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[PTL5] WO 2008/069889
[PTL6] WO 2010/054403
[PTL7] WO 95/29697
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[PTL9] WO 2004/007553
[PTL10] WO 2010/015608
[PTL11] WO 2009/125825
[PTL12] WO 2011/122011
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Non-Patent Literature

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[NPL2] Dmytrijuk et al., The Oncologist 13(9):993-1000 (2008)
[NPL3] Yeung et al., J Immunol. 182(12): 7663-7671 (2009)
[NPL4] Datta-Mannan et al., J Biol. Chem. 282(3):1709-1717 (2007)
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Summary ~~of Invention~~

[0020] The ~~invention~~ 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 ~~invention~~ disclosure also provides dosages and administrations of anti-C5 antibody or pharmaceutical compositions containing the anti-C5 antibody.

[0021] The inventors of the ~~invention~~ disclosure investigated effective dosages and administrations of anti-C5 antibody for use in the treatment and/or prevention of C5-related diseases. As a result, the inventors found that a plasma concentration of anti-C5 antibody rapidly increases to more than a therapeutically efficacious level by intravenously administering the antibody and the concentration is kept at the level by subcutaneously administrating the antibody after the intravenous administration.

[0022] The inventors also discovered suitable conditions for dosing, including a dose of the antibody, frequency and intervals of the intravenous administrations or subcutaneous administrations, an interval between the intravenous administration and the subcutaneous administration, and switching from other drugs.

[0022a] In one aspect, the present disclosure refers to a use of an anti-C5 antibody in the manufacture of a first and a second pharmaceutical compositions for treating or preventing a C5-related disease, wherein the first pharmaceutical composition is

formulated for intravenous injection, comprises the anti-C5 antibody, and is to be administered intravenously, wherein the second pharmaceutical composition is formulated for subcutaneous injection, comprises the anti-C5 antibody, and is to be administered subcutaneously, wherein administration of the first and the second pharmaceutical compositions is to be carried out in the order of one intravenous dose of the first pharmaceutical composition and two or more subcutaneous doses of the second pharmaceutical composition; wherein the C5-related disease is any one selected from the 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID NO: 18.

[0022b] In one aspect, the present disclosure refers to a use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease, wherein the pharmaceutical composition is formulated for subcutaneous injection, comprises the anti-C5 antibody, and is to be administered subcutaneously, wherein an initial dose of the pharmaceutical composition for subcutaneous injection is to be administered after a dose of another pharmaceutical composition is administered intravenously, and wherein the other pharmaceutical composition is formulated for intravenous injection and comprises the anti-C5 antibody; wherein administration of the pharmaceutical composition for subcutaneous injection is to be carried out in the order of one intravenous dose of the other pharmaceutical composition for intravenous injection and two or more subcutaneous doses of the pharmaceutical composition for subcutaneous injection; wherein the C5-related disease is any one selected from the 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID NO: 18.

[0022c] In yet another aspect, the present disclosure refers to a use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease, wherein the pharmaceutical composition is formulated for intravenous injection, comprises the anti-C5 antibody, and is to be administered intravenously, wherein a dose of the pharmaceutical composition for intravenous injection is to be administered before an initial dose of another pharmaceutical composition is administered subcutaneously, wherein the other pharmaceutical composition is formulated for subcutaneous injection and comprises the anti-C5 antibody; wherein administration of the pharmaceutical composition for intravenous injection is to be carried out in the order of one intravenous dose of the pharmaceutical composition for intravenous injection and two or more subcutaneous doses of the other pharmaceutical composition for subcutaneous injection; wherein the C5-related disease is any one selected from the 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID

NO: 18.

[0023] Specifically, the present ~~invention~~ disclosure relates to:

[1] A pharmaceutical composition for use in the treatment or prevention of a C5-related disease, wherein the composition is formulated for subcutaneous injection, comprises an anti-C5 antibody, and is administered subcutaneously, wherein the initial dose of the composition is administered after a dose of another pharmaceutical composition is administered intravenously, wherein the other pharmaceutical composition

Claims

[Claim 1]

Use of an anti-C5 antibody in the manufacture of a first and a second pharmaceutical compositions for treating or preventing a C5-related disease,

wherein the first pharmaceutical composition is formulated for intravenous injection, comprises the anti-C5 antibody, and is to be administered intravenously,

wherein the second pharmaceutical composition is formulated for subcutaneous injection, comprises the anti-C5 antibody, and is to be administered subcutaneously,

wherein administration of the first and the second pharmaceutical compositions is to be carried out in the order of one intravenous dose of the first pharmaceutical composition and two or more subcutaneous doses of the second pharmaceutical composition;

wherein the C5-related disease is any one selected from the 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and

wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID NO: 18.

[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 pharmaceutical composition is formulated for subcutaneous injection, comprises the anti-C5 antibody, and is to be administered subcutaneously,

wherein an initial dose of the pharmaceutical composition for subcutaneous injection is to be administered after a dose of another pharmaceutical composition is administered intravenously, and wherein the other pharmaceutical composition is formulated for intravenous injection and comprises the anti-C5 antibody;

wherein administration of the pharmaceutical composition for subcutaneous injection is to be carried out in the order of one intravenous dose of the other pharmaceutical

composition for intravenous injection and two or more subcutaneous doses of the pharmaceutical composition for subcutaneous injection;
wherein the C5-related disease is any one selected from the 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and
wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID NO: 18.
[Claim 3]
Use of an anti-C5 antibody in the manufacture of a pharmaceutical composition for treating or preventing a C5-related disease,
wherein the pharmaceutical composition is formulated for intravenous injection, comprises the anti-C5 antibody, and is to be administered intravenously,
wherein a dose of the pharmaceutical composition for intravenous injection is to be administered before an initial dose of another pharmaceutical composition is administered subcutaneously, wherein the other pharmaceutical composition is formulated for subcutaneous injection and comprises the anti-C5 antibody;
wherein administration of the pharmaceutical composition for intravenous injection is to be carried out in the order of one intravenous dose of the pharmaceutical composition for intravenous injection and two or more subcutaneous doses of the other pharmaceutical composition for subcutaneous injection;
wherein the C5-related disease is any one selected from the 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; and injury resulting from

myocardial infarction, cardiopulmonary bypass or hemodialysis; refractory generalized myasthenia gravis (gMG); neuromyelitis optica (NMO); and
wherein the anti-C5 antibody comprises the heavy chain variable domain (VH) consisting of the amino acid sequence of SEQ ID NO: 2, the light chain variable domain (VL) consisting of the amino acid sequence of SEQ ID NO: 6, the heavy chain constant domain (CH) consisting of the amino acid sequence of SEQ ID NO: 13, and the light chain constant domain (CL) consisting of the amino acid sequence of SEQ ID NO: 18.

[Claim 4]

The use of any one of claims 1 to 3,wherein the one intravenous dose of the pharmaceutical composition for intravenous injection is at 500 mg to 1,500 mg of the antibody.

[Claim 5]

The use of any one of claims 1 to 4,wherein the one intravenous dose of the pharmaceutical composition for intravenous injection is at 500 mg, 1,000 mg, or 1,500 mg of the antibody.

[Claim 6]

The use of any one of claims 1 to 5, wherein the two or more subcutaneous doses of the pharmaceutical composition for subcutaneous injection comprises doses at 170 mg to 2,000 mg of the antibody once every week, once every two weeks, or once every four weeks.

[Claim 7]

The use of any one of claims 1 to 6, wherein the two or more subcutaneous doses of the pharmaceutical composition for subcutaneous injection comprises (i) doses at 170 mg to 340 mg of the antibody once every week, or (ii) doses at 340 mg to 600 mg of the antibody once every two weeks, or (iii) doses at 600 mg to 2,000 mg of the antibody once every four weeks.

~~[Claim 1] A pharmaceutical composition for use in the treatment or prevention of a C5 related disease, wherein the composition is formulated for subcutaneous injection, comprises an anti-C5 antibody, and is administered subcutaneously, wherein the initial dose of the composition is administered after a dose of another pharmaceutical composition is administered intravenously, wherein the other pharmaceutical composition is formulated for intravenous injection and comprises the anti-C5 antibody.~~

~~[Claim 2] A pharmaceutical composition for use in the treatment or prevention of a C5 related disease, wherein the composition is formulated for intravenous injection, comprises an anti-C5 antibody, and is administered intravenously,~~

~~wherein a dose of the composition is administered before the initial dose of another pharmaceutical composition is administered subcutaneously, wherein the other pharmaceutical composition is formulated for subcutaneous injection and comprises the anti-C5 antibody.~~

[Claim ~~3~~8]

The ~~pharmaceutical composition~~use of any one of claims 1 to 7~~claim 1 or 2~~, wherein ~~the~~ an initial dose of the pharmaceutical composition for subcutaneous injection is to be administered on the same day as or 1 day to 28 days after the dose of the composition for intravenous injection.

[Claim 9]

The use of any one of claims 1 to 8, wherein the pharmaceutical composition for subcutaneous injection is to be given subcutaneously once every four weeks at a dose of 680 mg of the antibody.

[Claim 10]

The use of any one of claims 1 to 9, wherein the pharmaceutical composition for intravenous injection is to be given intravenously at a dose of 1,000 mg of the antibody.

~~[Claim 4] The pharmaceutical composition of any one of claims 1 to 3, wherein the composition for subcutaneous injection is given once every 3 to 42 days.~~

~~[Claim 5] The pharmaceutical composition of any one of claims 1 to 4, wherein the composition for the intravenous injection is administered twice or more times and is given once an hour to once every 14 days.~~

~~[Claim 6] The pharmaceutical composition of any one of claims 1 to 5, wherein the composition for subcutaneous injection is given at a dose of 17 to 6,000 mg of the antibody.~~

~~[Claim 7] The pharmaceutical composition of any one of claims 1 to 6, wherein the composition for intravenous injection is given at a dose of 50 to 5,000 mg of the antibody.~~

[Claim ~~8~~11]

The ~~pharmaceutical composition~~use of any one of claims 1 to ~~7~~10, wherein the pharmaceutical composition for intravenous injection and the pharmaceutical composition for subcutaneous injection are for treating or preventing ~~is for use in treatment or prevention of~~ the C5-related disease in a subject who has been treated with at least one pharmacological product for use in treatment or prevention of the disease, wherein the initial dose of the composition for intravenous injection is to be

administered after the final dose of the pharmacological product.

[Claim ~~9~~12]

The ~~pharmaceutical composition~~use of claim ~~8~~11, wherein the initial dose of the pharmaceutical composition for intravenous injection is to be administered on the third day or after 3 days after the final dose of the pharmacological product.

[Claim ~~10~~13]

The ~~pharmaceutical composition~~use of claim ~~8~~11 or ~~9~~12, 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.

[Claim ~~11~~14]

The ~~pharmaceutical composition~~use of any one of claims ~~8~~11 to ~~10~~13, wherein the pharmacological product comprises eculizumab or its derivative.

~~[Claim 12] A pharmaceutical composition for use in the treatment or prevention of a C5 related disease, wherein the composition is formulated for subcutaneous injection, comprises an anti-C5 antibody, and is administered subcutaneously at a dose of 17 to 6,000 mg of the antibody.~~

~~[Claim 13] A pharmaceutical composition for use in the treatment or prevention of a C5 related disease, wherein the composition is formulated for intravenous injection, comprises an anti-C5 antibody, and is administered intravenously at a dose of 50 to 5,000 mg of the antibody.~~

~~[Claim 14] The pharmaceutical composition of any one of claims 1 to 13, 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; and injury resulting from myocardial infarction, cardiopulmonary bypass or hemodialysis.~~