may lead to breakthrough hemolysis, which is a severe clinical complication in PNH patients. Biological stress (infection, surgery, pregnancy) leads to a physiological activation of the complement pathway with upregulation of C5 (Schutte *et al.,* Int Arch Allergy Appl Immunol. (1975), Vol. 48(5), pp. 706-720). In patients with PNH, it is therefore important to not only maintain complete blockade of the terminal complement activity throughout the dosing interval, but to also maintain a reserve of Crovalimab free binding sites to minimize the occurrence of breakthrough hemolysis.

Accordingly, there is a need to identify a dosing and administration regimen that (1) minimizes the formation of DTDCs in patients suffering from C5-related diseases, and particularly in patients switching from the anti-C5 antibody Eculizumab to Crovalimab, (2) maximizes the level of Crovalimab free binding sites, and (3) ensures that patients remain above an anti-C5 antibody target threshold concentration required for terminal complement inhibition despite the inter-individual variability.

SUMMARY

This need is addressed by the present disclosure by providing the examples as defined in the claims.

The present disclosure relates to an anti-C5 antibody for use in a method of treating or preventing a C5-related disease in a subject, wherein the method comprises the consecutive steps of:

(a) intravenously administering a loading dose of 1500 mg of the anti-C5 antibody to the subject once, followed by subcutaneously administering at least one loading dose of 340 mg of the anti-C5 antibody to the subject; and

(b) subcutaneously administering at least one maintenance dose of 1020 mg of the anti-C5 antibody to the subject.

In the context of the present disclosure, the subject to be treated is preferably a patient with a body weight of equal or greater than 100 kg. In the context of the present disclosure the subject to be treated is/are subject/s which suffer from a C5-related disease which require complement activity inhibition (for example PNH and aHUS). Moreover, the disclosure is directed to the use of the anti-C5 antibody for the treatment

or prevention of a C5-related disease, particularly PNH. In the context of the present disclosure, the present disclosure is directed to the treatment or prevention of a C5-related disease, preferably PNH, in patients that has been treated with one pharmaceutical product useful for the treatment or prevention of the C5-related disease, preferably PNH, and wherein the intravenously administered loading dose of the anti-C5 antibody is administered to the subject after the final dose of the pharmacological product. Accordingly, the herein described dosage and administration regimen of the anti-C5 antibody, particularly of the anti-C5 antibody Crovalimab, is given to patients who has been treated with one pharmaceutical product useful for the treatment or prevention of the C5-related disease, preferably PNH. As explained in more detail below, the pharmaceutical product useful for the treatment of the C5-related disease which has been given to the subjects before the start of the claimed dosage and treatment regimen refers to the anti-C5 antibody Eculizumab or Ravulizumab, preferably to the anti-C5 antibody Eculizumab.

As shown in the appended Examples, the dose and treatment regimen as defined in the claims ensure a sustained and consistent blockade of terminal complement activity (with approximately more than 95% of subjects being maintained above the target threshold of 100 µg/ml); see Figs. 4 and 7. Further, a terminal complement inhibition was achieved immediately following the initial dose and generally maintained throughout dosing interval; see Fig. 8. Further, the dosage and treatment regimen of the present disclosure also ensure sufficient reserve of free binding sites for the majority of the dosing interval in both treatment-naïve and Eculizumab pre-treated patients; see Figure 2. Crovalimab and Eculizumab bind to different C5 epitopes and thus DTDCs are expected to be formed. DTDCs are expected to develop if patients are exposed to Crovalimab and Eculizumab simultaneously (see Figure 5), during a switch period from Eculizumab to the anti-C5 antibody Crovalimab. The formation of DTDCs may contribute to increase Crovalimab clearance and may cause potential risks such as type III hypersensitivity reactions as explained above. In patients switching from Eculizumab to Crovalimab, the dose and treatment regimen as defined in the claims is expected to reduce the formation of DTDCs; see Figures 3 and 12. Accordingly, the herein described dosage and treatment regimen outlines a novel and improved dosage regimen of anti-C5 antibodies, preferably of the anti-C5 antibody Crovalimab for the treatment or prevention of a C5-related disease, preferably PNH. The safety and

therapeutic efficacy of the claimed dosage and treatment regimen is further reported in Figures 9 to 11.

Accordingly, the present disclosure relates to an anti-C5 antibody, preferably the anti-C5 antibody Crovalimab, for use in a method of treating or preventing a C5-related disease in a subject, preferably a subject with a body weight of equal or greater than 100 kg, wherein the method comprises the consecutive steps of:

(a) intravenously administering a loading dose of 1500 mg of the anti-C5 antibody to the subject once, followed by subcutaneously administering at least one loading dose of 340 mg of the anti-C5 antibody to the subject; and

(b) subcutaneously administering at least one maintenance dose of 1020 mg of the anti-C5 antibody to the subject.

In one aspect, the present disclosure relates to use of an anti-C5 antibody in the manufacture of a medicament for treating or preventing a C5-related disease in a subject, wherein:

(i) a loading dose of 1500 mg of the anti-C5 antibody is to be intravenously administered to the subject once;

(ii) a loading dose of 340 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 1 day after the start of the intravenous administration of the anti-C5 antibody;

(iii) a loading dose of 340 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 1 week, 2 weeks and 3 weeks after the start of the intravenous administration of the anti-C5 antibody once weekly;

(iv) a maintenance dose of 1020 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 4 weeks after the start of the intravenous administration of the anti-C5 antibody; and

(v) step (iv) is to be repeated several times with time intervals of 4 weeks,

wherein the anti-C5 antibody is Crovalimab, and

wherein the C5-related disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis (RA), lupus nephritis, ischemia-reperfusion injury, atypical hemolytic uremic syndrome (aHUS), dense deposit disease (DDD), macular degeneration, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, thrombotic thrombocytopenic purpura (TTP), spontaneous fetal loss, Pauci-immune vasculitis, epidermolysis bullosa, recurrent fetal loss, multiple sclerosis (MS), traumatic brain injury, an injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis, refractory generalized myasthenia gravis (gMG), and neuromyelitis optica (NMO).

The “loading dose” refers to the dose of the anti-C5 antibody administered to the subject suffering from a C5-related disease, preferably PNH, at the beginning of the treatment, i.e. at the start of the treatment regimen. In pharmacokinetics (PK), a “loading dose” is an initial higher dose of a drug that may be given to a patient at the beginning of a course of treatment before dropping down to a lower dose. In the context of the present invention, the loading dose is firstly given to subjects to be treated by intravenous administration, followed by subcutaneous administration. In the context of the present invention, the loading dose is given once at a dose of 1500 mg. Accordingly, in the context of the present invention, a loading dose of a composition formulated for intravenous administration is given intravenously once to the subject before one loading dose or more loading doses of a pharmaceutical composition formulated for subcutaneous administration is/are given subcutaneously.

In the context of the present invention, a loading dose or more loading doses of the anti-C5 antibody is/are subcutaneously administered to the patients after the intravenous administration of a loading dose of 1500 mg of the anti-C5 antibody. The subcutaneously administered loading dose(s) is (are) subcutaneously administered at a dose of 340 mg of the anti-C5 antibody at least once to the subject 1 day to 3 weeks (21 days) after the start of the intravenous administration of the anti-C5 antibody. Accordingly, in the context of the present invention, a loading dose of 340 mg of the anti-C5 antibody is subcutaneously administered at least once to the subject 1, 2, 3, 4,

CLAIMS

1. Use of an anti-C5 antibody in the manufacture of a medicament for treating or preventing a C5-related disease in a subject, wherein:

   (i) a loading dose of 1500 mg of the anti-C5 antibody is to be intravenously administered to the subject once;

   (ii) a loading dose of 340 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 1 day after the start of the intravenous administration of the anti-C5 antibody;

   (iii) a loading dose of 340 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 1 week, 2 weeks and 3 weeks after the start of the intravenous administration of the anti-C5 antibody once weekly;

   (iv) a maintenance dose of 1020 mg of the anti-C5 antibody is to be subcutaneously administered to the subject 4 weeks after the start of the intravenous administration of the anti-C5 antibody; and

   (v) step (iv) is to be repeated several times with time intervals of 4 weeks,

   wherein the anti-C5 antibody is Crovalimab, and

   wherein the C5-related disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis (RA), lupus nephritis, ischemia-reperfusion injury, atypical hemolytic uremic syndrome (aHUS), dense deposit disease (DDD), macular degeneration, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, thrombotic thrombocytopenic purpura (TTP), spontaneous fetal loss, Pauci-immune vasculitis, epidermolysis bullosa, recurrent fetal loss, multiple sclerosis (MS), traumatic brain injury, an injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis, refractory generalized myasthenia gravis (gMG), and neuromyelitis optica (NMO).

2. The use according to claim 1, wherein the subject had received prior treatment with at least one pharmacological product useful for the treatment or prevention of the C5-related disease, wherein the loading dose of 1500 mg of the anti-C5 antibody to be intravenously administered is to be administered to the subject after the final dose of the pharmacological product, wherein the pharmacological product comprises an siRNA targeting C5 mRNA, or an anti-C5 antibody which

is different from the anti-C5 antibody comprised in the composition for subcutaneous or intravenous injection.

3. The use according to claim 2, wherein the loading dose of 1500 mg of the anti-C5 antibody to be intravenously administered is to be administered to the subject on the third day or after 3 days after administration of the final dose of the pharmacological product.

4. The use according to claim 2 or claim 3, wherein the pharmacological product comprises Eculizumab or Ravulizumab.

5. The use according to any one of claims 1 to 4, wherein the subject has a body weight of equal or greater than 100 kg.

6. The use according to any one of claims 1 to 5, wherein the anti-C5 antibody concentration that had been determined in a biological sample of said subject is 100 µg/ml or more.

7. The use according to any one of claims 1 to 5, wherein the hemolytic activity that had been determined in a biological sample of said subject is less than 10 U/mL.

8. The use according to claim 6 or claim 7, wherein the biological sample is a blood sample.

9. The use according to claim 6 or claim 7, wherein the biological sample is a red-blood sample.

10. The use according to any one of claims 1 to 9, wherein the C5-related disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), refractory generalized myasthenia gravis (gMG), and neuromyelitis optica (NMO).