treatment period is shown in **Fig 11A** for Cohort 1 participants only. A box

plot showing change from baseline by treatment group at Last Assessment before IVIg and Last Assessment during treatment period is depicted in **Fig 11B** for both Cohort 1 and Cohort 2 participants. The data show that treatment with ARGX-117 results in improvement in FSS score compared to placebo.

[00322] A summary of efficacy endpoints is provided in **Table 26** below. Empasiprubart demonstrated improvement compared to baseline on 8/8 efficacy measurements. The safety profile was consistent with Phase 1 data. Empasiprubart was well tolerated overall, with most adverse events being mild or moderate.

Table 26: Summary of efficacy

Efficacy measure (Change from baseline)	Cohort 1		Cohort 2	
	EMPA IV 30/10 mg/kg (N=18)	Placebo IV (N=9)	EMPA IV 15/5 mg/kg (N=18)	Placebo IV (N=9)
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)
MMN-RODS total score (centile metric) ¹	6.0 (0.0, 14.0)	0.0 (-2.0, 0.0)	7.5 (0.0, 17.0)	0.0 (-5.0, 1.0)
CAP-PRI total score ²	-2.5 (-6.0, -1.0)	0.0 (-1.0, 2.0)	-2.0 (-5.0, -1.0)	1.0 (-1.0, 2.0)
GS – 3-day moving average (kPa) Most affected hand ¹	11.28 (0.00, 28.78)	0.89 (-0.67, 9.00)	17.06 (3.33, 38.89)	0.78 (-2.22, 7.89)
GS – 3-day moving average (kPa) Less affected hand ¹	6.50 (0.06, 12.61)	1.67 (-0.33, 5.44)	8.78 (3.67, 28.17)	2.22 (0.89, 4.89)
mMRC-10 sum score ¹	2.0 (0.0, 3.0)	1.0 (-5.0, 0.0)	3.0 (0.0, 4.0)	1.0 (-1.0, 4.0)
mMRC-14 sum score ¹	4.0 (2.0, 8.0)	0.0 (-8.0, 0.0)	7.0 (1.0, 11.0)	1.0 (-2.0, 8.0)
Average mMRC-14 sum score for the 2 most important muscle groups ¹	0.50 (0.50, 0.50)	0.00 (0.00, 0.50)	0.50 (0.00, 1.00)	0.00 (0.00, 0.50)
FSS average score ²	-0.444 (-1.11, 0.0)	1.000 (0.11, 1.22)		

¹A positive change indicates better condition.

²A negative change indicates better condition.

Pharmacokinetics

[00323] The arithmetic mean serum concentration-time profiles of empasiprubart are presented in **Figure 12**.

[00324] A summary of mean empasiprubart PK parameters by treatment arm is presented in **Table 27**.

Table 27: Summary of Serum Pharmacokinetic Parameters (Arithmetic Mean) Following Administration of Empasiprubart

Cohort 1 Dosing Regimen: 30mg/kg, 10 mg/kg Once Weekly (x4), 10 mg/kg Once Every 2 Weeks (x5)

		Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113
n		16	17	16	16	15	16	16	15	15	13	15
C_{max} (µg/mL)	Mean (SD)	777.1 (202.6)	590.8 (164.0)	672.3 (118.4)	802.3 (202.4)	725.2 (176.5)	797.3 (153.2)	819.9 (187.6)	871.9 (183.4)	876.3 (222.5)	891.8 (125.2)	NA
T_{max} (h)	Median (Min, Max)	2.38 (2.0 - 6.0)	1.05 (0.0 - 1.3)	1.04 (1.0 - 2.0)	1.12 (1.0 - 1.8)	1.03 (0.0 - 2.6)	1.08 (1.0 - 1.3)	1.08 (0.0 - 1.4)	6.00 (1.1 - 335.8)	1.08 (0.0 - 1.4)	1.08 (1.0 - 1.4)	NA
C_{trough} (µg/mL)	Mean (SD)	NA	445.2 (88.6)	530.9 (117.0)	604.9 (126.6)	591.2 (129.0)	625.5 (104.9)	609.1 (136.4)	640.5 (120.5)	653.7 (117.1)	670.3 (105.9)	653.7 (111.2)
AUC_{0-168hr} (h×µg/mL)	Mean (SD)	88504.6 (20312.6)	...	NA	NA	NA	NA	NA	12920.2 (24014.2)	NA	NA	NA
AUC_{0-168hr}/Dose (h× µg/mL)/mg	Mean (SD)	37.2 (9.3)	...	NA	NA	NA	NA	NA	165.7 (34.7)	NA	NA	NA
AUC_{0-336hr} (h×µg/mL)	Mean (SD)	NA	NA	NA	NA	NA	NA	NA	24308.9 (44051.1)	...	25805.3 (37493.3)	NA

Cohort 2 Dosing Regimen: 15 mg/kg, 5 mg/kg Once Weekly (x4), 5 mg/kg Once Every 2 Weeks (x2)

		Day 1	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113
n		18	18	17	17	17	14	14	10

		Day 1	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113
C_{max} (µg/mL)	Mean (SD)	400.1 (73.4)	273.8 (88.1)	338.9 (60.4)	355.6 (43.5)	392.8 (62.2)	393.4 (137.5)	355.6 (76.9)	NA
T_{max} (h)	Median (Min, Max)	2.12 (2.0 - 6.0)	1.13 (0.0 - 1.7)	1.05 (0.0 - 1.3)	1.10 (1.0 - 1.3)	1.08 (0.0 - 1.3)	1.08 (1.0 - 1.6)	1.10 (0.0 - 1.2)	NA
C_{trough} (µg/mL)	Mean (SD)	NA	230.6 (34.9)	259.4 (40.8)	305.3 (39.0)	293.5 (47.3)	267.3 (54.1)	298.5 (117.2)	240.3 (59.0)
AUC_{0-168hr} (h×µg/mL)	Mean (SD)	45398.7 (9970.2)	...	NA	NA	NA	NA	NA	NA
AUC_{0-168hr} /Dose (h×µg/mL)/mg	Mean (SD)	37.3 (7.5)	...	NA	NA	NA	NA	NA	NA

AUC_{0-xh} = Area under the concentration versus time curve from 0 to x hour; C_{max}=maximum observed serum concentration; C_{trough}=serum trough concentration; DBTP=double-blinded treatment period; EMPA=empasiprubarb; max=maximum; min=minimum; N=number of participants per treatment arm in the PK set; NA=not applicable; PBO=placebo; PK=pharmacokinetic; T_{max}=time to reach C_{max}

Pharmacodynamics

[00325] The median (IQR) serum concentration-time profiles of free C2 by study arm are presented in **Figure 13**. Additionally, the mean percent change from baseline and the median (IQR) percent change from baseline serum concentration-time profiles of free C2 for each dosing regimen of empasiprubarb are presented in **Figure 14A** and **Figure 4B**, respectively.

[00326] The median (IQR) serum concentration-time profiles of functional complement activity (CH50) by treatment arm are presented in **Figure 15**. Additionally, the median (IQR) percent change from baseline serum concentration-time profile of CH50 for each dosing regimen of empasiprubarb is presented in **Figure 16**.

[00327] The median (IQR) serum concentration-time profiles of total C2 by treatment arm are presented in **Figure 17**.

Safety

[00328] Adverse events (AEs) were coded by primary System Organ Class (SOC) and Preferred Term (PT) using MedDRA Version 24.1 (September 2021). The investigator assessed the grade (severity) of AEs according to the National Cancer Institute CTCAE v5.0.

[00329] Two serious adverse events (SAEs) were reported in the empasiprubart IV 30/10 mg/kg arm:

- Grade 3 *Pneumonia*, starting on day 34 during the DBTP, lasting 11 days. The investigator considered the SAE not related to IMP. The dose was not changed, and the outcome was recovered/resolved. This AE was an AESI (defined as a severe infection).
- Grade 4 *Acute coronary syndrome*, starting at day 71 of the DBTP, with a duration of 3 days. The SAE was considered related to IMP by the investigator and not related to IMP by the sponsor. IMP was discontinued, and the outcome was recovered/resolved.

[00330] As of the data cut-off date, no other SAEs were reported. An overview of AEs is presented in **Table 28**. The most frequently reported AEs (in at least 10% of participants in 1 empasiprubart treatment arm) by PT were *Headache, Cough, Nasopharyngitis, Urinary tract infection, Fatigue*, and *Protein urine*. An overview of all AEs by SOC and PT is presented in **Table 29**. A summary of the AEs related to IMP by MedDRA SOC and PT is presented in **Table 30**.

Table 28: Overview of AEs During DBTP

	Cohort 1						Cohort 2					
	EMPA IV 30/10 mg/kg (N=18; PYFU=5.55)			PBO IV (N=9; PYFU=2.62)			EMPA IV 15/5 mg/kg (N=18; PYFU=5.31)			PBO IV (N=9; PYFU=2.57)		
	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU
≥1 AE	14 (77.8)	33	594.3	5 (55.6)	14	534.9	14 (77.8)	54	1017.2	6 (66.7)	19	739.8
≥1 IMP Related AE	7 (38.9)	14	252.1	0 (0.0)	0	0	2 (11.1)	5	94.2	2 (22.2)	2	77.9
≥1 IVIg Related AE	1 (5.6)	1	18.0	1 (11.1)	2	76.4	0 (0.0)	0	0	0 (0.0)	0	0
≥1 Procedure Related AE	2 (11.1)	2	36.0	0 (0.0)	0	0	2 (11.1)	2	37.7	1 (11.1)	1	38.9

	Cohort 1						Cohort 2					
	EMPA IV 30/10 mg/kg (N=18; PYFU=5.55)			PBO IV (N=9; PYFU=2.62)			EMPA IV 15/5 mg/kg (N=18; PYFU=5.31)			PBO IV (N=9; PYFU=2.57)		
	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU	n (%)	m	ER/ 100 PYFU
≥1 SAE	2 (11.1)	2	36.0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 SAE related to IMP	1 (5.6)	1	18.0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AE for which the IMP was interrupted	0 (0.0)	0	0	1 (11.1)	1	38.2	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AE for which the IMP was discontinued	1 (5.6)	1	18.0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 Fatal AE	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AE grade ≥ 3	2 (11.1)	2	36.0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AESI	1 (5.6)	1	18.0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AE of hypersensiti ty reactions	2 (11.1)	3	54.0	1 (11.1)	1	38.2	2 (11.1)	3	56.5	1 (11.1)	1	38.9
≥1 AE of anaphylactic reactions	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0	0 (0.0)	0	0
≥1 AE of local reactions	0 (0.0)	0	0	0 (0.0)	0	0	3 (16.7)	4	75.3	2 (22.2)	2	77.9

AESI=adverse event of special interest; C1=cohort 1; C2=cohort 2; CTCAE=Common Terminology Criteria for Adverse Events; DBTP=double-blinded treatment period; EMPA=empasiprubarb; ER=event rate per 100 participants year of follow-up; IMP=investigational medicinal product; IVIg=intravenous immunoglobulin; IV=intravenous(ly); m=number of events; N=number of participants per treatment arm in the safety set; n(%)=number and percentage of participants with AEs per treatment arm; PBO=placebo; PYFU=participant-years of follow-up; SAE=serious adverse event

Notes: The denominator for the percentage calculation is the total number of participants in the safety set per treatment arm. ER was calculated as the number of events x 100 divided by the PYFU. PYFU was calculated as the sum of the follow-up times in DBTP of all participants per treatment arm, expressed in years. AESIs are defined as severe infections (CTCAE grade ≥ 3).

Table 29: All AEs by MedDRA SOC and PT During DBTP

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AE	14 (77.8)	33	5 (55.6)	14	14 (77.8)	54	6 (66.7)	19
Infections and infestations	6 (33.3)	6	3 (33.3)	3	5 (27.8)	9	4 (44.4)	4
Urinary tract infection	2 (11.1)	2	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Anal fungal infection	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
COVID-19	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Influenza	1 (5.6)	1	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0
Pneumonia	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastrointestinal infection	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Lower respiratory tract infection	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Nasopharyngitis	0 (0.0)	0	0 (0.0)	0	3 (16.7)	3	3 (33.3)	3
Paronychia	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Sinusitis bacterial	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Tooth abscess	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Upper respiratory tract infection	0 (0.0)	0	1 (11.1)	1	1 (5.6)	1	0 (0.0)	0
Nervous system disorders	6 (33.3)	7	2 (22.2)	2	6 (33.3)	7	2 (22.2)	2
Headache	5 (27.8)	6	1 (11.1)	1	5 (27.8)	6	2 (22.2)	2
Somnolence	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Amnesia	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Fine motor skill dysfunction	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Gastrointestinal disorders	2 (11.1)	2	0 (0.0)	0	2 (11.1)	2	0 (0.0)	0
Dysphagia	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastritis	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Abdominal rigidity	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Diarrhoea	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
General disorders and administration site conditions	2 (11.1)	3	2 (22.2)	2	7 (38.9)	9	3 (33.3)	4
Chills	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Feeling cold	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Pyrexia	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Asthenia	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Catheter site haematoma	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Chest discomfort	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Chest pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Fatigue	0 (0.0)	0	0 (0.0)	0	2 (11.1)	2	2 (22.2)	2
Infusion site rash	0 (0.0)	0	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0
Injection site pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Oedema peripheral	0 (0.0)	0	1 (11.1)	1	1 (5.6)	1	0 (0.0)	0
Vaccination site pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	1 (11.1)	1
Musculoskeletal and connective tissue disorders	2 (11.1)	5	3 (33.3)	3	5 (27.8)	7	1 (11.1)	1
Arthralgia	1 (5.6)	4	1 (11.1)	1	0 (0.0)	0	1 (11.1)	1

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Arthritis	1 (5.6)	1	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Back pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Muscle spasms	0 (0.0)	0	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0
Myalgia	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Neck pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Pain in extremity	0 (0.0)	0	1 (11.1)	1	1 (5.6)	1	0 (0.0)	0
Spinal pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	2 (11.1)	2	1 (11.1)	1	4 (22.2)	5	1 (11.1)	1
Nasal congestion	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Sneezing	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Asthma	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Choking	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Cough	0 (0.0)	0	0 (0.0)	0	3 (16.7)	3	0 (0.0)	0
Oropharyngeal pain	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	1 (11.1)	1
Skin and subcutaneous tissue disorders	2 (11.1)	3	0 (0.0)	0	2 (11.1)	2	2 (22.2)	2
Rash	1 (5.6)	1	0 (0.0)	0	1 (5.6)	1	1 (11.1)	1
Rash pruritic	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Urticaria	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Pigmentation disorder	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Rash popular	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Cardiac disorders	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Acute coronary syndrome	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Injury, poisoning and procedural complications	1 (5.6)	2	1 (11.1)	1	3 (16.7)	4	1 (11.1)	3
Arthropod bite	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Contusion	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Fall	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Foot fracture	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Head injury	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Limb crushing injury	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Procedural headache	0 (0.0)	0	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0
Skin abrasion	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Traumatic haematoma	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Investigations	1 (5.6)	1	0 (0.0)	0	3 (16.7)	7	1 (11.1)	1
Alanine aminotransferase increased	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Antinuclear antibody increased	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Bilirubin urine	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Blood urine present	0 (0.0)	0	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0
Haemoglobin decreased	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Protein urine	0 (0.0)	0	0 (0.0)	0	2 (11.1)	2	0 (0.0)	0
Serum ferritin decreased	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Renal and urinary disorders	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Haematuria	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Ear and labyrinth disorders	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Ear pain	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Eye disorders	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Eye irritation	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Immune system disorders	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Hypersensitivity	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Psychiatric disorders	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0
Insomnia	0 (0.0)	0	1 (11.1)	1	0 (0.0)	0	0 (0.0)	0

AE=adverse event; DBTP= double-blinded treatment period; EMPA=empasiprubart; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants per treatment arm in the safety set; n (%)=number and percentage of participants with adverse events per treatment arm; PBO=placebo; PT=Preferred Term; SOC=System Organ Class
 Note: The denominator for the percentage calculation is the total number of participants in the safety set per treatment arm.

Table 30: AEs Related to IMP by MedDRA SOC and PT During DBTP

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 IMP-related AE	7 (38.9)	14	0 (0.0)	0	2 (11.1)	5	2 (22.2)	2
Nervous system disorders	3 (16.7)	3	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Headache	3 (16.7)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Fine motor skill dysfunction	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Skin and subcutaneous tissue disorders	2 (11.1)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Rash	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Rash pruritic	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Urticaria	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Cardiac disorders	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Acute coronary syndrome	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
General disorders and administration site conditions	1 (5.6)	2	0 (0.0)	0	1 (5.6)	1	1 (11.1)	1
Chills	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Feeling cold	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Asthenia	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Fatigue	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Musculoskeletal and connective tissue disorders	1 (5.6)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Arthralgia	1 (5.6)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Nasal congestion	1 (5.6)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Injury, poisoning and procedural complications	0 (0.0)	0	0 (0.0)	0	2 (11.1)	3	0 (0.0)	0
Fall	0 (0.0)	0	0 (0.0)	0	1 (5.6)	1	0 (0.0)	0
Procedural headache	0 (0.0)	0	0 (0.0)	0	1 (5.6)	2	0 (0.0)	0

SOC or PT	Cohort 1				Cohort 2			
	EMPA IV 30/10 mg/kg (N=18)		PBO IV (N=9)		EMPA IV 15/5 mg/kg (N=18)		PBO IV (N=9)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Investigations	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1
Antinuclear antibody increased	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (11.1)	1

AE=adverse event; DBTP=double-blinded treatment period; EMPA=empasiprubart; IMP=investigational medicinal product; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants per treatment arm in the safety set; n(%)=number and percentage of participants with AEs per treatment arm; PBO=placebo; PT=preferred term; SOC=system organ class

Notes: The denominator for the percentage calculation is the total number of participants in the safety set per treatment arm.

Example 3 Investigation of ARGX-117 (empasiprubart) in adults with multifocal motor neuropathy (MMN) in a long-term extension study

[00331] A long-term extension (LTE) of the ARGX-117-2002 trial is being carried out to evaluate the Long-term Safety and Tolerability, Efficacy, Pharmacodynamics, Pharmacokinetics, and Immunogenicity of ARGX-117 in Adults With Multifocal Motor Neuropathy. This multicenter long-term extension study is “ARGX-117-2003”.

[00332] Participants in the ARGX-117-2002 study who completed the 16-week double-blinded treatment period had the possibility to enter ARGX-117-2003. ARGX-117-2003 includes a 4-week double-blinded rollover treatment period (DTP) and an open-label treatment period. Patients from Cohorts 1 and 2 of ARGX-117-2002 described in Examples 1 and 2 above are being treated according to the Regimens shown in **Table 31** below.

Table 31: Summary of dosage regimens

Regimen in <u>ARGX-117-2002</u>	Regimen in <u>ARGX-117-2003</u>		
	DTP	OTP	
		Once every 4 weeks	Once every 8 weeks or once every 4 weeks
Cohort 1: EMPA 30/10 mg/kg	EMPA 10 mg/kg at D1, D15, Placebo at D8, D22	EMPA 10 mg/kg at D29, D57, D85, D113	EMPA 10 mg/kg once every 8 weeks (or once every 4 weeks for participants who have worsening of MMN)
Cohort 1: placebo	EMPA 30 mg/kg at D1, EMPA 10 mg/kg at D8, D15, D22		
Cohort 2: EMPA 15/5 mg/kg	EMPA 5 mg/kg at D1, Placebo at D8, D15, D22	EMPA 5 mg/kg at D29, D57, D85, D113	EMPA 5 mg/kg every 8 weeks (or once every 4 weeks for participants who have worsening of MMN)
Cohort 2: placebo	EMPA 15 mg/kg at D1, EMPA 5 mg/kg at D8, D15, D22		

D=day; DTP=double-blinded rollover treatment period; EMPA=empasiprubart; MMN=multifocal motor neuropathy; OTP=open-label treatment period

[00333] During the open-label treatment period (OTP), participants are receiving empasiprubart IV once every 4 weeks for 12 weeks, followed by empasiprubart once every 8 weeks or once every 4 weeks, depending on the participant's MMN symptoms. Participants demonstrating worsening symptoms of MMN during the OTP receive empasiprubart IV at an increased frequency or are discontinued from treatment at the discretion of the investigator. IVIg treatment is not permitted in this study; participants requiring IVIg have been or will be discontinued from the OTP and will enter the safety follow-up period.

[00334] For the analysis of efficacy endpoints, the following study periods have been defined to assess the impact of dose interval on the endpoints:

- **DTP:** from the first IMP administration in ARGX-117-2003 until day 29, when participants receive empasiprubart IV and placebo
- **Q4WP:** from day 29 until day 113, when participants receive empasiprubart IV once every 4 weeks

- **Q8WP/Q4WP:** from day 113 until the end of the OTP. If participants have worsening symptoms and transition from once-every-8-week administration to once-every-4-week administration, this will be included in this period.

[00335] In addition to the study baseline, a baseline is defined for the Q4WP and Q8WP/Q4WP periods, for each efficacy endpoint.

Example 4 Interim results from the long-term extension study

[00336] An interim analysis of the data being generated in the ARGX-117-2003 study has been carried out with a data cut-off date of 21 March 2024 (15 February 2024 for the PK and PD data).

[00337] The objectives and endpoints assessed in the interim analysis are identified in **Table 32** below.

Table 32: Objectives and endpoints of the long-term extension study

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of empasiprubarb in adult participants with MMN	• Safety outcomes based on AE monitoring
Secondary	
• To evaluate the long-term efficacy of empasiprubarb on muscle strength and/or motor function in adult participants with MMN	mMRC • Value and change from baseline in the mMRC-10 sum score • Value and change from baseline in the mMRC-14 sum score • Value and change from baseline in the average score of the 2 most important muscle groups as assessed by the mMRC-14 sum score

	GS Values and change from baseline in GS
To evaluate the long-term efficacy of empasiprubart on functional ability, arm and hand function, QOL, and fatigue in adult participants with MMN	- Values and change from baseline in the Rasch-built overall disability scale MMN-RODS - Values and change from baseline in the CAP-PRI - Values of the PGIC scale - Proportion of participants by level of severity of MMN as assessed by the PGIS
To assess the PD of empasiprubart	Values and change from baseline in free C2, total C2, and functional complement activity (CH50)

[00338] Participants have been classified according to the IMP and dose received in ARGX-117-2002 and ARGX-117-2003. For the interim analysis reported herein, the following treatment groups were considered:

- ARGX-117-2002 EMPA IV 30/10 mg/kg / EMPA IV 10 mg/kg: participants of cohort 1 who received empasiprubart IV 30/10 mg/kg in ARGX-117-2002
- ARGX-117-2002 PBO / EMPA IV 30/10 mg/kg: participants of cohort 1 who received placebo in ARGX-117-2002
- ARGX-117-2002 EMPA IV 15/5 mg/kg / EMPA IV 5 mg/kg: participants of cohort 2 who received empasiprubart IV 15/5 mg/kg in ARGX-117-2002
- ARGX-117-2002 PBO / EMPA IV 15/5 mg/kg: participants of cohort 2 who received placebo in ARGX-117-2002

SUMMARY

[00339] Forty-eight of the 49 participants who completed the 16-week treatment period in ARGX-117-2002 have been enrolled and are receiving treatment in ARGX-117-2003, so the population of ARGX-117-2003 is similar to the population in ARGX-117-2002.

[00340] For participants who received empasiprubart IV in ARGX-117-2002, efficacy outcome measures have remained stable in ARGX-117-2003. For Cohort 1 participants who received placebo in ARGX-117-2002, an improvement in efficacy measures was observed in the first 4 weeks after receiving empasiprubart IV in the DTP and then tended to stabilize. For Cohort 2 participants who received placebo in ARGX-117-2002, efficacy measures have remained stable in ARGX-117-2003 after empasiprubart IV administration.

[00341] The safety profile of empasiprubart IV remains favorable following longer exposure to empasiprubart IV, and the overall safety profile of Cohort 1 and Cohort 2 is similar in ARGX-117-2003. No new safety concerns have been observed.

[00342] For the participants who received placebo in ARGX-117-2002, the empasiprubart IV induction regimen in ARGX-117-2003 reduced the mean free C2 levels below the predefined target threshold. For participants who received empasiprubart in ARGX-117-2003, free C2 levels were maintained below the predefined target threshold.

[00343] Results from the Q4WP and Q8WP/Q4WP periods show that increasing the interval between doses of empasiprubart IV slowly increases the mean free C2 and CH50 concentrations over time.

PRELIMINARY RESULTS

Disposition

[00344] 48 of the 49 (98.0%) participants who completed the 16-week treatment period in ARGX-117-2003, enrolled and received treatment in ARGX-117-2003. At the time of the data cut-off date, 44 (91.7%) of participants were still ongoing in ARGX-117-2003 and receiving empasiprubart IV. In total, 4 participants had discontinued IMP: 1 participant in cohort 1 and 1 participant in cohort 2 who were in the Q4WP period and 2 participants in cohort 1 who were in the Q8W/Q4WP period. The reasons for IMP discontinuation were lack of efficacy, physician decision, and AE. There was 1 participant who withdrew from the study (withdrawal of consent).

Demographic and Other Baseline Characteristics

[00345] Considering the high rollover rate from ARGX-117-2002 to ARGX-117-2003, the participant population in ARGX-117-2003 is similar to the participant population in ARGX-117-2002.

Exposure

[00346] As of the data cut-off date, the median duration of treatment in ARGX-117-2003 was 16.4 weeks (minimum 0; maximum 58), and the median number of infusions was 8.0 (minimum 1; maximum 16).

[00347] In Cohort 1, the majority of participants who received at least 2 doses in the Q8WP/Q4WP (14 of 22) had Q8W dosing intervals and did not transition to Q4W dosing.

[00348] In the ARGX-117-2002 PBO / EMPA IV 30/10 mg/kg group, all 5 participants remained on Q8W dosing from the start of the Q8WP/Q4WP period until the data cut-off date.

[00349] In the ARGX-117-2002 EMPA IV 30/10 mg/kg / EMPA IV 10 mg/kg group, 9 of 17 participants remained on Q8W dosing; 6 participants had both Q8W and Q4W dosing intervals; and 2 participants remained on Q4W dosing.

[00350] None of the Cohort 2 participants (ARGX-117-2002 EMPA IV 15/5 mg/kg / EMPA IV 5 mg/kg and ARGX-117-2002 PBO / EMPA IV 15/5 mg/kg groups) had exposure after day 113.

Efficacy

[00351] The median (Q1, Q3) change from baseline within each period for the efficacy endpoints is shown in **Table 33**. The change from baseline within the Q4WP (for Cohort 2) and Q8WP/Q4WP (for Cohort 1 and Cohort 2) should be interpreted with caution because the majority of participants are still ongoing in the periods and the last available assessment is at varying time points for the participants.

Table 33: Efficacy Endpoints – Change From DTP, Q4WP, and Q8WP/Q4WP Baseline at Last Assessment during DTP, Q4WP, and Q8WP/Q4WP

Endpoint	ARGX-117-2002 EMPA IV 30/10 mg/kg => EMPA IV 10 mg/kg (N=17)		ARGX-117-2002 PBO C1 => EMPA IV 30/10 mg/kg (N=7)		ARGX-117-2002 EMPA IV 15/5 mg/kg => EMPA IV 5 mg/kg (N=16)		ARGX-117-2002 PBO C2 => EMPA IV 15/5 mg/kg (N=8)	
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)
Change from study baseline at last assessment during DTP								
mMRC-10 sum score ^a	17	0.0 (0.0, 1.0)	7	1.0 (0.0, 2.0)	15	0.0 (-1.0, 1.0)	7	0.0 (-2.0, 2.0)

Endpoint	ARGX-117-2002 EMPA IV 30/10 mg/kg => EMPA IV 10 mg/kg (N=17)		ARGX-117-2002 PBO C1 => EMPA IV 30/10 mg/kg (N=7)		ARGX-117-2002 EMPA IV 15/5 mg/kg => EMPA IV 5 mg/kg (N=16)		ARGX-117-2002 PBO C2 => EMPA IV 15/5 mg/kg (N=8)	
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)
Grip Strength daily average (kPa) - most affected hand ^a	17	1.33 (-2.00, 5.00)	7	6.00 (-5.00, 9.33)	15	2.00 (-0.33, 7.00)	7	3.33 (1.00, 5.33)
Grip Strength daily average (kPa) - less affected hand ^a	17	0.33 (-1.00, 4.00)	7	-0.67 (-4.67, 4.00)	15	2.00 (-1.33, 5.00)	7	2.33 (1.67, 11.33)
MMN-RODS total score (centile metric) ^a	17	0.0 (-2.0, 0.0)	7	6.0 (0.0, 16.0)	15	0.0 (-2.0, 1.0)	7	0.0 (-5.0, 2.0)
CAP-PRI total score ^b	17	0.0 (-1.0, 0.0)	7	0.0 (-5.0, 2.0)	13	0.0 (0.0, 1.0)	7	0.0 (-1.0, 2.0)
Change from Q4WP baseline at last assessment during Q4WP								
mMRC-10 sum score ^a	17	0.0 (-1.0, 0.0)	7	0.0 (0.0, 1.0)	9	0.0 (-1.0, 0.0)	5	0.0 (-1.0, 1.0)
Grip Strength daily average (kPa) - most affected hand ^a	17	0.33 (-1.33, 2.67)	7	-0.67 (-4.67, 4.00)	9	2.33 (-2.00, 2.67)	5	-0.67 (-1.33, 0.67)
Grip Strength daily average (kPa) - less affected hand ^a	17	0.00 (-3.33, 1.33)	7	-2.67 (-3.33, -1.33)	9	-2.67 (-4.00, 0.00)	5	-1.00 (-5.33, -0.33)
MMN-RODS total score (centile metric) ^a	17	0.0 (-2.0, 2.0)	7	0.0 (-6.0, 6.0)	9	0.0 (0.0, 0.0)	5	0.0 (0.0, 0.0)
CAP-PRI total score ^b	17	0.0 (-1.0, 1.0)	7	2.0 (-1.0, 4.0)	9	0.0 (0.0, 1.0)	5	1.0 (0.0, 1.0)
Change from Q8WP/Q4WP baseline at last assessment during Q8WP/Q4WP								
mMRC-10 sum score ^a	17	0.0 (0.0, 2.0)	6	0.0 (0.0, 0.0)	0		0	
Grip Strength daily average (kPa) - most affected hand ^a	17	0.67 (0.00, 5.67)	6	1.00 (-3.00, 10.67)	0		0	
Grip Strength daily average (kPa) - less affected hand ^a	17	2.00 (-0.67, 4.00)	6	1.00 (-1.67, 6.67)	0		0	
MMN-RODS total score (centile metric) ^a	17	0.0 (0.0, 2.0)	6	0.5 (-3.0, 5.0)	0		0	
CAP-PRI total score ^b	17	-1.0 (-2.0, 1.0)	6	-2.0 (-2.0, -1.0)	0		1	0.0 (0.0, 0.0)

ARGX-117-2002=ARGX-117-2002; C1=cohort 1; C2=cohort 2; CAP-PRI=Chronic Acquired Polyneuropathy patient-Reported Index; DTP=double-blinded rollover treatment period; EMPA=empasiprubart; IV=intravenous(ly); kPa=kilopascal; MMN-RODS=Rasch-built overall disability scale for MMN; mMRC=modified Medical Research Counsel; N=number of participants per treatment group; n=number of participants with data; PBO=placebo; Q1=quartile 1; Q3=quartile; Q4WP=period of once-every-4-week administration; Q8WP/Q4WP=period during which once-every-8-week administration was allowed

Notes: The baseline of each reference period is taken into account. Results should be interpreted with caution as the number of participants in the period is small.

^a A positive change indicates better condition.

^b A negative change indicates better condition.

Pharmacodynamics

[00352] For both cohorts, the mean free C2 levels were reduced to or maintained below the predefined thresholds for all treatment groups during the DTP. These thresholds were 0.4 mg/L and 0.8 mg/L for the cohort 1 and cohort 2 dosing regimens, respectively. CH50 levels were reduced or maintained low for both cohorts during the DTP.

[00353] For participants in Cohort 1 in the Q4WP and Q8WP/Q4WP periods, increasing the interval between dosing increased the mean free C2 concentration above the target of 0.4 mg/L (and close to the cohort 2 target of 0.8 mg/L). Mean CH50 concentrations also increased over time.

[00354] For participants in Cohort 2 in the Q4WP period, mean free C2 levels and CH50 levels increased slowly over time, based on the limited available data.

Safety

[00355] The safety profile of empasiprubart IV was similar to ARGX-117-2002 and remains favorable with longer exposure to the drug. Considering the difference in patient years of exposure, the event rates (ER/100 PYFU) for AEs in Cohort 1 and Cohort 2 were similar. There were no hypersensitivity concerns overall.

INCORPORATION BY REFERENCE

All patent and non-patent literature references cited above are incorporated herein by reference in their entirety.

The invention may also be understood with reference to the following numbered embodiments:

1. A method of treating multifocal motor neuropathy (MMN) in a subject in need thereof, the method comprising administering to the subject an effective amount of a complement component 2 (C2) inhibitor.
2. The method of embodiment 1, wherein the C2 inhibitor is administered at a dose of 0.1 mg/kg to 100 mg/kg.
3. The method of embodiment 1 or 2, wherein the C2 inhibitor is administered at a dose of 5 mg/kg to 60 mg/kg.
4. The method of embodiment 1 or embodiment 2, wherein the C2 inhibitor is administered at a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg.
5. The method of any one of embodiments 1-4, wherein the C2 inhibitor is administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, or 60 mg/kg.
6. The method of embodiment 1, wherein the C2 inhibitor is administered at a fixed dose of 500 mg to 1500 mg.
7. The method of embodiment 6, wherein the C2 inhibitor is administered at a fixed dose of 1200 mg.
8. The method of any one of embodiments 1-7, wherein the C2 inhibitor is administered intravenously.
9. The method of any one of embodiments 1-7, wherein the C2 inhibitor is administered subcutaneously.

10. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered once weekly.
11. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered once every 2 weeks.
12. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered once every 4 weeks.
13. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered once every 8 weeks.
14. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 5 mg/kg once weekly, every 2 weeks, every 4 weeks, or every 8 weeks.
15. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 10 mg/kg once weekly, every 2 weeks, every 4 weeks, or every 8 weeks.
16. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 10 mg/kg every 4 weeks.
17. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 15 mg/kg once weekly, every 2 weeks, every 4 weeks, or every 8 weeks.
18. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 30 mg/kg once weekly, every 2 weeks, every 4 weeks, or every 8 weeks.
19. The method of any one of embodiments 1-9, wherein the C2 inhibitor is administered at a dose of 60 mg/kg once weekly, every 2 weeks, every 4 weeks, or every 8 weeks.

20. The method of any one of embodiments 1-19, wherein the C2 inhibitor is administered according to a loading regimen.
21. The method of embodiment 20, wherein the loading regimen reduces the level of free C2 in the blood of the subject to or below a threshold level.
22. The method of embodiment 20 or 21, further comprising a maintenance regimen following the loading regimen.
23. The method of embodiment 22, wherein the maintenance regimen comprises administration of the C2 inhibitor according to a regimen that maintains the level of free C2 in the blood of the subject at or below the threshold level.
24. The method of embodiment 21 or 23, wherein the threshold level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, or 0.8 $\mu\text{g/mL}$.
25. The method of embodiment 21 or 23, wherein the threshold level is 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% of the subject's baseline level of free C2.
26. The method of any one of embodiments 20-25, wherein the loading regimen is a single initial dose followed by one or more subsequent doses.
27. The method of embodiment 26, wherein the one or more subsequent doses are each a lower amount than the single initial dose.
28. The method of embodiments 26, wherein the one or more subsequent doses are each the same as the single initial dose.
29. The method of any one of embodiments 26-28, wherein the single initial dose is followed by 1, 2, 3, 4, 5, or 6 subsequent doses.

30. The method of embodiment 29, wherein the single initial dose is followed by one subsequent dose.
31. The method of any one of embodiments 26-30, wherein the subsequent doses are administered once weekly or every 2 weeks.
32. The method of any one of embodiments 26-31, wherein the single initial dose is followed by at least 4 or by 4 subsequent doses, and wherein the subsequent doses are administered once weekly.
33. The method of any one of embodiments 26-32, wherein the first subsequent dose is administered one week after the single initial dose.
34. The method of any one of embodiments 26-33, wherein the single initial dose is 0.1 mg/kg to 100 mg/kg.
35. The method of any one of embodiments 26-33, wherein the single initial dose is 10 mg/kg to 60 mg/kg.
36. The method of embodiment 35, wherein the single initial dose is 15 mg/kg.
37. The method of embodiment 35, wherein the single initial dose is 30 mg/kg.
38. The method of embodiment 35, wherein the single initial dose is 60 mg/kg.
39. The method of any one of embodiments 26-33, wherein the single initial dose is a fixed dose of 500 mg to 1500 mg.
40. The method of embodiment 39, wherein the single initial dose is a fixed dose of 1200 mg.

41. The method of any one of embodiments 26-40, wherein the subsequent dose or doses are each 0.1 mg/kg to 100 mg/kg.
42. The method of embodiment 41, wherein the subsequent dose or doses are each 5 mg/kg to 60 mg/kg.
43. The method of embodiment 41, wherein the subsequent dose or doses are each 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg.
44. The method of embodiment 43, wherein the subsequent dose or doses are each 5 mg/kg.
45. The method of embodiment 43, wherein the subsequent dose or doses are each 10 mg/kg.,
46. The method of embodiment 43, wherein the subsequent dose or doses are each 30 mg/kg.
47. The method of any one of embodiments 26-40, wherein the subsequent dose or doses are each a fixed dose of 500 mg to 1500 mg.
48. The method of embodiment 47, wherein the subsequent dose or doses are each a fixed dose of 1200 mg.
49. The method of embodiment 36, wherein the single initial dose is 15 mg/kg and the subsequent dose or doses are each 5 mg/kg.
50. The method of embodiment 37, wherein the single initial dose is 30 mg/kg and the subsequent dose or doses are each 10 mg/kg.
51. The method of embodiment 37, wherein the single initial dose is 30 mg/kg and the subsequent dose or doses are each 30 mg/kg.

52. The method of embodiment 38, wherein the single initial dose is 60 mg/kg and the subsequent dose or doses are each 30 mg/kg.
53. The method of any one of embodiments 20-52, wherein the loading regimen is administered intravenously.
54. The method of any one of embodiments 20-52, wherein the loading regimen is administered subcutaneously.
55. The method of any one of embodiments 20-54, wherein the loading regimen reduces the level of free C2 to or below the threshold level in 1, 2, 3, 4, 5, 6, or 7 days.
56. The method of any one of embodiments 20-54, wherein the loading regimen reduces the level of free C2 to or below the threshold level in 1, 2, 3, 4, or 5 weeks.
57. The method of any one of embodiments 22-56, wherein the maintenance regimen is a dose of 0.1-100 mg/kg administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks.
58. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once weekly.
59. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 2 weeks.
60. The method of embodiment 59, wherein the maintenance regimen is a dose of 10 mg/kg, administered once every 2 weeks.

61. The method of embodiment 59, wherein the maintenance regimen is a dose of 30 mg/kg, administered once every 2 weeks.

62. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 3 weeks.

63. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 4 weeks.

64. The method of embodiment 63, wherein the maintenance regimen is a dose of 5 mg/kg, administered once every 4 weeks.

65. The method of embodiment 63, wherein the maintenance regimen is a dose of 10 mg/kg, administered once every 4 weeks.

66. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 5 weeks.

67. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 6 weeks.

68. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 7 weeks.

69. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 0.1 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, or 80 mg/kg, administered once every 8 weeks.
70. The method of embodiment 69, wherein the maintenance regimen is a dose of 5 mg/kg administered once every 8 weeks.
71. The method of embodiment 69, wherein the maintenance regimen is a dose of 10 mg/kg administered once every 8 weeks.
72. The method of embodiments 57-71, wherein the frequency of dosing in the maintenance regimen is increased if the subject shows signs of clinical deterioration.
73. The method of embodiment 72, wherein the frequency of dosing in the maintenance regimen is increased from administration once every 8 weeks to administration once every 4 weeks if the subject shows signs of clinical deterioration.
74. The method of embodiments 57-71, wherein the frequency of dosing in the maintenance regimen is decreased if the subject shows signs of clinical improvement.
75. The method of embodiment 74, wherein the frequency of dosing in the maintenance regimen is decreased from administration once every 4 weeks to administration once every 8 weeks if the subject shows signs of clinical improvement.
76. The method of any one of embodiments 72-75, wherein clinical deterioration and/or clinical improvement is assessed according to a clinical efficacy measurement selected from one or more of the following: time until first retreatment with IVIg, Patient Global Impression of Change (PGIC) 7-point score, modified Medical Research Counsel-10 (mMRC-10) sum score, modified Medical Research Counsel-14 (mMRC-14) sum score, grip strength three day moving average score in a most affected hand, grip strength three day moving average score in a less affected hand, MMN Rasch-built Overall Disability Scale for MMN (MMN-RODS), Chronic

Acquired Polyneuropathy-Patient Reported Index (CAP-PRI) score, and Fatigue Severity Scale (FSS) average score.

77. The method of embodiments 72 or 73, wherein clinical deterioration is defined as a >30% decline in grip strength of either hand observed on at least 2 consecutive days and/or a decline of at least 2 points on the mMRC-10 sum score.

78. The method of any one of embodiments 22-57, wherein the maintenance regimen is a dose of 500 mg to 1500 mg, administered once weekly, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks.

79. The method of embodiment 78, wherein the doses are each a fixed dose of 1200 mg.

80. The method of any one of embodiments 22-79, wherein the maintenance regimen is administered 1, 2, 3, 4, 5, 6, 7, or 8 weeks after the loading regimen.

81. The method of any one of embodiments 22-80, wherein the maintenance regimen is administered if the level of free C2 in the blood of the subject is above a threshold level.

82. The method of any one of embodiments 22-81, wherein the maintenance regimen is administered intravenously.

83. The method of any one of embodiments 22-81, wherein the maintenance regimen is administered subcutaneously.

84. The method of any one of embodiments 22-83, wherein
(i) the loading regimen is administration of a single initial dose of 10mg/kg to 60 mg/kg followed by administration of one or more subsequent doses each of 5 mg/kg to 30 mg/kg; and
(ii) the maintenance regimen is administration of a dose of 10 mg/kg or 30 mg/kg once every two weeks or administration of a dose of 5 mg/kg once every four weeks.

85. The method of any one of embodiments 22-83, wherein

(i) the loading regimen is administration of a single initial dose of 10mg/kg to 60 mg/kg followed by administration of one or more subsequent doses each of 5 mg/kg to 30 mg/kg; and

(ii) the maintenance regimen is administration of a dose of 5 mg/kg, 10 mg/kg or 30 mg/kg once every two weeks or once every four weeks.

86. The method of any one of embodiments 84 or 85, wherein the one or more subsequent doses are each a lower amount than the single initial dose.

87. The method of any one of embodiments 84 or 85, wherein the one or more subsequent doses are each the same amount as the single initial dose.

88. The method of any one of embodiments 84-87, wherein the one or more subsequent doses are administered once weekly.

89. The method of any one of embodiments 84-88, wherein the maintenance regimen comprises administration of two or more doses and the dosing interval is longer in the maintenance regimen than in the loading regimen.

90. The method of any one of embodiments 84-89, wherein

(i) the loading regimen is administration of a single initial dose of 30 mg/kg or 15 mg/kg followed by once weekly administration of one or more subsequent doses each of 10 mg/kg or 5 mg/kg; and

(ii) the maintenance regimen is administration of a dose of 10 mg/kg once every two weeks or administration of a dose of 5 mg/kg once every four weeks.

91. The method of embodiment 84 or 85, wherein:

the loading regimen is:

a single initial dose of 15 mg/kg; and

four subsequent doses, each of 5 mg/kg administered once weekly beginning one week after the single initial dose; and

the maintenance regimen is:

a dose of 5 mg/kg administered once every four weeks.

92. The method of embodiment 91, wherein the frequency of dosing in the maintenance regimen is decreased to administration once every 8 weeks if the subject shows signs of clinical improvement.

93. The method of embodiment 84 or 85, wherein:

the loading regimen is:

a single initial dose of 30 mg/kg; and

four subsequent doses, each of 10 mg/kg administered once weekly beginning one week after the single initial dose; and

the maintenance regimen is:

a dose of 10 mg/kg administered once every two weeks.

94. The method of embodiment 93, wherein the frequency of dosing in the maintenance regimen is decreased to administration once every 4 weeks or once every 8 weeks if the subject shows signs of clinical improvement.

95. The method of embodiment 84 or 85, wherein:

the loading regimen is:

a single initial dose of 60 mg/kg; and

four subsequent doses, each of 30 mg/kg administered once weekly beginning one week after the single initial dose; and

the maintenance regimen is:

a dose of 30 mg/kg administered once every two weeks.

96. The method of embodiment 95, wherein the frequency of dosing in the maintenance regimen is decreased to administration once every 4 weeks or once every 8 weeks if the subject shows signs of clinical improvement.

97. The method of embodiment 85, wherein:

the loading regimen is:

a single initial dose of 30 mg/kg; and
one subsequent doses of 30 mg/kg administered one week after the single initial dose; and

the maintenance regimen is:

a dose of 10 mg/kg administered once every four weeks.

98. The method of embodiment 97, wherein the frequency of dosing in the maintenance regimen is decreased to administration once every 8 weeks if the subject shows signs of clinical improvement.

99. The method of any one of embodiments 84-98, wherein the maintenance regimen begins 1 week after the last subsequent dose of the loading regimen.

100. The method of any one of embodiments 84-98, wherein the maintenance regimen begins 2 weeks after the last subsequent dose of the loading regimen.

101. The method of any one of embodiments 22-100, wherein the loading regimen is administered intravenously and the maintenance regimen is administered subcutaneously.

102. The method of any one of embodiments 22-100, wherein the loading regimen is administered subcutaneously and the maintenance regimen is administered intravenously.

103. The method of any one of embodiments 22-100, wherein the loading regimen and the maintenance regimen are both administered intravenously.

104. The method of any one of embodiments 22-100, wherein the loading regimen and the maintenance regimen are both administered subcutaneously.

105. The method of any one of embodiments 1-104, wherein the subject shows one or more of the following improved responses compared to baseline measurements: increased time until first

retreatment with IVIg; improved patient report on the Patient Global Impression of Change (PGIC) 7-point scale; improved scores in clinical endpoints selected from the group consisting of: modified Medical Research Counsel-10 (mMRC-10) sum score, modified Medical Research Counsel-14 (mMRC-14) sum score, grip strength three day moving average score in a most affected hand, grip strength three day moving average score in a less affected hand, MMN Rasch-built Overall Disability Scale for MMN (MMN-RODS), Chronic Acquired Polyneuropathy-Patient Reported Index (CAP-PRI) score, and Fatigue Severity Scale (FSS) average score.

106. The method of any one of embodiments 1-105, wherein the subject's motor strength is improved compared to the subject's motor strength and/or the subject's sensory symptoms achieved with standard-of-care treatment using intravenous immunoglobulin (IVIg).

107. The method of any one of embodiments 1-105, wherein the subject shows a reduction in the level of free C2 in the blood of the subject following administration of the C2 inhibitor, compared to a baseline level of free C2 in the blood of the subject.

108. The method of embodiment 107, wherein the level of free C2 in the blood of the subject is reduced by at least about 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % compared to a baseline level of free C2 in the blood of the subject.

109. The method of any one of embodiments 1-108, further comprising administering an additional therapeutic agent to the subject.

110. The method of embodiment 109, wherein the additional therapeutic agent is IVIg.

111. The method of embodiment 109, wherein the additional therapeutic is rituximab, eculizumab, cyclophosphamide, or mycophenolate mofetil.

112. The method of embodiment 110, wherein the IVIg is administered to the subject once every two weeks, once every three weeks, once every four weeks, or once every five weeks.

113. The method of any one of embodiments 1-112, wherein the subject has a detectable baseline serum level of an anti-ganglioside IgM antibody.
114. The method of any one of embodiments 1-113, wherein the subject has been previously treated with IVIg.
115. The method of any one of embodiments 1-114, wherein the subject has been previously stabilized with IVIg.
116. The method of any one of embodiments 1-115, wherein the subject is dependent on IVIg.
117. The method of any one of embodiments 1-109, wherein the subject is not receiving concomitant IVIg.
118. The method of embodiment 109, wherein the subject does not require IVIg retreatment following administration of the C2 inhibitor.
119. The method of any one of embodiments 1-101, wherein administration of the C2 inhibitor increases the time to IVIg retreatment.
120. The method of any one of embodiments 1-119, wherein the subject shows an increase in a modified Medical Research Council (mMRC) score following administration of the C2 inhibitor, compared to the subject's baseline mMRC score.
121. The method of embodiment 120, wherein the mMRC score is an mMRC-10 sum score or an mMRC-14 sum score.
122. The method of any one of embodiments 1-121, wherein the subject shows improved grip strength following administration of the C2 inhibitor, compared to the subject's baseline grip strength.

123. The method of any one of embodiments 1-122, wherein the subject shows an increase in MMN Rasch-built Overall Disability Scale (MMN-RODS) score following administration of the C2 inhibitor, compared to the subject's baseline MMN-RODS score.

124. The method of any one of embodiments 1-123, wherein the C2 inhibitor is an antibody that specifically binds to C2.

125. The method of any one of embodiments 1-124, wherein the C2 inhibitor is an antibody that specifically binds to C2b.

126. The method of embodiment 124 or embodiment 125, wherein the antibody comprises: a heavy chain variable region (VH) comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in SEQ ID NO: 7, or a variant thereof comprising 1-5 amino acid changes in any one of the CDRH1, CDRH2, or CDRH3 amino acid sequences; and/or a light chain variable region (VL) comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in SEQ ID NO: 8, or a variant thereof comprising 1-5 amino acid changes in any one of the CDRL1, CDRL2, or CDRL3 amino acid sequences.

127. The method of embodiment 124 or embodiment 125, wherein:

(a) the VH comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of:

SEQ ID NO: 1, or a variant thereof comprising 1-5 amino acid changes,

SEQ ID NO: 2, or a variant thereof comprising 1-5 amino acid changes, and

SEQ ID NO: 3, or a variant thereof comprising 1-5 amino acid changes; and/or

(b) the VL comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of

SEQ ID NO: 4, or a variant thereof comprising 1-5 amino acid changes,

SEQ ID NO: 5, or a variant thereof comprising 1-5 amino acid changes, and

SEQ ID NO: 6, or a variant thereof comprising 1-5 amino acid changes.

128. The method of embodiment 127, wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 1, 2, 3, 4, 5, and 6, respectively.

129. The method of any one of embodiments 124-128, wherein the antibody comprises: a VH comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 7; and/or a VL comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 8.

130. The method of embodiment 124 or embodiment 125, wherein the antibody comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 7 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 8.

131. The method of any one of embodiments 124-130, wherein the antibody comprises a heavy chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 9 and/or a light chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 10.

132. The method of any one of embodiments 124-130, wherein the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 9 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 10.

133. The method of any one of embodiments 1-124, wherein the antibody is empasiprubart or a biosimilar thereof.

134. A C2 inhibitor for use in the treatment of multifocal motor neuropathy, wherein the treatment is performed according to the method of any one of the previous embodiments.

135. A C2 inhibitor for use in the manufacture of a medicament for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to the method of any one of the previous embodiments.

136. Use of a C2 inhibitor for the treatment of multifocal motor neuropathy, wherein the treatment is performed according to the method of any one of the previous embodiments.

CLAIMS

1. A method of treating multifocal motor neuropathy (MMN) in a subject in need thereof, the method comprising administering to the subject an effective amount of a complement component 2 (C2) inhibitor, and wherein the C2 inhibitor is administered according to a dosage regimen comprising:
 - (i) a loading regimen comprising administration of a single initial dose of the C2 inhibitor followed by one or more subsequent doses of the C2 inhibitor, followed by
 - (ii) a maintenance regimen comprising administration of two or more subsequent doses of the C2 inhibitor, and wherein the dosing interval is longer in the maintenance regimen than in the loading regimen, andwherein the subject shows one or more of the following improved responses compared to baseline measurements: increased time until first retreatment with IVIg; improved patient report on the Patient Global Impression of Change (PGIC) 7-point scale; improved scores in clinical endpoints selected from the group consisting of: modified Medical Research Counsel-10 (mMRC-10) sum score, modified Medical Research Counsel-14 (mMRC-14) sum score, grip strength three day moving average score in a most affected hand, grip strength three day moving average score in a less affected hand, MMN Rasch-built Overall Disability Scale for MMN (MMN-RODS), Chronic Acquired Polyneuropathy-Patient Reported Index (CAP-PRI) score, and Fatigue Severity Scale (FSS) average score.
2. The method of claim 1, wherein the subsequent doses of the C2 inhibitor of the loading regimen and/or the maintenance regimen is/are each a lower dose than the single initial dose of the C2 inhibitor.
3. The method of claim 1, wherein the one or more subsequent doses of the C2 inhibitor of the loading regimen is/are the same as the single initial dose of the C2 inhibitor.
4. The method of claim 2 or claim 3, wherein the two or more subsequent doses of the C2 inhibitor of the maintenance regimen are lower than the single initial dose of the C2 inhibitor of the loading regimen.

5. The method of any one of claims 1-4, wherein
- (i) the loading regimen is administration of a single initial dose of 10mg/kg to 60 mg/kg followed by administration of one or more subsequent doses each of 5 mg/kg to 30 mg/kg, optionally wherein the single initial dose and/or the subsequent doses are administered weekly; and
- (ii) the maintenance regimen is administration of two or more subsequent doses of 10 mg/kg or 30 mg/kg once every two weeks or administration of a dose of 5 mg/kg once every four weeks.
6. The method of any one of claims 1-4, wherein
- (i) the loading regimen is administration of a single initial dose of 10mg/kg to 60 mg/kg followed by administration of one or more subsequent doses each of 5 mg/kg to 30 mg/kg, optionally wherein the single initial dose and/or the subsequent doses are administered weekly; and
- (ii) the maintenance regimen is administration of two or more subsequent doses of 5 mg/kg, 10 mg/kg or 30 mg/kg once every two weeks or once every four weeks.
7. The method of any one of claims 1-6, wherein the single initial dose of the loading regimen is 30 mg/kg.
8. The method of any one of claims 1-6, wherein the single initial dose of the loading regimen is 15 mg/kg.
9. The method of claim 7, wherein the loading regimen comprises administration of one subsequent dose of 30 mg/kg, administered one week after the single initial dose.
10. The method of any one of claims 1-8, wherein the loading regimen comprises administration of two or more subsequent doses, each of 10 mg/kg and administered weekly.
11. The method of any one of claims 1-8, wherein the loading regimen comprises administration of two or more subsequent doses, each of 5 mg/kg and administered weekly.

12. The method of any one of the preceding claims, wherein the one or more subsequent doses of the loading regimen commence one week after the single initial dose.
13. The method of any one of the preceding claims, wherein the two or more subsequent doses of the maintenance regimen are each 10 mg/kg, administered once every 2 weeks, once every 4 weeks or once every 8 weeks.
14. The method of claim 13, wherein the two or more subsequent doses of the maintenance regimen are each 10 mg/kg, administered once every 4 weeks.
15. The method of any one of the preceding claims, wherein the two or more subsequent doses of the maintenance regimen are each 5 mg/kg, administered once every 4 weeks or once every 8 weeks.
16. The method of any one of the preceding claims, wherein the frequency of administration of the doses of the maintenance regimen is altered depending on whether the subject shows signs of clinical improvement or clinical deterioration.
17. The method of any one of claim 1-16, wherein
 - (i) the loading regimen is a single initial dose of 30 mg/kg; and one subsequent dose of 30 mg/kg administered one week after the single initial dose; and
 - (ii) the maintenance regimen is two or more doses of 10 mg/kg administered once every four weeks.
18. The method of any one of claims 1-16, wherein
 - (i) the loading regimen is a single initial dose of 30 mg/kg; and one or more subsequent doses, each of 10 mg/kg administered once weekly beginning one week after the single initial dose; and
 - (ii) the maintenance regimen is two or more doses of 10 mg/kg administered once every two weeks.

19. The method of any one of claims 1-16, wherein
 - (i) the loading regimen is a single initial dose of 15 mg/kg; and one or more subsequent doses, each of 5 mg/kg administered once weekly beginning one week after the single initial dose; and
 - (ii) the maintenance regimen is two or more doses of 5 mg/kg administered once every four weeks.
20. The method of claim 18 or claim 19, wherein the loading regimen consists of four subsequent doses.
21. The method of any one of the preceding claims, wherein the maintenance regimen commences one week after administration of the last dose of the loading regimen.
22. The method of any one of the preceding claims, wherein the maintenance regimen commences two weeks after administration of the last dose of the loading regimen.
23. The method of any one of the preceding claims, wherein the maintenance regimen commences four weeks after administration of the last dose of the loading regimen.
24. The method of any one of the preceding claims, wherein the loading regimen and the maintenance regimen are administered intravenously.
25. The method of any one of the preceding claims, wherein the subject has been previously treated with IVIg.
26. The method of any one of the preceding claims, wherein the subject has been previously stabilized with IVIg.
27. The method of any one of the preceding claims, wherein the subject is not receiving concomitant IVIg at the time of commencing administration of the C2 inhibitor.

28. The method of any one of the preceding claims, wherein the subject shows an increase in a modified Medical Research Council (mMRC) score following administration of the C2 inhibitor, compared to the subject's baseline mMRC score.
29. The method of claim 28, wherein the mMRC score is an mMRC-10 sum score or an mMRC-14 sum score.
30. The method of claim 29, wherein following administration of the C2 inhibitor, the subject shows an increase in the mMRC-10 or mMRC-14 sum score of 1 or more, compared to the subject's baseline mMRC sum score.
31. The method of claim 30, wherein the subject shows an increase in the mMRC-10 sum score of 1.5 or more, 2 or more, or 3 or more, optionally wherein the subject shows an increase in the mMRC-10 sum score of 1.5, 2 or 3.
32. The method of claim 30, wherein the subject shows an increase in the mMRC-14 sum score of 4 or more, or 7 or more, optionally wherein the subject shows an increase in the mMRC-14 sum score of 4 or 7.
33. The method of any one of the preceding claims, wherein the subject shows improved grip strength following administration of the C2 inhibitor, compared to the subject's baseline grip strength.
34. The method of claim 33, wherein the subject shows improved grip strength in the most affected hand, in the less affected hand, or in both hands.
35. The method of claim 34, wherein the subject shows improved grip strength in the most affected hand of greater than 10 kPa or greater than 15 kPa.

36. The method of claim 35, wherein the subject shows improved grip strength in the most affected hand of 11.28 kPa or 17.06 kPa.
37. The method of claim 34, wherein the subject shows improved grip strength in the less affected hand of greater than 5 kPa or greater than 8 kPa.
38. The method of claim 37, wherein the subject shows improved grip strength in the less affected hand of 6.5 kPa, 6.61 kPa, 8.78 kPa, or 9.94 kPa.
39. The method of any one of the preceding claims, wherein the subject shows an increase in MMN Rasch-built Overall Disability Scale (MMN-RODS) score following administration of the C2 inhibitor, compared to the subject's baseline MMN-RODS score.
40. The method of claim 39, wherein the subject shows an increase in MMN-RODS score of 5 or more, optionally 6 or more.
41. The method of claim 40, wherein the subject shows an increase in MMN-RODS score of 6.
42. The method of any one of the preceding claims, wherein following administration of the C2 inhibitor, the subject shows an increase in disease-specific quality of life, as measured using the Chronic Acquired Polyneuropathy – Patient Report Index (CAP-PRI), compared to the subject's score at baseline.
43. The method of claim 42, wherein following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2 or more.
44. The method of claim 43, wherein following administration of the C2 inhibitor, the subject shows an improved CAP-PRI score with a reduction of 2.

45. The method of any one of the preceding claims, wherein following administration of the C2 inhibitor, the subject reports an improvement in the Patient Global Impression of Change (PGIC) 7-point scale, compared to the subject's baseline PGIC score.

46. The method of claim 45, wherein a population of MMN subjects are treated, and at least 50% or at least 60% of subjects treated report their condition much improved or very much improved.

47. The method of claim 46, wherein a population of MMN subjects are treated, and 55.6% of subjects treated report their condition much improved or very much improved.

48. The method of claim 45, wherein a population of MMN subjects are treated, and at least 90% of subjects treated report any improvement (minimally improved, much improved, or very much improved).

49. The method of claim 48, wherein a population of MMN subjects are treated, and 94.4% of subjects treated report any improvement (minimally improved, much improved, or very much improved).

50. The method of any one of the preceding claims, wherein following administration of the C2 inhibitor, the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS), compared to the subject's baseline FSS score.

51. The method of claim 50, wherein the subject shows an improvement in the 9-item Fatigue Severity Scale (FSS) comprising a reduction of 0.1 or more, 0.2 or more, or 0.4 or more.

52. The method of claim 51, wherein the reduction is 0.11 or 0.444.

53. The method of any one of the preceding claims, wherein the C2 inhibitor is an antibody that specifically binds to C2b.

54. The method of claim 53, wherein the antibody comprises a heavy chain variable region (VH) comprising CDRH1 as represented by SEQ ID NO: 1, CDRH2 as represented by SEQ ID NO: 2 and CDRH3 as represented by SEQ ID NO: 3 and a light chain variable region (VL) comprising CDRL1 as represented by SEQ ID NO: 4, CDRL2 as represented by SEQ ID NO: 5 and CDRL3 as represented by SEQ ID NO: 6.

55. The method of claim 54, wherein the antibody comprises: a VH comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 7; and/or a VL comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 8.

56. The method of claim 55, wherein the antibody comprises a VH comprising the amino acid sequence set forth in SEQ ID NO: 7 and a VL comprising the amino acid sequence set forth in SEQ ID NO: 8.

57. The method of any one of claims 54-56, wherein the antibody comprises a heavy chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 9 and/or a light chain comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 10.

58. The method of claim 57, wherein the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 9 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 10.

59. The method of any one of claims 1-58, wherein the C2 inhibitor is empasiprubart or a biosimilar thereof.

60. A C2 inhibitor for use in the treatment of multifocal motor neuropathy (MMN), wherein the treatment is performed according to the method of any one of the previous claims.

61. A C2 inhibitor for use in the manufacture of a medicament for the treatment of multifocal motor neuropathy (MMN), wherein the treatment is performed according to the method of any one of the previous claims.

62. Use of a C2 inhibitor for the treatment of multifocal motor neuropathy (MMN), wherein the treatment is performed according to the method of any one of the previous claims.