[PTL4] WO 2007/106585

[PTL5] WO 2008/069889

[PTL6] WO 2010/054403

[PTL7] WO 95/29697

[PTL8] WO 2002/30985

[PTL9] WO 2004/007553

[PTL10] WO 2010/015608

[PTL11] WO 2009/125825

[PTL12] WO 2011/122011

[PTL13] WO 2011/111007

**Non Patent Literature**

**[0019]** [NPL1] Holers et al., Immunol. Rev. 223:300-316 (2008)

[NPL2] Dmytrijuk et al., The Oncologist 13(9):993-1000 (2008)

a[NPL3] Yeung et al., J Immunol. 182(12): 7663-7671 (2009)

[NPL4] Datta-Mannan et al., J Biol. Chem. 282(3):1709-1717 (2007)

[NPL5] Dall'Acqua et al., J. Immunol. 169(9):5171-5180 (2002)

**Summary**

**[0020]** The disclosure provides pharmaceutical compositions for use in the treatment or prevention of a C5-related disease and methods for treating or preventing a C5-related disease. The disclosure also provides dosages and administrations of anti-C5 antibody or pharmaceutical compositions containing the anti-C5 antibody.

**[0021]** The inventors of the disclosure investigated more effective and safer dosages and administrations of anti-C5 antibody for use in the treatment and/or prevention of C5-related diseases, which can also reduce burden on patients. From such standpoints, the inventors found that administration in a lower dose at least once before administration in high doses at long intervals is favorable for the treatment or prevention of a C5-related disease by subcutaneous admininstration of anti-C5 antibody.

**[0022]** The inventors also discovered suitable conditions for dosing, including a dose of the antibody, frequency and intervals of the subcutaneous administrations.

**[0022a]** In one aspect, the present disclosure refers to the use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease, wherein the composition is formulated for subcutaneous injection, comprises the anti-C5 antibody, wherein the composition is to be subcutaneously administered in two phases after one dose of another pharmaceutical composition is to be intravenously administered, wherein said another pharmaceutical composition is a pharmaceutical composition formulated for intravenous administration which comprises the anti-C5 antibody, wherein (i) a first subcutaneous administration of a first phase is to be administered after the intravenous administration and the first subcutaneous administration of the first

phase is to be administered any of 0 day (i.e., within 24 hours), 1 day, or 2 days after the administration of the pharmaceutical composition for intravenous administration, and(ii) an antibody dose for the intravenous administration is 100 to 2,000 mg, wherein for the subcutaneous administration in two phases, in both phases there is an interval between every two subcutaneous administrations, wherein each phase comprises at least one interval, wherein in the first phase (i) the interval is shorter than the interval in the second phase and is 5 to 14 days, and (ii) a dose of the antibody per administration is lower than a dose of the antibody per administration in the second phase and is 50 mg to 350 mg, and wherein in the second phase (i) the dose of the antibody per administration is 650 to 700 mg, and (ii) the interval is 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, or 35 days, and further wherein the anti-C5 antibody comprises a heavy chain variable domain (VH) that comprises a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 3, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 4, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 5 and a light chain variable domain (VL) that comprises a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 7, a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 8, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 9.

**[0022b]** In another aspect, the present disclosure refers to the use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease, wherein the composition is formulated for intravenous administration, comprises the anti-C5 antibody, wherein, after one dose of the composition is to be intravenously administered, another pharmaceutical composition is to be subcutaneously administered in two phases, wherein said another pharmaceutical composition is a pharmaceutical composition formulated for subcutaneous injection which comprises the anti-C5 antibody, wherein (i) a first subcutaneous administration of a first phase is to be administered after the intravenous administration and the first subcutaneous administration of the first phase is to be administered any of 0 day (i.e., within 24 hours), 1 day, or 2 days after the administration of the pharmaceutical composition for intravenous administration, and (ii) an antibody dose for the intravenous administration is 100 to 2,000 mg,wherein for the subcutaneous administration in two phases, in both phases there is an interval between every two subcutaneous administrations, and each phase comprises at least one interval, wherein in the first phase (i) the interval is shorter than the interval in the second phase and is 5 to 14 days, and (ii) a dose of the antibody per administration is lower than a dose of the antibody per administration in the second phase and is 50 mg to 350 mg, and wherein in the second phase (i) the dose of the antibody per administration is 650 to 700 mg, and (ii) the interval is 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, or 35 days, and further wherein the anti-C5 antibody comprises a

heavy chain variable domain (VH) that comprises a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 3, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 4, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 5 and a light chain variable domain (VL) that comprises a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 7, a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 8, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 9.

**[0023]** Specifically, the present disclosure relates to:

[1] A pharmaceutical composition for use in a method of treatment or prevention of a C5-related disease, which is formulated for subcutaneous injection, and comprises an anti-C5 antibody, wherein the composition is subcutaneously administered in two phases, wherein in both phases there is an interval between every two subcutaneous administrations, wherein each phase comprises at least one interval, and wherein in the first phase

[CLAIMS]
[Claim 1]
Use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease,
wherein the composition is formulated for subcutaneous injection, comprises the anti-C5 antibody,
wherein the composition is to be subcutaneously administered in two phases after one dose of another pharmaceutical composition is to be intravenously administered,
wherein said another pharmaceutical composition is a pharmaceutical composition formulated for intravenous administration which comprises the anti-C5 antibody,
wherein
(i) a first subcutaneous administration of a first phase is to be administered after the intravenous administration and the first subcutaneous administration of the first phase is to be administered any of 0 day (i.e., within 24 hours), 1 day, or 2 days after the administration of the pharmaceutical composition for intravenous administration, and
(ii) an antibody dose for the intravenous administration is 100 to 2,000 mg,
wherein for the subcutaneous administration in two phases,
in both phases there is an interval between every two subcutaneous administrations,
wherein each phase comprises at least one interval,
wherein in the first phase
(i) the interval is shorter than the interval in the second phase and is 5 to 14 days, and
(ii) a dose of the antibody per administration is lower than a dose of the antibody per administration in the second phase and is 50 mg to 350 mg, and wherein in the second phase
(i) the dose of the antibody per administration is 650 to 700 mg, and
(ii) the interval is 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, or 35 days, and
further wherein the anti-C5 antibody comprises
a heavy chain variable domain (VH) that comprises a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 3, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 4, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 5 and
a light chain variable domain (VL) that comprises a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 7, a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 8, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 9.

[Claim 2]
Use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease,

wherein the composition is formulated for intravenous administration, comprises the anti-C5 antibody,

wherein, after one dose of the composition is to be intravenously administered, another pharmaceutical composition is to be subcutaneously administered in two phases,

wherein said another pharmaceutical composition is a pharmaceutical composition formulated for subcutaneous injection which comprises the anti-C5 antibody,

wherein

(i) a first subcutaneous administration of a first phase is to be administered after the intravenous administration and the first subcutaneous administration of the first phase is to be administered any of 0 day (i.e., within 24 hours), 1 day, or 2 days after the administration of the pharmaceutical composition for intravenous administration, and

(ii) an antibody dose for the intravenous administration is 100 to 2,000 mg,

wherein for the subcutaneous administration in two phases, in both phases there is an interval between every two subcutaneous administrations, and each phase comprises at least one interval,

wherein in the first phase

(i) the interval is shorter than the interval in the second phase and is 5 to 14 days, and

(ii) a dose of the antibody per administration is lower than a dose of the antibody per administration in the second phase and is 50 mg to 350 mg, and wherein in the second phase

(i) the dose of the antibody per administration is 650 to 700 mg, and

(ii) the interval is 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, 33 days, 34 days, or 35 days, and

further wherein the anti-C5 antibody comprises

a heavy chain variable domain (VH) that comprises a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 3, a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 4, and a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 5 and

a light chain variable domain (VL) that comprises a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 7, a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 8, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 9.

[Claim 3]

The use of claim 1 or 2, wherein the interval in the first phase is any of 5 days, 6 days, 7 days, or 8 days.

[Claim 4]

The use of any one of claims 1 to 3, wherein subcutaneous administration in the first phase is carried out once every week (weekly).

[Claim 5]

The use of any one of claims 1 to 4, wherein the interval in the second phase is any of 27 days, 28 days, or 29 days.

[Claim 6]
The use of any one of claims 1 to 5, wherein subcutaneous administration in the first phase is carried out once every week (weekly) with the dose of the antibody of 340 mg.

[Claim 7]
The use of any one of claims 1 to 6, wherein the number of subcutaneous administrations in the first phase is 5 to 10.

[Claim 8]
The use of any one of claims 1 to 7, wherein subcutaneous administration in the second phase is carried out four-weekly or monthly with the dose of the antibody of 680 mg.

[Claim 9]
The use of any one of claims 1 to 8, wherein the antibody dose for the intravenous administration is 1,000 mg.

[Claim 10]
The use of any one of claims 1 to 9, wherein the pharmaceutical composition is for treatment or prevention of the disease in a subject who has been treated with at least one pharmacological product for use in treatment or prevention of the C5-related disease and the one dose of the pharmaceutical composition for intravenous administration is to be administered after administration of a final dose of the pharmacological product.

[Claim 11]
The use of claim 10, wherein the one dose of the pharmaceutical composition for intravenous administration is to be administered 3 or more days after the final dose of the pharmacological product.

[Claim 12]
The use of claim 10 or 11, 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 as defined in any one of claims 1 to 11.

[Claim 13]
The use of any one of claims 10 to 12, wherein the pharmacological product comprises eculizumab.

[Claim 14]
The use of any one of claims 1 to 13, wherein the anti-C5 antibody has pH-dependent binding characteristics.

[Claim 15]
The use of any one of claims 1 to 14, wherein the anti-C5 antibody comprised in the pharmaceutical composition formulated for subcutaneous injection and the pharmaceutical composition formulated for intravenous administration comprises
the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, and
the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6.

[Claim 16]
The use of claim 15, wherein the anti-C5 antibody further comprises
the modified human IgG1 heavy chain constant domain (CH) consisting of SEQ ID NO: 13, and
the human light chain constant domain (CL) consisting of SEQ ID NO: 18.

[Claim 17]
The use of any one of claims 1 to 16, wherein the C5-related disease is any one selected from a group consisting of rheumatoid arthritis (RA); lupus nephritis; ischemia-reperfusion injury; paroxysmal nocturnal hemoglobinuria (PNH); atypical hemolytic uremic syndrome (aHUS); dense deposit disease (DDD); macular degeneration; hemolysis, elevated liver enzymes, and 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; injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); and neuromyelitis optica (NMO).

[Claim 18]
The use of claim 17, wherein the C5-related disease is paroxysmal nocturnal hemoglobinuria (PNH).

[Claim 19]
The use of claim 17, wherein the C5-related disease is atypical hemolytic uremic syndrome (aHUS).