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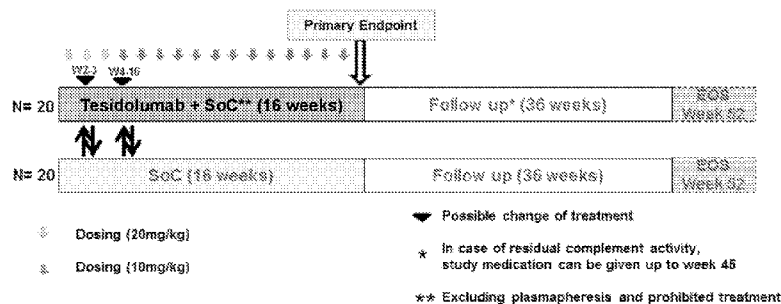
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(54) **Title:** USE OF C5 INHIBITORS IN TRANSPLANT ASSOCIATED MICROANGIOPATHY

Figure 1



(57) **Abstract:** The present invention relates to methods of using drugs, e.g. antibodies such as e.g. anti-C5 antibodies, disease that are capable of inhibiting the complement pathway for treating Transplant Associated Microangiopathy, in particular after hematopoietic cell transplantation.

Use of C5 inhibitors in Transplant Associated Microangiopathy**Background**

Transplant Associated Microangiopathy (TAM; or Transplant-Associated Thrombotic MicroAngiopathy (TA-TMA)) may be a complication of allogeneic hematopoietic cell transplantation (HSCT). TAM is a secondary microangiopathy associated with total body irradiation, high dose chemotherapy, viral reactivation and use of calcineurin inhibitors and rapamycin. TAM does not fall into the other categories of thrombotic microangiopathies (TMA), i.e. atypical hemolytic uremic syndrome (aHUS) or thrombotic thrombocytopenic purpura (TTP) (Chapin et al (2014) Clin Adv Hematol Oncol; 12(9): 565-73). The exact mechanism of TAM is poorly understood, but is thought to involve initial complement activation and C5-dependent effector mechanisms, which also lead to immunoglobulin consumption. The trigger appears to be endothelial cell damage, leading to a prothrombotic state in the microvasculature. TAM can give rise to renal, gastrointestinal and neurological dysfunction depending on the area of the vascular bed involved. TAM is associated with high morbidity and mortality, with some estimates of associated mortality as high as 80% (Chapin et al 2014, *ibid*). Complement involvement is suggested by recent clinical data with the C5 targeted antibody eculizumab. Preliminary data indicates that 4 of 6 subjects undergoing HSCT procedures had a beneficial response after eculizumab administration (Jodele et al (2014) Biol Blood Marrow Transplant; 20(4): 518-25). As of March 2015, 25 patients have been reported to have undergone eculizumab treatment with mixed results. Positive response in the published cases seems to be associated with low body weight, high dose per weight and absence of severe acute graft versus host disease.

Therefore there is a need for an improved therapy for treating or preventing TAM, in particular when associated with cell transplantation, e.g. Stem Cell Transplantation (TAM-SCT) or Hematopoietic Stem Cell Transplantation (TAM-HSCT).

Summary of the Invention

The present invention relates to methods of using drugs, e.g. antibodies such as e.g. anti-C5 antibodies, that are capable of inhibiting the complement pathway for use in treating Transplant Associated Microangiopathy after transplantation, in particular after cell transplantation, e.g. after precursor cell transplantation (TAM-PCT) or hematopoietic precursor cell transplantation (TAM-HPCT), in a subject in need thereof

In particular it refers to specific dosing regimens of such C5 inhibitors, e.g. comprising a first induction phase optionally followed by a maintenance period, wherein the maintenance dose is optionally lower than the induction dose.

According to the invention, there is provided:

- 1.1 A C5 inhibitor, e.g. anti-C5 antibody, e.g. Coversin, for use in prevention or treatment of Transplant Associated Microangiopathy (TAM), e.g. TAM after cell transplantation, in a patient in need thereof.
- 1.2 The C5 inhibitor as defined under 1.1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 50mg/kg, e.g. 20mg/kg; or at doses of about 800mg to about 2000mg, e.g. about 1000mg to about 2000mg.
- 1.3 The C5 inhibitor as defined under 1.1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 30mg/kg, e.g. 10mg/kg; or at doses of about 400mg to about 1000mg, e.g. about 500mg to about 1000mg.
- 1.4 The C5 inhibitor as defined under 1.1 to 1.3, wherein the C5 inhibitor is administered to a patient in need thereof during a period comprised between 1 week and 8 weeks, e.g. 3 weeks or 4 weeks.
- 1.5 The C5 inhibitor as defined under 1.1 to 1.3, wherein the C5 inhibitor is administered to a patient in need thereof during a period comprised between 1 month and 11 months, e.g. 4 or 5 months.
- 1.6 The C5 inhibitor as defined under 1.1, 1.2. or 1.3., wherein the C5 inhibitor is administered to a patient in need thereof first at an induction dose during an induction phase and thereafter at a maintenance dose during a maintenance period, wherein optionally the maintenance dose is lower than the induction dose.
- 1.7 The C5 inhibitor as defined under 1.6, wherein the induction dose is about 50mg/kg, e.g. 20mg/kg; or at doses of about 800mg to about 2000mg, e.g. about 1000mg to about 2000mg.
- 1.8 The C5 inhibitor as defined under 1.6 or 1.7, wherein the induction phase is comprised between 1 week and 8 weeks, e.g. 3 weeks or 4 weeks.
- 1.9 The C5 inhibitor as defined under 1.6 to 1.8, wherein the maintenance dose is about 30mg/kg, e.g. 10mg/kg; or at doses of about 400mg to about 1000mg, e.g. about 500mg to about 1000mg.
- 1.10 The C5 inhibitor as defined under 1.6 to 1.9, wherein the maintenance period is comprised between 1 month and 11 months, e.g. 4 or 5 months.
- 1.11 The C5 inhibitor as defined under 1.1 to 1.10 wherein the C5 inhibitor is administered weekly.
- 1.12 The C5 inhibitor as defined under 1.1 to 1.11 wherein the C5 inhibitor is administered until hematologic signs of TAM are resolved.
- 1.13 The C5 inhibitor as defined under 1.1 to 1.12 for use in prevention or treatment of TAM after Precursor Cell Transplantation (TAM-PCT) or Hematopoietic Precursor Cell Transplantation (TAM-HPCT) or after allogeneic Hematopoietic Stem cCell Transplantation (TAM-HSCT).

1.14 The C5 inhibitor as defined under 1.1. to 1.13, that is selected from the group consisting of tesidolumab, eculizumab, 305 variant antibodies and a homologous antibody thereof as herein defined, e.g. an antibody homologous to tesidolumab, e.g. is tesidolumab.

2.1 A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT or allogeneic TAM-HSCT in a subject that has undergone transplantation such as HSCT, comprising the steps of

- a. measuring total complement activity (CH50) in a sample of said subject and
- b. administering tesidolumab, e.g. in a regime as defined under any one of 1.1 to 1.14.

2.2 A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT or allogeneic TAM-HSCT in a subject that has undergone transplantation such as HSCT, comprising the steps of

- a. measuring total complement activity (CH50) in a sample of said subject and
- b. administering an C5 inhibitor, e.g. an anti-C5 antibody, in a regime as defined under any one of 1.1 to 1.14.

2.3 A method for treating or preventing TAM, e.g. TAM after cell transplantation, comprising administering to the patient in need thereof a therapeutic amount of a C5 inhibitor according to the use as defined under any one of 1.1 to 1.14.

2.4 A method for treating or preventing TAM, e.g. TAM after cell transplantation, comprising administering to the patient in need thereof a therapeutic amount of tesidolumab or a homologous antibody thereof as herein defined.

2.5 A method as defined under any one of 2.1 to 2.4, wherein the C5 inhibitor is Coversin or an anti-C5 antibody, e.g. is selected from the group consisting of tesidolumab, eculizumab, 305 variant antibodies and a homologous antibody thereof as herein defined, e.g. an antibody homologous to tesidolumab, e.g. is tesidolumab.

3.1 Use of a C5 inhibitor, e.g. anti-C5 antibody, for the preparation of a medicament for use in prevention or treatment of TAM, e.g. TAM after cell transplantation, e.g. TAM after Precursor Cell Transplantation (TAM-PCT) or Hematopoietic Precursor Cell Transplantation (TAM-HPCT) or after allogeneic Hematopoietic Stem Cell Transplantation (TAM-HSCT).

3.2 Use of a C5 inhibitor, e.g. anti-C5 antibody, for the preparation of a medicament for use in prevention or treatment of TAM, wherein the C5 inhibitor, e.g. anti-C5 antibody, is administered according to a dose or dosing regimen as defined under 1.2. to 1.12 above.

3.3 Use of a C5 inhibitor, e.g. Coversin or an anti-C5 antibody, for the preparation of a medicament as defined under 3.1 or 3.2 above, wherein the C5 inhibitor is selected from the group consisting of tesidolumab, eculizumab, a 305 variant antibody and a homologous antibody thereof as herein defined, e.g. an antibody homologous to tesidolumab, e.g. is tesidolumab.

Description of the Figure

Figure 1 shows the study design of a randomized, SoC-controlled, open-label, multi-center study in patients with TAM after hematopoietic precursor cell transplantation (HPCT) from a related or unrelated donor. The study consists of up to 28 days of screening period, 16 weeks treatment period that can be extended to maximum of total 45 weeks (in case of inadequate suppression of serum complement after 16 weeks), 36 weeks follow up, and end of study visit (EOS) at week 52.

Detailed Description

Unless otherwise stated, terms are to be understood according to conventional usage by those of ordinary skill in the art.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, e.g., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, or up to 10%, or up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

As used herein, the term "treating" means the administration of a composition to a subject, who has a disorder as described herein, with the purpose to cure, alleviate, relieve, remedy, prevent, or ameliorate the disorder, the symptom of the disorder, the disease state secondary to the disorder, or the predisposition toward the disorder.

As used herein, the term "therapeutically effective amount" or "effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, e.g., healing of chronic conditions or in an increase in rate of healing of such conditions, or in a reduction in aberrant conditions. This includes both therapeutic and prophylactic treatments. Accordingly, the compounds can be used at very early stages of a disease, or before early onset, or after significant progression. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone.

The terms "individual", "host", "subject", and "patient" are used interchangeably to refer to an animal that is the object of treatment, observation and/or experiment. In general, such individual, host, subject or patient is a human, though other mammals are within the scope of the invention.

Disease

As herein defined, TAM is meant for Transplant Associated Microangiopathy; can also be named Transplant-Associated Thrombotic MicroAngiopathy (TA-TMA).

According to the invention, the targeted diseases are TAM and in particular TAM after (or as a complication of) solid transplantation or after (or as a complication of) cell transplantation, e.g. Stem Cell Transplantation (TAM-SCT), e.g. Precursor Cell Transplantation (TAM-PCT), e.g. Hematopoietic Precursor Cell Transplantation (TAM-HPCT), e.g. Hematopoietic Stem Cell Transplantation (TAM-HSCT).

The cell transplantation herein refers to autologous cell transplantation (the donor is the patient that receives his or her own stem cells), or allogeneic cell transplantation (the patient receives the stem cells from another subject).

In particular the invention concerns subjects that have undergone transplantation, e.g. cell transplantation, e.g. Precursor or Stem Cell Transplantation, e.g. Hematopoietic Precursor Cell Transplantation or Hematopoietic Stem Cell Transplantation, in particular HSCT, e.g. autologous or allogeneic HSCT is disclosed.

Risk factors associated in retrospective studies with the development of TAM after allogeneic HSCT include medications used in the course of transplant and infectious complications. Conditioning agents including busulfan, fludarabine, cisplatin, and radiation may increase the risk of later TAM-HSCT. Other medications commonly reported to be associated with TAM-HSCT include the calcineurin inhibitors tacrolimus and cyclosporine and the newer mammalian target of rapamycin (mTOR) inhibitors. Viral infections are often considered to be a "trigger" for TAM-HSCT, as patients showing signs of small vessel injury can also have concomitant infections such as CMV, adenovirus, parvovirus B19, HHV-6, and BK virus.

Compositions

In one aspect, there is provided a drug, e.g. antibody, capable of inhibiting the complement pathway, e.g. an anti-C5 antibody, for use for treating Transplant Associated Microangiopathy (TAM) after transplantation (or as a complication of transplantation), e.g. solid transplantation or cell transplantation, e.g. after Precursor Cell Transplantation (TAM-PCT) or Stem Cell Transplantation (TAM-SCT), e.g. after Hematopoietic Precursor Cell Transplantation (TAM-HPCT) or Hematopoietic Stem Cell Transplantation (TAM-HSCT) in a subject, in particular a subject that has undergone Stem Cell Transplantation or Hematopoietic Stem Cell Transplantation, e.g. allogeneic HSCT.

In a certain aspect, the drug may comprise a complement inhibitor, e.g. Coversin or an antibody capable of inhibiting the complement pathway, e.g. an anti-C5 antibody capable of inhibiting the complement pathway. In one aspect, the antibody may comprise a monoclonal antibody capable of inhibiting the complement pathway. In other aspects, the drug may comprise a human monoclonal antibody or a humanized monoclonal antibody capable of inhibiting the complement pathway, e.g. a human monoclonal or humanized monoclonal anti-C5 antibody capable of inhibiting the complement pathway.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of the membrane attack complex (MAC). For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., US Patent 6,534,058; US patent application US 20030129187; and US Patent 5,660,825). WO2010015608 and WO199529697 teach antibodies which binds to C5 and inhibit cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

In certain embodiments, said antibody is a fully human Fc-silentTM IgG1/lambda monoclonal antibody that targets C5, such as tesidolumab. SEQ ID Nos: 1-10 of Table 1 show the heavy and light chain CDR, heavy and light chain variable domain and full heavy and light chain sequences of tesidolumab. In an alternative embodiment, the antibody may be a humanized monoclonal antibody such as eculizumab, available from Alexion Pharmaceuticals, and sold under the trade name Soliris®. SEQ ID Nos: 11-20 of Table 1 show the heavy and light chain CDR, heavy and light chain variable domain and full heavy and light chain sequences of eculizumab. In an alternative embodiment, the antibody fragment is pexelizumab, a Fab fragment of eculizumab. In an alternative embodiment, the antibody may be selected from the optimized variants of the 305 antibody as described in Tables 7 and 8 of WO2016098356A1 (as herein defined as "305 variant antibodies"; SEQ ID Nos: 21-84 of Table 1 show the heavy and light chain CDR, and heavy and light chain variable domain sequences of the 305 variant antibodies).

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, or SEQ ID NO:6. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 7 and the light chain variable region consists of SEQ ID NO: 8. In certain embodiments, the pharmaceutical composition comprises tesidolumab. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 9 and the light chain consists of SEQ ID NO: 10.

In another embodiment of the invention, the anti-C5 antibody is a homologous antibody of eculizumab (eculizumab homologous antibody), tesidolumab (tesidolumab homologous antibody) or a 305 variant antibody, e.g. an isolated recombinant homologous antibody

According to the invention, there is also provided a functional protein comprising an antigen binding portion thereof that specifically bind to a C5 protein, and cross compete with eculizumab, tesidolumab or a 305 variant antibody. In some embodiments, the present invention provides isolated anti-C5 antibodies or antigen binding fragments thereof that bind to the same epitope of C5 protein than eculizumab, tesidolumab or a 305 variant antibody. In some embodiments, the antibodies of the invention are isolated monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated human or humanized monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated chimeric antibodies that specifically bind to a C5 protein. In some embodiments, the anti-C5 antibodies are single chain antibodies, e.g. Fab fragments, e.g. scFv.

The homologous antibody may retain the desired functional properties of binding to C5 and inhibiting cleavage of C5 into C5a and C5b, in particular the homologous antibody may retain the binding efficacy of the corresponding tesidolumab, eculizumab or 305 variant antibody.

Thus according to the invention the anti-C5 antibody may have full length heavy and light chain amino acid sequences, variable region heavy and light chain amino acid sequences or heavy and light chain CDR amino acid sequences that are homologous to the amino acid sequences of tesidolumab as described herein, or eculizumab or a 305 variant antibody.

In some embodiments, the homologous antibody comprises some of the heavy and light chain amino acid sequences, in particular the heavy and light chain CDR amino acid sequences, that are 100% identical to the corresponding tesidolumab, eculizumab or 305 variant antibody sequences, and the other amino acid sequences that are about 80 to 99% identical to the corresponding tesidolumab, eculizumab or 305 variant antibody sequences.

In an example, the invention provides an isolated recombinant antibody (or a functional protein comprising an antigen binding portion thereof) comprising a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises an amino acid sequence that is at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence of SEQ ID NO: 7; the light chain variable region comprises an amino acid sequence that is at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence of SEQ ID NO: 8, as herein above defined.

In a further example, the invention provides an isolated recombinant antibody, (or a functional protein comprising an antigen binding portion thereof) comprising a full length heavy chain and a full length light chain, wherein: the full length heavy chain comprises an amino acid sequence that is at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence of SEQ ID NO: 9; the full length light chain comprises an amino acid sequence that is at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence of SEQ ID NO: 10.

As used herein, the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i. e., % identity = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent

identity between two sequences can be accomplished using a mathematical algorithm, as described below.

The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:1 1-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol. Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Furthermore, in another embodiment, modifications can be made to improve one or more binding properties (e.g., affinity) of the antibody of interest, known as "affinity maturation". Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated *in vitro* or *in vivo* assays. Conservative modifications can be introduced and the mutations may be amino acid substitutions, additions or deletions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered. As such, the invention provides isolated anti-C5 monoclonal antibodies, or a functional antigen binding portion thereof, consisting of a heavy chain variable region having: a VH CDR1 region having an amino acid sequence of SEQ ID NO: 1 or an amino acid sequence having one, two, three or four amino acid substitutions, deletions or additions as compared to SEQ ID NO: 1; a VH CDR2 region having an amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NO:2; a VH CDR3 region having an amino acid sequence of SEQ ID NO: 3, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NO: 3; a VL CDR1 region having an amino acid sequence of SEQ ID NO: 4, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NO: 4; a VL CDR2 region having an amino acid sequence of SEQ ID NO: 5, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NO: 5; and a VL CDR3 region having an amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NO: 6.

In other aspects, the complement inhibitor is Coversin. Coversin, in development by Akari Therapeutics, is a recombinant small protein derived from the saliva of the tick *Ornithodoros moubata*. Coversin binds to complement factor C5 and inhibits activation of C5, the release of C5a and the formation of the membrane attack complex.

Methods

Disclosed is a method of treating Transplant Associated Microangiopathy after as a complication of transplantation, e.g. solid transplantation or cell transplantation, e.g. Stem Cell Transplantation (TAM-

SCT), e.g. Precursor Cell Transplantation (TAM-PCT), e.g. Hematopoietic Precursor Cell Transplantation (TAM-HPCT), e.g. Hematopoietic Stem Cell Transplantation (TAM-HSCT), e.g. autologous or allogeneic hematopoietic stem cell transplantation in a subject in need thereof.

The method may comprise the step of administering a drug, e.g. Coversin, or an antibody capable of inhibiting terminal complement, e.g. an anti-C5 antibody. The terminal complement may comprise a monoclonal antibody capable of inhibiting terminal complement, or in another embodiment, a human or humanized monoclonal antibody capable of inhibiting terminal complement. In one embodiment, the antibody may be tesidolumab or a homologous antibody thereof as herein above defined. In another embodiment, the antibody may be eculizumab or a homologous antibody thereof as herein above defined. In another embodiment the antibody may be a 305 variant antibody as described in Tables 7 and 8 of WO2016098356A1 ("305 variant antibody").

Subject

In some embodiments, the subject is a human e.g. a patient. The patient may be an adult of any weight or any patient with a body weight that is greater than or equal to 40kg. Alternatively, the patient may have a body weight that is less than 40kg but greater than or equal to 30kg, a body weight that is less than 30kg but greater than or equal to 20kg, a body weight that is less than 20kg but greater than or equal to 10kg.

In some embodiments, the subject is a child $\geq$ two years old. In an alternative embodiment, the subject is a child greater than 2 years old but less than 12 years old. In an alternative embodiment, the subject is older than or equal to 12 years old. In an alternative embodiment, the subject is an adult older than or equal to 16 years old, e.g. 18 years old.

Suitable methods for identifying a subject as one having, suspected of having or at risk for developing TAM-PCT or TAM-HSCT are known in the art of medicine. Symptoms include systemic vascular injury, kidney damage, serotitis, pulmonary hypertension, multisystem organ failure. Thus a variety of tests can be performed on a subject to determine whether the subject has:

- Elevated lactate dehydrogenase (any elevation above normal range);
- Thrombocytopenia with platelet count $< 50 \times 10^9/L$ or greater than $>50\%$ decrease in platelet count from the highest value achieved after transplant;
- Anemia below lower limit of normal or anemia requiring transfusion support as per center standard;
- Schistocytes on peripheral blood smear (>2 per HPF) or histologic evidence of Microangiopathy; and/or
- Absence of coagulopathy (no uncompensated disseminated intravascular coagulation, DIC) at screening.

Prior to treatment the subject may receive *N. meningitides* vaccine(s). Such vaccine(s) should take into account the serotypes prevalent in the geographic areas in which the subject is being treated. In

addition, subjects less than 18 years old may be vaccinated for the prevention of *S. pneumoniae* and *H. influenzae* type b.

Dosing regimen

Previous studies in which patients diagnosed with thrombotic Microangiopathy after HSCT utilized a treatment regimen that followed the classic dosing schedule used in aHUS (900 mg infusions of eculizumab every week during 4 weeks, followed by a maintenance dose of 1200 mg every 14 days)(Legendre CM et al (2013) N. Engl. J. Med, 368: 21169). However in some studies, a lower initial dose was used based on the patient's weight and then this was increased. For example, Okano M et al ((2014) Bone Marrow Transplantation, 49: 1116-8) administered eculizumab to a patient with TA-TMA according to the dose for aHUS (600 mg weekly as an initial dose based on the patient's body weight – 23kg). The dose was then increased for the next 3 doses to 900mg every week. The dose of 6th eculizumab administration was decreased to 600mg, and then for the 7th-14th (last) administration, eculizumab was administered every two weeks.

Jodele S *et al* (2014) Biol. Blood Marrow Transplant, 20: 518-525 describe a dosing regime in which dose adjustments were based on the trough level of eculizumab and whether this was deemed therapeutic. Patients weighing <40kg started with 600mg i.v. as a first dose. Patients weighing >40kg started with 900mg i.v. as a first dose. Subsequent dose adjustments were as follows:

- If a trough level was reported as therapeutic before the next weekly dose, the same induction dose was continued weekly.
- If the patient was due for the next weekly dose and the eculizumab trough concentration was sub therapeutic, the dose was increased by 300mg/dose.
- If a sub therapeutic result was reported 4 to 5 days after the prior dose, an extra induction dose was given when the result was obtained.
- If results were not available for dose adjustment, the same eculizumab induction dose was continued weekly until the trough eculizumab concentration was documented to be above the therapeutic level.

Lab markers of TMA were documented daily during inpatient stay and at least twice weekly in the outpatient setting. Weekly induction therapy was continued until patients achieved a hematologic TMA response and had documented eculizumab levels >99µg/ml, at which point a maintenance schedule was started. The criteria for stopping eculizumab included normalization of hematologic TMA parameters and improvement in renal function.

According to the invention, there is provided an improved dosing regimen for treating or preventing TAM, in particular TAM after (or as a complication of) solid transplantation or after (or as a complication of) cell transplantation, e.g. Stem Cell Transplantation (TAM-SCT), e.g. Precursor Cell Transplantation (TAM-PCT), e.g. Hematopoietic Precursor Cell Transplantation (TAM-HPCT), e.g. Hematopoietic Stem Cell Transplantation (TAM-HSCT), wherein said regime comprises administering a C5 inhibitor, e.g. an anti-C5

antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody, or an homologous antibody thereof as herein above defined, e.g. comprises administering tesidolumab.

In one aspect, the administration of the drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, may be repeated every day, or every two days, or every three days, every 4 days, every 5 days, every 6 days, every 7 days, every 8 days, every 9 days, every 10 days. In certain aspects, the drug, e.g. the anti-C5 antibody as herein defined, is administered weekly.

In another embodiment, the drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, is administered weekly during 1 to 5 weeks, e.g. during 2 weeks, e.g. during 3 weeks, e.g. during 4 weeks, and then is administered every 2 weeks or every 3 weeks.

The drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, may be used in at least one dose, or at least two doses, or at least three doses, or at least four doses, or at least five doses, or at least six doses, or at least seven doses, or at least eight doses, or at least nine doses, or at least 10 doses, or at least 11 doses, or at least 12 doses, or at least 13 doses, or at least 14 doses, or at least 15 doses, or at least 16 doses, or at least 17 doses, or at least 18 doses, or at least 19 doses, or at least 20 doses, or in certain aspects, even more doses. In one aspect, the use may be carried out until a hematological response or a complete disease response is achieved in the subject.

In certain aspects, the administration of the drug, e.g. the antibody, e.g. the anti-C5 antibody, e.g. anti-C5 antibody selected from the group consisting of eculizumab, tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, may be carried out over a period of about three to about 30 weeks, or about four to about 30 weeks, or longer, e.g. about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 25 weeks. During that period of treatment, e.g. during 1 to 30 weeks, e.g. during 1 to 20 weeks, e.g. during 1 to 17 weeks, e.g. during 1 to 15 weeks, e.g. during 1 to 12 weeks, the drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, e.g. tesidolumab, may be administered weekly.

In other aspects, the administration of the drug, e.g. the antibody, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody, or a homologous antibody thereof as herein above defined, may be carried out over a period of up to 50 weeks, e.g. up to 45 weeks, e.g. up to 40 weeks, e.g. up to 35 weeks, e.g. up to 30 weeks.

In another aspect, the administration of the drug, e.g. the antibody, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody, or a homologous antibody thereof as herein above defined, may be carried out over a period of 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or longer, e.g. one year or longer. During that period of treatment, the drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, e.g. tesidolumab, may be administered weekly.

In another aspect, the administration of the drug, e.g. the antibody, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody, or a homologous antibody thereof as herein above

defined, may be carried out over a period between 1 to 6 months, e.g. 1 to 5 months, e.g. 1 to 4 months, e.g. 1 and 3 months, e.g. 2 to 6 months, e.g. 2 to 5 months, e.g. 2 to 4 months, e.g. 2 to 3 months, e.g. 3 to 6, e.g. 3 to 5 months, e.g. 3 to 4 months, e.g. 4 to 6 months, e.g. 4 to 5 months, e.g. 5 to 6 months. During that period of treatment, the drug, e.g. the antibody, e.g. the anti-C5 antibody as herein defined, e.g. tesidolumab, may be administered weekly.

In some aspects, the C5 inhibitor, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody, or a homologous antibody thereof as herein above defined, is administered at two different dosages, firstly at an induction dose during a first period of time, also called induction phase, and later at a second different dose, during a maintenance period. The total duration of the induction phase plus the maintenance period may be as defined herein above.

The induction phase may last 1 to 8 weeks, e.g. 1 to 6 weeks, e.g. 1 to 4 weeks, e.g. 1 week, e.g. 2 weeks, e.g. 3 weeks, e.g. 4 weeks, e.g. 5 weeks, e.g. 6 weeks, e.g. 7 weeks, e.g. 8 weeks, e.g. for an C5 inhibitor that is an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

The maintenance period may last 1 to 11 months, e.g. 1 to 8 months, e.g. 1 to 6 months, e.g. 1 to 4 months, e.g. 2 to 6 months, e.g. 2 to 5 months, e.g. 2 to 4 months, e.g. 3 to 6 months, e.g. 3 to 4 months, e.g. 3 months, e.g. 4 months, e.g. 5 months, e.g. 6 months, e.g. for an C5 inhibitor that is an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

The induction dose may be about 2000mg, 1700mg, e.g. about 1500mg, e.g. about 1400 mg, e.g. about 1300mg, e.g. about 1200mg, e.g. about 1100 mg, e.g. about 1000mg, e.g. about 900 mg, e.g. about 800mg, of the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined. For example for subjects weighing 40 kg or greater, about 900mg, e.g. about 800mg, e.g. about 700mg, e.g. about 600 mg tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, for subjects weighing about 30 kg to about 40 kg; about 600 mg tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, for subjects weighing about 20 kg to about 30 kg; about 600 mg tesidolumab, eculizumab, a 305 variant antibody or an homologous antibody thereof as herein above defined, for subjects weighing about 10 kg to about 20 kg; about 300 mg tesidolumab, eculizumab, or a 305 variant antibody or a homologous antibody thereof as herein above defined, for subjects weighing about 5 kg to about 10 kg.

The induction dose of the C5 inhibitor, e.g. anti-C5 antibody, e.g. an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab, or a 305 variant antibody, may be comprised in a range of about 10mg/kg to 40mg/kg, e.g. about 10mg/kg to 35mg/kg, e.g. about 10mg/kg to 30mg/kg, e.g. about 10mg/kg to 25mg/kg, e.g. about 10mg/kg to 20mg/kg, e.g. is about

40mg/kg, e.g. about 35mg/kg, e.g. about 30mg/kg, e.g. about 25mg/kg, e.g. about 20mg/kg, e.g. about 15mg/kg, e.g. about 10mg/kg. In one aspect the induction dose is about 15mg/kg, e.g. for an C5 inhibitor that is an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab or a 305 variant antibody, and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody. In another aspect the induction dose is about 20mg/kg, e.g. for an C5 inhibitor that is an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab or a 305 variant antibody, and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody. In a further aspect the induction dose is about 25mg/kg, e.g. in case of an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab a 305 variant antibody, and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

The maintenance dose of the drug of the invention may be about 1500mg, about 1200mg, about 1000mg, about 800mg, about 700mg, about 500mg, about 400mg, about 300mg, e.g. of the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined. For example the maintenance dose may be comprised between about 300mg to about 1500mg, e.g. about 300mg to about 1200mg, e.g. about 300mg to about 1000mg, e.g. about 300mg to about 800mg, e.g. about 400mg to about 1500mg, e.g. about 400mg to about 1200mg, e.g. about 400mg to about 1000mg, e.g. about 400mg to about 800mg, e.g. about 500mg to about 1500mg, e.g. about 500mg to about 1200mg, e.g. about 500mg to about 1000mg, e.g. about 500mg to about 800mg, e.g. in case of an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

For example for subjects weighing 40 kg or greater, about 600mg, e.g. about 400mg, about 300mg, of an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody, and an homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

The maintenance dose may be comprised in a range of about 5g/kg to 25mg/kg, e.g. about 5mg/kg to 20mg/kg, e.g. about 5mg/kg to 10mg/kg, e.g. is about 30mg/kg, e.g. about 25mg/kg, e.g. about 20mg/kg, e.g. about 15mg/kg, e.g. about 10mg/kg, e.g. about 5mg/kg, e.g. in case of an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

In one aspect the maintenance dose is about 5mg/kg, e.g. in case of an anti-C5 antibody selected from the group selected from eculizumab, tesidolumab, a 305 variant antibody, and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

In another aspect the induction dose is about 10mg/kg. In a further aspect the induction dose is about 15mg/kg, e.g. in case of an anti-C5 antibody selected from the group selected from eculizumab,

tesidolumab, a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody.

In certain aspects wherein the drug is an anti C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, the administration step may be carried until is attained a blood serum level of greater than or at least about 99 µg/mL, or at least or greater than about 100 µg/mL, or at least or greater than about 200 µg/ml, or at least or greater than about 300 µg/ml. The administration step may be repeated daily, or every two days, or every three days, or every 4 days, or every 5 days, or every 6 days, or every 7 days, until a serum level of greater than or at least about 99 µg/mL, or at least or greater than about 100 µg/mL, or at least or greater than about 150 µg /ml, or at least or greater than about 200 µg/ml, or at least or greater than about 300 µg/ml is achieved in the subject. The administration step may be repeated daily, or every two days, or every three days until a serum level of greater than or at least about 99 µg/mL, or at least or greater than about 100 µg/mL, or at least or greater than about 200 µg/ml, or at least or greater than about 300 µg/ml is achieved in the subject. Determination of the dosage in a patient based on patient weight will be readily understood by one of ordinary skill in the art.

The administration step may be carried out in a manner sufficient to achieve a therapeutic level of the C5 inhibitor, in particular of anti-C5 antibody e.g. selected from the group selected from eculizumab, tesidolumab, or a 305 variant antibody and a homologous antibody thereof as herein above defined, e.g. eculizumab, tesidolumab or a 305 variant antibody in the subject. The administration step may comprise at least one dose, or at least two doses, or at least three doses, or at least four doses, or, in some aspects, more than four doses.

According to the invention, the C5 inhibitor, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody or a homologous antibody thereof as defined herein, may further comprise the step of measuring total complement activity (CH50) to obtain a CH50 measurement, wherein the subject is administered the C5 inhibitor until the CH50 measurement obtained from the patient is from about 0-3 CAE units as measured by enzyme immunoassay, or wherein the CH50 measurement is 0-15 CH50 units as measured using a hemolytic method using standardized sheep erythrocytes.

In certain aspects, there is provided a method for treating or preventing TAM, e.g. TAM-PCT, e.g. TAM-SCT, e.g. TAM-HPCT, e.g. TAM-HSCT, which comprises the step of administering the C5 inhibitor, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody or a homologous antibody thereof as hereinabove described.

In another embodiment, there is provided a method for treating or preventing TAM, e.g. TAM-PCT, e.g. TAM-SCT, e.g. TAM-HPCT, e.g. TAM-HSCT, which comprises the steps of

- a) measuring total complement activity (CH50) prior to treatment with a complement inhibitor, e.g. the anti-C5 antibody, e.g. eculizumab, tesidolumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, to obtain an initial CH50 measurement;
- b) administering said complement inhibitor as defined in a); and

c) measuring total CH50 activity after administration of said complement inhibitor to obtain a post-treatment CH50 measurement, wherein said complement inhibitor is administered until said post-treatment CH50 measurement is from about 0-3 CAE units as measured by enzyme immunoassay, or wherein the CH50 measurement is 0-15 CH50 units as measured using a hemolytic method using standardized sheep erythrocytes.

The administration step may comprise administering an anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, and the administration step may be carried out for a period of time sufficient to resolve HSCT-TMA. In some aspects, the administration step is carried out over a period as herein above defined, e.g. of about three to 30 weeks, e.g. four to about 15 weeks, e.g. four to about 17 weeks, or up to 20 weeks, or up to 25 weeks, or until the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, is administered at a dosage sufficient to reduce CH50 levels to 0-3 CAE units as measured by enzyme immunoassay, or wherein the CH50 measurement is 0-15 CH50 units as measured using a hemolytic method using standardized sheep erythrocytes.

The administration step may comprise administering the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, and the administration step may be carried out for a period of time as herein above defined, e.g. sufficient to achieve a favorable hematologic response, wherein a favorable hematological response comprises resolution of hematologic HSCT-TMA markers; or sufficient to adequately suppress CH50 levels. The markers may include, but are not limited to, normalization of LDH, resolution of need for red cell and platelet transfusions, and disappearance of schistocytes, or any other such criteria as will be readily understood by one of ordinary skill in the art. For example, the administration can be continued until Schistocytes <2/microscopic high power field (HPF) is attained.

The administration step may be carried out over a period of time sufficient to achieve a complete response, wherein the complete response comprises normalization of said subject's hematologic parameters and renal response, including, but not limited to, a doubling of the cystatin C-estimated glomerular filtration rate (eGFR) and improvement of proteinuria to values below the nephrotic range as defined by random spot urine protein to creatinine ratio below 2 mg/mg, or other criteria as will be readily understood by one of ordinary skill in the art.

In certain aspects, the subject may be administered the drug, e.g. the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, at the same dose during the period of treatment as hereinabove defined, e.g. multiple times a day, daily, weekly, or monthly. If the initial or subsequent dose does not resolve HSCT-TMA or is not sufficient to achieve a favorable hematologic response as herein above defined, or not sufficient to adequately suppress CH50 level, an additional dose may be administered on a daily, weekly, or monthly basis. In such cases, the additional dose may be a larger dose than the initial or most recent dose administered. In certain aspects, the dose may be increased by about 100 mg, or about 200 mg, or about 300 mg, or about 400 mg, or about 500 mg.

As used herein 'adequately suppressed CH50 level' refers to 0-3 CAE units as measured by enzyme immunoassay, or 0-15 CH50 units as measured using a hemolytic method using standardized sheep erythrocytes, as described herein.

In one aspect, a method of determining the relative levels of a complement inhibitor in a subject administered a complement inhibitor is disclosed. In this aspect, the method may comprise the step of measuring total complement activity (CH50) in a sample obtained from the subject. The total complement inhibitor may comprise, for example, tesidolumab, eculizumab or a 305 variant antibody.

In one aspect, there is provided a method of optimizing an anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, dosing schedule in a subject having any syndrome of TMA, post-HSCT or not, is disclosed. In this aspect, the method may comprise the steps of

- a) determining total complement activity (CH50) in said subject who is treated by an induction dose of said anti-C5 antibody;
- b1) either administering a second induction dose if CH50 levels are not adequately suppressed; or
- b2) administering a weekly induction dose if CH50 levels are adequately suppressed;
- c) administering an induction dose increased, by from about 100 mg to about 400 mg, e.g. about 300 mg, if CH50 levels are inadequately suppressed after said second induction dose;

wherein said subject is administered the anti-C5 antibody, e.g. tesidolumab, eculizumab, a 305 variant antibody or a homologous antibody thereof as herein above defined, until hematologic signs of TAM are resolved, e.g. resolution of hematologic HSCT-TAM markers; or sufficient to adequately suppress CH50 levels, as hereinabove defined.

The method may further comprise the step of providing a maintenance dose to maintain CH50 suppression.

The drug, e.g. the antibody, e.g. the anti-C5 antibody as defined herewith, may be administered via any method as is known in the art, for example, intravenously, subcutaneously, intramuscularly, and/or orally.

Table 1

SEQ ID NO	Description	Sequence
Tesidolumab		
1	CDRH1	SYAIS
2	CDRH2	GIGPFFGTANYAQKFQG
3	CDRH3	DTPYFDY
4	CDRL1	SGDSIPNYYVY
5	CDRL2	DDSNRPS

6	CDRL3	QSFDSLSNAEV
7	VH	EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAISWVRQAPGQGLEWMGGIG PFFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDTPYFDYW GQGTLLTVSS
8	VL	SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPS GIPERFSGSNSGNTATLTISRAGDEADYYCQSFDSLSNAEVFGGGTKLTVL
9	Heavy chain	EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAISWVRQAPGQGLEWMGGIG PFFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDTPYFDYW GQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQWTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
10	Light chain	SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPS GIPERFSGSNSGNTATLTISRAGDEADYYCQSFDSLSNAEVFGGGTKLTVLG QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETT TPSKQSNKNYAASSYLSLTPEQWKSHRYSYSCQVTHEGSTVEKTVAPTECS
Eculizumab		
11	CDRH1	NYWIIQ
12	CDRH2	EILPGSGSTEYTENFKD
13	CDRH3	YFFGSSPNWYFDV
14	CDRL1	GASENIYGALN
15	CDRL2	GATNLAD
16	CDRL3	QNVLNTPLT
17	VH	QVQLVQSGAEVKKPGASVKVSCASGYIFSNIWYIQWVRQAPGQGLEWMGEIL PGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPN WYFDVWGQGTLLTVSSA
18	VL	MDMRVPAQLLGLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYG ALNWKYQQKPGKAPKLLIYGATNLADGVPSRFGSGSGSGTDFTLTISLQPEDFATY YCQNVLNTPLTFGQGTKVEIKRT
19	Heavy chain	QVQLVQSGAEVKKPGASVKVSCASGYIFSNIWYIQWVRQAPGQGLEWMGEIL PGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPN WYFDVWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNT KVDKTVKCCVECPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLGLK
20	Light chain	MDMRVPAQLLGLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYG ALNWKYQQKPGKAPKLLIYGATNLADGVPSRFGSGSGSGTDFTLTISLQPEDFATY YCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACE VTHQGLSPVTKSFNRGEC

305 Variants		
305L05		
21	CDRH1	SSYYVA
22	CDRH2	AIYTGSGATYKASWAKG
23	CDRH3	DGGYDYPHAMHY
24	CDRL1	QASQNIGSSLA
25	CDRL2	GASKTHS
26	CDRL3	QSTKVGSSYGNH
27	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTSHSSYYVAWVRQAPGKGLEWVGAI YTGSGATYKASWAKGRFTISKDTSKNQVVLTMNMDPVDATYYCASDGGYD YPTAMHYWGQGLVTVSS
28	VL	DVVMTQSPSSLSASVGDRVTITCQASQNIGSSSLAWYQQKPGQAPRLIYGASKT HSGVPSRFSGSGSGTDFTLTISLQPEDVATYYCQSTKVGSSYGNHFGGGTKVEI K
305L015		
29	CDRH1	SSYYMA
30	CDRH2	AIFTGSGAEYKAEWAKG
31	CDRH3	DAGYDYPHAMHY
32	CDRL1	RASQGISSSLA
33	CDRL2	GASETES
34	CDRL3	QNTKVGSSYGNT
35	VH	QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKAEWAKGRVTISKDTSKNQVVLTMNMDPVDATYYCASDAGYD YPTAMHYWGQGLVTVSS
36	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGASETE SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNFTFGGGTKVEIK
305L016		
37	CDRH1	SSYYMA
38	CDRH2	AIFTGSGAEYKAEWVKG
39	CDRH3	DAGYDYPHAMHY
40	CDRL1	RASQGISSSLA
41	CDRL2	GASETES
42	CDRL3	QNTKVGSSYGNT
43	VH	QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKAEWVKGRTISRDNKNTLYLQMNSLRAEDTAVYYCASDAGYD PTAMHYWGRGTLTVSS
44	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGASETE SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNFTFGGGTKVEIK
305L018		
45	CDRH1	SSYYMA
46	CDRH2	AIFTGSGAEYKAEWAKG
47	CDRH3	DAGYDYPHAMHY
48	CDRL1	RASQGISSSLA
49	CDRL2	GASETES
50	CDRL3	QNTKVGSSYGNT

51	VH	QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKA EWAKGRVTISKDTSKNQVVLMTNMDPVDATYYCASDAGYD YPTHAMHYWGRGTLTVSS
52	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGASETE SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK
305L019		
53	CDRH1	SSYYMA
54	CDRH2	AFTGSGAEYKA EWAKG
55	CDRH3	DAGYDYPHAMHY
56	CDRL1	RASQGISSLA
57	CDRL2	GASETES
58	CDRL3	QNTKVGSSYGNT
59	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKA EWAKGRVTISKDTSKNQVVLMTNMDPVDATYYCASDAGYD YPTHAMHYWGQGT LTVSS
60	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGASETE SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK
305L020		
61	CDRH1	SSYYMA
62	CDRH2	AFTGSGAEYKA EWAKG
63	CDRH3	DAGYDYPHAMHY
64	CDRL1	RASQGISSLA
65	CDRL2	GASETES
66	CDRL3	QNTKVGSSYGNT
67	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKA EWAKGRVTISKDTSKNQVVLMTNMDPVDATYYCASDAGYD YPTHAMHYWGQGT LTVSS
68	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGQAPRLLIYGASETE SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK
305L022		
69	CDRH1	SSYYMA
70	CDRH2	AFTGSGAEYKA EWAKG
71	CDRH3	DAGYDYPHAMHY
72	CDRL1	RASQGISSLA
73	CDRL2	GASTTQS
74	CDRL3	QNTKVGSSYGNT
75	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAI FTGSGAEYKA EWAKGRVTISKDTSKNQVVLMTNMDPVDATYYCASDAGYD YPTHAMHYWGQGT LTVSS
76	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGQAPRLLIYGASTTQ SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK
305L023		
77	CDRH1	SSYYMA
78	CDRH2	GIFTGSGATYKA EWAKG
79	CDRH3	DAGYDYPHAMHY

80	CDRL1	RASQGISSSLA
81	CDRL2	GASTTQS
82	CDRL3	QNTKVGSSYGNT
83	VH	QVQLVESGGGLVQPGGSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVSGI FTGSGATYKAEWAKGRVTISKDTSKNQVVLMTNMDPVDATYYCASDAGYD YPTHAMHYWGQGLTVTVSS
84	VL	DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGQAPRLLIYGASTTQ SGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK

Example

In order to determine the effect of the anti-C5 antibody tesidolumab in patients with TAM-HSCT, a randomized, standard of care (SoC)-controlled, open-label, multi-center study was designed. The study group was patients with TAM after hematopoietic precursor cell transplantation from a related or unrelated donor for malignant and nonmalignant disease after myeloablative or non-myeloablative conditioning.

The study consists of up to 28 days of screening period, 16 weeks treatment period that can be extended to maximum of total 45 weeks (in case of inadequate suppression of serum complement after 16 weeks), 36 weeks follow up, and end of study visit (EOS) at week 52 (Figure 1). Duration of follow up depends on duration of treatment. Patients who are treated for more than 41 weeks proceed directly to EOS visit.

Approximately 40 patients are randomized to receive standard of care treatment (SoC) (including but not limited to immunosuppressive drugs, such as rituximab, and plasmapheresis) or tesidolumab plus SoC (excluding plasmapheresis and prohibited treatments such as eculizumab, high dose IVIG, plasmapheresis in the tesidolumab treatment arm or live vaccinations in the tesidolumab treatment arm). Patients are included in the study if they have diagnosis of TAM and poor prognostic markers. Inclusion of pediatric patients ≥ 2 years old are allowed only after 5 patients ≥ 12 years old have been dosed with tesidolumab and interim analysis reveals no safety issues after 4 weeks of treatment.

Patients randomized to tesidolumab receive 20 mg/kg body weight on study days 1, 8, and 15, followed by weekly doses of 10 mg/kg for remaining treatment duration of total 16 weeks. In case of inadequate suppression of serum complement activity (CH50 assay below LLoQ) after 10 mg/kg dose, it is possible to change back to 20 mg/kg weekly injection until the end of treatment.

Patients showing worsening disease (definition below) after two weeks of treatment (day 15) or later, are considered failures and can be switched to receive the alternative treatment (SoC or tesidolumab).

- increasing schistocyte count (+50% or more as compared to baseline),
- and/or increase in erythrocyte or platelet transfusion need (+50% or more as compared to two weeks before treatment initiation),
- and/or increasing proteinuria (+50% or more as compared to baseline)

Patients showing no response (definition below) at 4 weeks (day 29) or later until visit at week 16 are considered to be treatment failures and can be switched to the other treatment arm. Switching the treatment can occur immediately after data is available.

- no decrease in schistocyte count (less than 25% improvement as compared to baseline)
- continued erythrocyte or platelet transfusion need (less than 25% improvement of number needed two weeks before treatment initiation)
- and/or non-responding proteinuria (less than 25% reduction in proteinuria compared to baseline)

Patients can only switch study treatment arms once.

Unscheduled visits are allowed to check for above parameters in case the data is not available at day 15 or day 29 or at later scheduled visits and there is suspicion of insufficient improvement. Patients who switch from SoC to tesidolumab need to repeat the visit and dosing schedule starting from visit 3 when first dose of study medication is administered. Patients who change from tesidolumab to SoC continue with their visits as per Assessment schedule.

Patients who have inadequate suppression of serum complement activity (based on CH50 assay) may be continued on tesidolumab for maximum of total 45 weeks if deemed safe by the investigator. Decision on continuation of the dose after week 16 is discussed and agreed with the sponsor on a case by case basis.

All patients receive prophylactic doses of antibiotics active against *N. meningitidis* during the entire treatment period and 4 weeks after the last treatment. The choice of antibiotic medication is as per hospital standard.

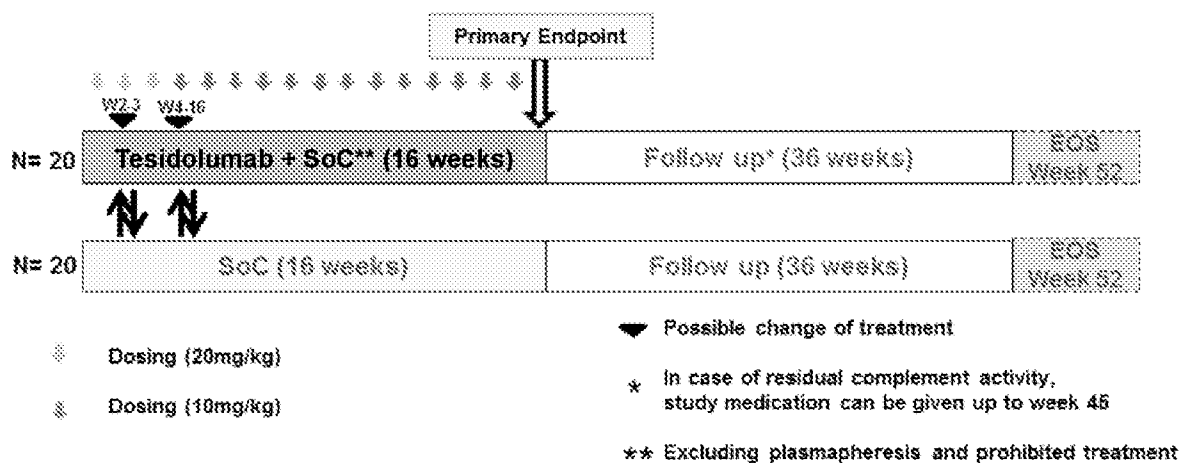
The primary endpoint assessment is done at week 17 (i.e. 1 week after last dose on week 16).

CLAIMS

1. A C5 inhibitor, e.g. anti-C5 antibody, for use in prevention or treatment of Transplant Associated Microangiopathy (TAM), e.g. TAM after cell transplantation, in a patient in need thereof.
2. The C5 inhibitor according to claim 1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 50mg/kg, e.g. 20mg/kg.
3. The C5 inhibitor according to claim 1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 800mg to about 2000mg, e.g. about 1000mg to about 2000mg.
4. The C5 inhibitor according to claim 1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 30mg/kg, e.g. 10mg/kg.
5. A C5 inhibitor according to claim 1, wherein the C5 inhibitor is administered to a patient in need thereof at doses of about 400mg to about 1000mg, e.g. about 500mg to about 1000mg.
6. The C5 inhibitor according to any one of claims 1 to 5, wherein the C5 inhibitor is administered to a patient in need thereof during a period comprised between 1 week and 8 weeks, e.g. 3 weeks or 4 weeks.
7. The C5 inhibitor according to any one of claims 1 to 5, wherein the C5 inhibitor is administered to a patient in need thereof during a period comprised between 1 month and 11 months, e.g. 4 or 5 months.
8. The C5 inhibitor according to claim 1, wherein the C5 inhibitor is administered to a patient in need thereof first at an induction dose during an induction phase and thereafter at a maintenance dose during a maintenance period, wherein optionally the maintenance dose is lower than the induction dose.
9. The C5 inhibitor according to claim 8, wherein the induction dose is as defined in claim 2 or 3.
10. The C5 inhibitor according to claim 8 or 9, wherein the induction phase is as defined in claim 6.
11. The C5 inhibitor according to any one of claims 9 to 10, wherein the maintenance dose is as defined in claim 4 or 5.

12. The C5 inhibitor according to any one of claims 9 to 11, wherein the maintenance period is defined as in claim 7.
13. The C5 inhibitor according to any one of the preceding claims wherein the C5 inhibitor is administered weekly.
14. The C5 inhibitor according to any one of the preceding claims wherein the C5 inhibitor is administered until hematologic signs of TMA are resolved.
15. The C5 inhibitor according to any one of the preceding claims for use in prevention or treatment of TAM after Precursor Cell Transplantation (TAM-PCT) or after Hematopoietic Stem Cell Transplantation, e.g. after allogeneic Hematopoietic Stem Cell Transplantation (TAM-HSCT).
16. The C5 inhibitor according to any preceding claims for use in prevention or treatment of TAM in a patient that has undergone transplantation, e.g. HPCT or HSCT.
17. A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT, e.g. allogeneic TAM-HSCT, in a subject that has undergone transplantation such as HSCT, comprising the steps of
 - a. measuring total complement activity (CH50) in a sample of said subject and
 - b. administering tesidolumab, e.g. in a regime as defined in any one of claims 2 to 14.
18. A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT, e.g. allogeneic TAM-HSCT, in a subject that has undergone transplantation such as HSCT, comprising the steps of
 - a. measuring total complement activity (CH50) in a sample of said subject and
 - b. administering an C5 inhibitor, e.g. an anti-C5 antibody, in a regime as defined in any one of claims 2 to 14.
19. A method for treating or preventing TAM, e.g. TAM after cell transplantation, comprising administering to the patient in need thereof a therapeutic amount of a C5 inhibitor according to the use as defined in any one of claims 1 to 16.
20. A method for treating or preventing TAM, e.g. TAM after cell transplantation, comprising administering to the patient in need thereof a therapeutic amount of tesidolumab or a homologous antibody thereof as herein defined.
21. A C5 inhibitor according to any one of claims 1 to 16 or a method according to any one of claims 17 to 20, wherein the C5 inhibitor is selected from the group consisting of tesidolumab, eculizumab, a homologous antibody thereof as herein defined, e.g. tesidolumab.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/056073

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 A61P7/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/039126 A1 (CHILDREN HOSPITAL MEDICAL CT [US]) 19 March 2015 (2015-03-19)	1-16, 18, 19, 21
Y	paragraphs [0007], [0013] - [0017], [0025], [0026], [0032] - [0049], [0066] - [0079], [0134] - [0157]; claims 1-33; figure 10 ----- -/--	17, 20

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

13 January 2017

Date of mailing of the international search report

24/01/2017

Name and mailing address of the ISA/

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Authorized officer

Bayer, Annette

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/056073

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JODELE SONATA ET AL: "Eculizumab Therapy in Children with Severe Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiop", BIOLOGY OF BLOOD AND MARROW TRANSPLANTATION, vol. 20, no. 4, 1 January 2014 (2014-01-01), pages 518-525, XP028636297, ISSN: 1083-8791, DOI: 10.1016/J.BBMT.2013.12.565 cited in the application	1-16,18, 19,21
Y	the whole document, in particular figures 1-3 -----	17,20
X	FLORE SICRE DE FONTBRUNE ET AL: "Use of Eculizumab in Patients With Allogeneic Stem Cell Transplant-Associated Thrombotic Microangiopathy", TRANSPLANTATION, vol. 99, no. 9, 1 September 2015 (2015-09-01), pages 1953-1959, XP055331429, GB ISSN: 0041-1337, DOI: 10.1097/TP.0000000000000601	1-16,18, 19,21
Y	the whole document, in particular page 1954, left-hand column, second full paragraph; page 1957, left-hand column, second paragraph and figure 2 -----	17,20
X	M OKANO ET AL: "Recovery from life-threatening transplantation-associated thrombotic microangiopathy using eculizumab in a patient with very severe aplastic anemia", BONE MARROW TRANSPLANTATION, vol. 49, no. 8, 1 August 2014 (2014-08-01), pages 1116-1118, XP055331440, GB ISSN: 0268-3369, DOI: 10.1038/bmt.2014.97 the whole document, in particular page 1116, right-hand column, paragraph 2 and page 1116-1117 bridging paragraph , figure 2 ----- -/--	1-16,19, 21

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/056073

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/015608 A1 (NOVARTIS AG [CH]; DIEFENBACH-STREIBER BEATE [DE]; EBERTH ADINA [DE]; G) 11 February 2010 (2010-02-11) cited in the application page 2, line 3 - line 9 page 5, line 28 - page 6, line 10 page 18, line 11 - page 19, line 7; table 1; sequences 1-10 page 97, line 32 - page 99, line 11; claims 34-39; example 7 -----	17,20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/056073

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-21

Methods and means for treating or preventing Transplant Associated Microangiopathy (TAM).

1.1. claims: 1-16, 21(all partially)

A C5 inhibitor for use in prevention or treatment of Transplant Associated Microangiopathy (TAM), and related subject-matter.

1.2. claim: 17(partially)

A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT comprising administering tesidolumab.

1.3. claim: 18(partially)

A method for monitoring the efficacy of treatment against TAM-PCT or TAM-HSCT comprising administering an C5 inhibitor.

1.4. claims: 20, 21(partially)

A method for treating or preventing TAM comprising administration of tesidolumab.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/056073

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