

TREATMENT OF ANCA-ASSOCIATED VASCULITIS

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/546,329, filed on October 30, 2023, and U.S. Provisional No. 63/700,966, filed on September 30, 2024. The entire contents of each of the aforementioned applications are incorporated herein by reference.

REFERENCE TO SEQUENCE LISTING

[0002] The application contains a Sequence Listing which has been submitted electronically in .XML format. Said .XML copy, created on October 24, 2024, is named “132301-01120.xml” and is 20,924 bytes in size. The sequence listing contained in this .XML file is part of the specification and is hereby incorporated by reference in its entirety.

BACKGROUND

[0003] ANCA stands for Anti-Neutrophilic Cytoplasmic Autoantibody. ANCA associated vasculitis, also known as “AAV” for short, is an umbrella term for a group of autoimmune diseases affecting small blood vessels in the body, caused by autoantibodies ANCA that target and attack neutrophils. When ANCAs (the auto-antibodies) attach to neutrophils, the neutrophils attack small blood vessels in the body to cause the blood vessels to become swollen and inflamed – or vasculitis (swelling or inflammation of blood vessels).

[0004] AAV can present at any age, and is divided into three groups according to clinical features: granulomatosis with polyangiitis (GPA, formerly called Wegener’s granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly called Churg-Strauss syndrome).

[0005] In granulomatosis with polyangiitis (GPA), ANCA antibodies cause inflammation and swelling in small blood vessels, leading to granulomatous inflammation observable under the microscope. GPA often affects the lungs and/or sinuses.

[0006] In microscopic polyangiitis (MPA), ANCA antibodies cause inflammation and swelling in small blood vessels in one or more organs such as kidney, lung, skin, heart, nose, eye, muscle, joint, nervous system, and digestive system, etc. Sometimes only the kidney is affected, in patients known as having “renal-limited ANCA vasculitis.”

[0007] Eosinophilic granulomatosis with polyangiitis (EGPA) is similar to GPA, in that granulomatous inflammation is observable under the microscope, and that the lungs and/or sinuses are often affected. However, EGPA can be associated with asthma, and higher levels of eosinophils are present in blood tests.

[0008] There are two main types of autoantibodies that can be involved in ANCA vasculitis. One is P-ANCA (perinuclear ANCA). P-ANCA usually targets and attaches to myeloperoxidase (MPO) that is inside of neutrophils. The other type is C-ANCA (cytoplasmic ANCA). C-ANCA usually targets and attaches to proteinase 3 (PR3), which is also inside of neutrophils. Blood tests can detect and distinguish these autoantibodies (P-ANCA vs. C-ANCA) in the bloodstream. A small percentage of AAV individuals will not test positive for either C-ANCA or P-ANCA, who are known as having ANCA-negative autoimmune vasculitis.

[0009] Thus, AAV can be characterized by the presence of proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA in the serum. GPA is predominantly associated with PR3-ANCA, while MPA and EGPA are predominantly associated with MPO-ANCA, but are also occasionally ANCA-negative. EGPA is often divided into two subtypes, MPO-ANCA⁺ EGPA and ANCA⁻ EGPA. Vasculitis can occur in any organ or tissue, commonly affecting the respiratory tract and kidneys, causing life-threatening kidney failure or pulmonary hemorrhage.

[0010] AAV has an estimated prevalence of 48–184/1,000,000 individuals worldwide, and about 100,000 patients in the US alone. Among them, about 10,000 US patients suffer from severe AAV, or are in major relapse. It is diagnosed most commonly in the late middle age (50s and 60s), but can also appear in older or younger individuals (though it is uncommon in children). It is equally common in men and women, and is much more common in Europeans than in other races. The annual incidence in Europe is 4.9–10.6/1,000,000 individuals for GPA, 2.7–11.6/1,000,000 individuals for MPA, and 0.5–3.1/1,000,000 individuals for EGPA. The epidemiological manifestations of AAV differ among geographical regions; GPA and PR3-ANCA AAV are more common in Europeans, while MPA and MPO-ANCA AAV are more common in Asians.

[0011] The AAV diseases are characterized by formation of granulomas and inflammation of small arteries, arterioles, venules, and capillaries. Inflamed vessels may rupture (for example, causing alveolar haemorrhage or a purpuric rash) or become occluded (for example, causing segmental glomerular infarction), giving rise to a broad array of

clinical symptoms and signs related to a systemic inflammatory response, end organ microvascular injury, or the mass effect of granulomas.

[0012] That is, ANCA vasculitis can cause different symptoms depending on what organ or part of the body that is involved. When blood vessels in the skin are affected, it can cause a rash. When blood vessels in the kidney are affected, it can cause blood and protein to leak into the urine, as well as kidney damage. Not all small blood vessels in the body are attacked. It is yet unclear as to why some organs / body parts are affected in some individual with ANCA vasculitis and different ones are affected in other individuals.

[0013] When ANCA vasculitis involves the kidneys, it affects the filtration units of the kidney - glomeruli (plural for glomerulus). The glomeruli are composed of a bundle / ball of capillaries. Since ANCA antibodies affect small blood vessels, these capillaries in the glomeruli can be attacked and damaged, leading to ANCA glomerulonephritis. When there is inflammation and swelling in the glomerulus due to ANCA vasculitis, red blood cells and protein can leak into the urine, causing positive urine dipstick results or proteinuria. Prolonged inflammation in the kidneys from the antibodies (ANCAs) attacking the glomeruli will eventually lead to kidney function decline or even failure, which will necessitate dialysis or kidney transplant. Sometimes ANCA vasculitis can affect kidney function slowly (*e.g.*, over weeks, months, or even years), but in many individuals, it can progress very quickly (*e.g.*, in days), and the inflammation leads to scarring, or permanent damage to the kidney. Thus, it is usually important to treat ANCA glomerulonephritis quickly, in order to prevent or decrease the amount of damage and scarring in the kidney.

[0014] Most people do not have ANCAs. Although the pathogenesis of AAV is still unclear, genetic and environmental factors and the immune system are thought to be involved. Genetic factors have been confirmed to play an important role in AAV. Genome-wide association studies have identified numerous genetic variants in MHC and non-MHC regions associated with AAV. The strongest evidence of MHC association in AAV is human leukocyte antigen (HLA)-DP. A significant association between AAV and genetic variations in non-MHC regions, such as CTLA-4, FCGR2A, PTPN22, SERPINA1, and TLR9 has also been found. Moreover, different clinical subtypes of AAV have distinct genetic backgrounds. GPA is associated with HLA-DP1, MPA with HLA-DQ, and EGPA with HLA-DRB4.

[0015] On the other hand, environmental factors, including silica exposure, bacterial or viral infections, and drugs suggest an association with the occurrence and relapse of AAV.

[0016] Treatment of patients with microscopic polyangiitis and Wegener's granulomatosis has three phases: (1) induction of remission, (2) maintenance of remission,

and (3) treatment of relapse. Current induction therapy often consists of cyclophosphamide (Cytoxan) and corticosteroids. For aggressive disease, use of high-dose intravenous methylprednisolone for three days is recommended, combined with intravenous or oral cyclophosphamide. Tapering doses of prednisone follows, along with cyclophosphamide maintenance for 12 to 18 months. The lowest dosage of steroids that controls the disease is typically used, and infection is considered if the symptoms appear to exacerbate. For patients in sustained remission at 12 months, the use of all medications may be gradually discontinued. Patients whose symptoms are under good control must, nevertheless, be closely followed at six-month intervals for signs and symptoms of relapse. During treatment with these agents, complete blood counts and liver function tests are performed periodically.

[0017] Other treatment regimens may include methotrexate (MTX), azathioprine (Imuran), trimethoprim-sulfamethoxazole (Bactrim, Septra), plasma exchange, cyclosporine (Sandimmune), intravenous immunoglobulin, and monoclonal antibodies.

[0018] During the use of potentially ulcerogenic immunosuppressive therapy, patients may be given H2-blockers or proton-pump inhibitors. Prophylactic treatment with fluconazole (Diflucan) orally for fungal infection may be considered, as well as trimethoprim-sulfamethoxazole (480 mg) three times weekly for prophylactic treatment of patients with pneumocystis carinii prophylaxis.

[0019] AAV is difficult to manage, with a 2.7-fold increased mortality risk, which rises to 7.5-fold in patients >65, primarily due to Tx-associated infection, ESRD. Furthermore, up to 50% of relapse occurs within 5 years of diagnosis, often within 12-18 months after IST discontinuation.

[0020] Meanwhile, treatment option for AAV is limited. The small molecule compound Avacopan (sold under the brand name Tavneos) was approved for medical use in Japan in September 2021, in the European Union in January 2022, and in the United States in October 2021, as the first orally-administered inhibitor of the complement C5a receptor approved. In the United States, Avacopan is indicated as an adjunctive treatment of adults with severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy including glucocorticoids. In the European Union, Avacopan, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adults with severe, active granulomatosis with polyangiitis or microscopic polyangiitis.

[0021] Avacopan may reduce GC exposure, but is unfortunately characterized by limited efficacy, liver signal, inability to taper steroids, and similar incidence of serious infections to steroid regimen.

[0022] Thus, there is a need to develop effective treatment to alleviate AAV.

SUMMARY

[0023] Provided is a method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising: 1) an antibody or an antigen binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and, (b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6, and 2) a complement modulator polypeptide, wherein the complement modulator polypeptide comprises factor H or a biologically active fragment thereof, wherein the composition comprising the fusion protein construct is administered to the subject to maintain plasma concentration of the fusion protein construct at ≥ 0.3 $\mu\text{g/mL}$, such as ≥ 3.2 $\mu\text{g/mL}$, throughout dosing, such that the AAV is treated in the subject.

[0024] Also provided is a method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising: 1) an antibody that specifically binds to complement protein 3d (c3d), wherein the antibody comprises: (a) two heavy chains, each comprising the amino acid sequence of SEQ ID NO: 9; and, (b) two light chains, each comprising the amino acid sequence of SEQ ID NO: 12; and, 2) two complement modulator polypeptides each comprising a biologically active fragment of factor H, wherein each of said complement modulator polypeptide has the amino acid sequence of SEQ ID NO: 15; wherein each said two complement modulator polypeptides is linked to the C-terminus of one of said two heavy chains via a linker having the amino acid sequence of SEQ ID NO: 14; wherein the composition comprising the fusion protein construct is

administered to the subject via an initial IV dose followed by one or more maintenance doses; wherein the initial IV dose comprises about 1400 mg of the fusion protein construct administered intravenously (IV) to the subject; wherein each of the one or more maintenance doses comprises about 450 mg of the fusion protein constructed administered subcutaneously (SC) to the subject, once every week; and, wherein the first of said one or more maintenance doses is administered about 4 days (*e.g.*, 96 hrs) after the initial IV dose, such that the AAV in the subject is treated.

[0025] It should be understood that any embodiment described herein, including those described only in the examples, can be combined with any one or more other embodiments, unless such combination is expressly disclaimed or is improper.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIGs. 1A and 1B show the clinical trial scheme for the Phase 2a trial described in Example 2.

[0027] FIG. 2 is a representative dosing scheme showing predicted PK and plasma concentration (ng/mL) of a subject fusion protein complement inhibitor (referred to herein as “COMPOUND B”), dosed with one initial IV dose of 1,400 mg, followed by 12 weekly subcutaneous (SC) maintenance doses of 450 mg each.

[0028] FIG. 3 shows percentage decrease from baseline Wieslab AP, based on the same dosing regimen in FIG. 2.

[0029] FIG. 4 tabulates selected PK parameters of the initial IV dose.

[0030] FIG. 5 tabulates selected PK parameters of the SC maintenance doses.

[0031] FIG. 6 illustrates the risks for progression to CKD (chronic kidney disease).

Green or “0” represents low risk, yellow or “1” represents moderately increased risk, orange or “2” represents high risk, red or “3” represents very high risk, and deep red or “4” represents highest risk.

[0032] FIG. 7A shows the scheme of the Phase 1 trial described in Example 1.

[0033] FIG. 7B shows the summary and baseline characteristics of the subjects enrolled in the Phase 1 study. Abbreviations: BMI: body mass index; MAD: multiple ascending dose; max: maximum; min: minimum; SAD: single ascending dose; SD: standard deviation. Note: Percentages of participants are based on the number in each analysis group. Number of participants (n) for each assessment is shown when different from total shown in header for each analysis group. BMI (kg/m^2) is calculated as $\text{Weight (kg)} / [\text{Height(m)}^2]$.

[0034] FIG. 7C shows the most frequently reported treatment emergent adverse events (TEAEs) (occurred in ≥ 2 subjects). MAD: multiple ascending dose; SAD: single ascending dose.

[0035] FIGs. 7D and 7E show mean (SD) of COMPOUND B plasma concentration-time profiles (semi-logarithmic scale) following single intravenous (IV) doses (FIG. 7D) or single and multiple subcutaneous (SC) doses (FIG. 7E).

[0036] FIGs. 7F and 7G show normalized mean (SD) of serum Wieslab alternative pathway (AP) activity over time after single IV doses (FIG. 7F) or single and multiple SC doses (FIG. 7G) of COMPOUND B or placebo. Data shown as percent change from pre-dose baseline and normalized to the minimum measurable activity of the assay which is expressed as 0; The minimum measurable activity of the assay is 26% or 35% of pre-dose baseline dependent on dilution factor applied.

[0037] FIGs. 7H and 7I show normalized mean (SD) of serum Wieslab complement classic pathway (CP) activity over time after single IV doses (FIG. 7H) or single and multiple SC doses (FIG. 7I) of COMPOUND B or placebo. Data shown as percent change from pre-dose baseline. The minimum measurable activity of the assay which is expressed as 26% or 35% of pre-dose baseline dependent on dilution factor applied. LLOQ: lower limit of quantitation.

[0038] FIGs. 7J and 7K show model-predicted plasma concentrations (FIG. 7J) and Wieslab AP activity (FIG. 7K) versus time profiles following 26 SC doses of 450 mg every week (QW). IC₅₀: half maximal inhibitory concentration. Solid line: predicted median; Shaded areas: [5%-95%] prediction intervals; Dotted lines: dosing times; Horizontal PK lines in FIG. 7J: 3.2 $\mu\text{g/mL}$ (dash-and-dot line); 0.2 $\mu\text{g/mL}$ (dark solid line); Horizontal PD line in FIG. 7K: 50% inhibition of Wieslab activity threshold (thick dark line) – IC₅₀.

DETAILED DESCRIPTION

[0039] COMPOUND B is a recombinant bifunctional fusion protein designed to restore proper complement regulation through a unique, tissue-targeted therapeutic approach. COMPOUND B has (a) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 9, the amino acid sequence of SEQ ID NO: 14, and the amino acid sequence of SEQ ID NO: 15; and, (b) two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 12.

[0040] The targeting antibody domain of COMPOUND B was characterized for nanomolar binding affinity to C3 cleavage fragment C3d. When COMPOUND B binds to C3d, it presents the Factor H (fH)₁₋₅ protein to surface-bound C3/C5 AP convertases (serine protease protein complexes) that drive complement activation in tissue. The fH₁₋₅ protein potently induces dissociation and irreversible catalytic degradation of the convertase protein complex, thereby blocking AP complement activation. As fH₁₋₅ interrupts ongoing and further complement activation, it turns off the amplification loop such that COMPOUND B has the potential to restore control of the complement system at specific tissue sites of ongoing injury.

[0041] Preclinical studies in fH-knockout mice and rodent models of complement-driven renal injury have demonstrated that COMPOUND B distributes to tissues and provides potent, local complement inhibition without systemic blockade, thereby having little effect on the pharmacological complement sink that is a key part of the host defense mechanism. Consequently, the localized, targeted activity of COMPOUND B predicts that it will not be associated with increased risk of infection (as seen with other complement pathway inhibitors).

[0042] Further nonclinical studies in rodent disease models have confirmed that COMPOUND B distributes and binds to C3d present in the kidney, liver, and skin; can provide durable anticomplement activity in tissue (>7 days after 1 mg/kg subcutaneous dosing) with only limited and transient systemic inhibition; reduces glomerular C3 fragment deposition and improves renal function in rodent models of kidney disease; and provides no evidence of disease exacerbation in rodent models driven by immune complex formation. A 29-day Good Laboratory Practice (GLP) repeat-dose toxicology study in cynomolgus monkeys demonstrated acceptable pharmacological safety at up to 150 mg/kg.

[0043] Thus, COMPOUND B is a promising tissue-targeted complement inhibitor because of its potential to restore control of the complement system at tissue-specific sites of ongoing injury and thereby provide therapeutic benefit in ANCA-Associated Vasculitis (AAV).

[0044] Provided is a method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising: 1) an antibody or an antigen binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the

CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and, (b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6, and 2) a complement modulator polypeptide, wherein the complement modulator polypeptide comprises factor H or a biologically active fragment thereof, wherein the composition comprising the fusion protein construct is administered to the subject to maintain plasma concentration of the fusion protein construct at $\geq 0.3 \mu\text{g/mL}$, such as $\geq 3.2 \mu\text{g/mL}$, throughout dosing, such that the AAV is treated in the subject.

[0045] In some embodiments, the antibody or antigen binding fragment thereof comprises: (a) a first heavy chain and a second heavy chain, wherein each of the first and the second heavy chain comprises three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and (b) a first light chain and a second light chain, wherein each of the first and the second light chain comprises three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6.

[0046] In some embodiments, each of the first and the second heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 7, and wherein each of the first and the second light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8.

[0047] In some embodiments, the first and the second heavy chain each comprises the same amino acid sequence of SEQ ID NO: 9, 10 or 11, and wherein the first and the second light chain each comprises the amino acid sequence of SEQ ID NO: 12.

[0048] In some embodiments, the fusion protein further comprises: (c) a first linker bound to the C-terminus of the first heavy chain and comprising the amino acid sequence of SEQ ID NO: 14; and (d) a second linker bound to the C-terminus of the second heavy chain and comprising the amino acid sequence of SEQ ID NO: 14.

[0049] In some embodiments, the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 15 or 16.

[0050] In some embodiments, the fusion protein construct comprises (a) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 9, the amino acid sequence of SEQ ID NO: 14, and the amino acid sequence of SEQ ID NO: 15; and, (b) two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 12.

[0051] In some embodiments, the fusion protein is administered to the subject subcutaneously (*s.c.*), each as a maintenance dose.

[0052] In some embodiments, prior to the subcutaneous administration of the maintenance dose(s), the subject is administered an initial IV dose.

[0053] In some embodiments, the initial IV dose is administered to the subject at a dose ranging from 3-30 mg/kg, and/or to achieve a target plasma concentration of the fusion protein construct in the subject at ≥ 0.3 $\mu\text{g/mL}$.

[0054] In some embodiments, the first maintenance dose is administered about 3-4 days (*e.g.*, about 4 days), about 5 days (*e.g.*, about 120 hrs), about 6 days (*e.g.*, about 144 hrs), or no later than about 7 days (*e.g.*, about 168 hrs), after the initial IV dose.

[0055] In some embodiments, the initial IV dose comprises two or more IV administrations administered QD (once a day), Q3D (once every three days), QW (once a week), Q2W (once every two weeks), Q3W (once every three weeks), or Q4W (once every four weeks).

[0056] In some embodiments, each IV administration of the initial IV dose comprises about 3-30 mg/kg or about 200-2,000 mg of the fusion protein, in order to achieve a plasma concentration of the fusion protein in the subject of ≥ 0.3 $\mu\text{g/mL}$, such as ≥ 32 $\mu\text{g/mL}$, for about 96 hours before the first maintenance dose is administered.

[0057] In some embodiments, each IV administration of the initial IV dose, starting from the second administration, is separated from the immediate prior administration by the same number of days, preferably around the same time of the day of the administration.

[0058] In some embodiments, each maintenance dose, starting from the second dose, is separated from the immediate prior maintenance dose by the same number of days, preferably around the same time of the day of the administration.

[0059] In some embodiments, the fusion protein is administered once a week, preferably, each administration starting from the second dose of the maintenance dose is separated by 7

days from the immediate prior administration, preferably around the same time of the day of the administration.

[0060] In some embodiments, the fusion protein is administered for an infinite number of maintenance doses, which can be useful for, *e.g.*, treating a chronic condition. In some embodiments, the maintenance doses are administered intermittently (*prn*).

[0061] In some embodiments, the fusion protein is administered for a total of about 10-60 maintenance doses, about 20-55 maintenance doses, about 25-51 maintenance doses, about 22-28 maintenance doses, about 22, 23, 24, 25, 26, 27, or 28 maintenance doses, about 50-55 maintenance doses, about 50, 51, 52, 53, 54, or 55 maintenance doses. In some embodiments, the fusion protein is administered for 22 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 23 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 24 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 25 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 26 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 27 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 28 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 29 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 30 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 50 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 51 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 52 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 53 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 54 consecutive maintenance doses. In some embodiments, the fusion protein is administered for 55 consecutive maintenance doses.

[0062] In some embodiments, each maintenance dose comprises about 5 – 1,800 mg or about 0.1 - 20 mg/kg of the fusion protein, in order to maintain a plasma concentration of the fusion protein in the subject of between about 0.3-32 $\mu\text{g/mL}$, such as between about 3.2-32 $\mu\text{g/mL}$ (*e.g.*, after 2, 3, 4, or 5 doses of maintenance doses).

[0063] In some embodiments, the maintenance doses are administered BID (twice a day), QD (once daily), Q2D (once every two days), Q3D (once every three days), Q4D (once every four days), Q1W (once every week), Q2W (once every two weeks), Q3W (once every three

weeks), Q4W (once every four weeks), Q6W (once every six weeks), Q8W (once every eight weeks), Q12W (once every twelve weeks), or intermittent prn.

[0064] In some embodiments, the fusion protein is administered to the subject based on a dosing regimen comprising an initial IV dose followed by one or more maintenance doses, wherein the maintenance doses are administered according to any of the weight-based dosing regimens, body surface area (BSA)-based dosing regimens, or fixed dose dosing regimens described herein.

[0065] In some embodiments, the fusion protein is administered to the subject based on a weight-based dosing regimen.

[0066] In some embodiments, the fusion protein is administered to the subject at about 3 mg/kg – about 30 mg/kg initial IV dose, about 5 mg/kg – about 30 mg/kg initial IV dose, about 6 mg/kg – about 28 mg/kg initial IV dose, about 7 mg/kg – about 26 mg/kg initial IV dose, about 8 mg/kg – about 24 mg/kg initial IV dose, about 10 mg/kg – about 22 mg/kg initial IV dose, about 12 mg/kg – about 20 mg/kg initial IV dose, about 16 mg/kg initial IV dose, about 18 mg/kg initial IV dose, about 20 mg/kg initial IV dose, about 22 mg/kg initial IV dose, or about 25 mg/kg initial IV dose.

[0067] In some embodiments, the fusion protein is administered to the subject at about 0.1 mg/kg – about 20 mg/kg per SC maintenance dose, about 0.5 mg/kg – about 15 mg/kg per SC maintenance dose, about 1 mg/kg – about 10 mg/kg per SC maintenance dose, about 3 mg/kg – about 8 mg/kg per SC maintenance dose, about 5 mg/kg – about 7 mg/kg per SC maintenance dose, about 5 mg/kg per SC maintenance dose, about 6 mg/kg per SC maintenance dose, about 7 mg/kg per SC maintenance dose, or about 8 mg/kg per SC maintenance dose.

[0068] In some embodiments, the fusion protein is administered to the subject based on a body surface area (BSA)-based dosing regimen. For example, the dose for an adult male patient of any weight (in kg) and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard male weight of 91 kg and height of 175 cm, to reach a dose of about 200 mg – about 2000 mg initial IV dose and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 mg initial IV dose and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose and/or about 200 mg - 600 mg SC maintenance dose, or about 1400 mg initial IV dose and/or about 450 mg SC maintenance dose.

[0069] The dose for an adult female patient of any weight (in kg) and height (in cm) can be calculated / converted, based on a BSA Base Dose used for a standard female weight of 77.5 kg and height of 160 cm, to reach a dose of about 200 mg – about 2000 mg initial IV dose and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 mg initial IV dose and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose and/or about 200 mg - 600 mg SC maintenance dose, or about 1400 mg initial IV dose and/or about 450 mg SC maintenance dose.

[0070] In some embodiments, the BSA dosing is based on Dubois Formula for BSA Dosing, in which $\text{Dose} = \text{BSA Based Dose} \times 0.007184 \times \text{Height (cm)}^{0.725} \times \text{Weight (kg)}^{0.425}$.

[0071] In some embodiments, the BSA dosing is based on Monteller Formula for BSA Dosing, in which $\text{Dose} = \text{BSA Based Dose} \times \text{square root} [(\text{Height (cm)} \times \text{Weight (kg)}) / 3600]$.

[0072] In some embodiments, the fusion protein is administered to the subject based on a fixed / flat dosing regimen.

[0073] In certain embodiments, the fusion protein is administered to the subject at about 100 mg – about 1200 mg per maintenance dose, about 150 mg – about 800 mg per maintenance dose, about 300 mg – about 600 mg per maintenance dose, about 400 mg – about 500 mg per maintenance dose, or about 450 mg per maintenance dose.

[0074] In some embodiments, the fusion protein is administered to the subject at about 200 mg – about 2000 mg initial IV dose and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 initial IV dose and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose and/or about 200 mg - 600 mg SC maintenance dose, or about 1400 mg initial IV dose and/or about 450 mg SC maintenance dose.

[0075] In some embodiments, the antibody is administered to the subject based on a weight-banded dosing regimen, in which patients within certain ranges of weights (weight-bands) are dosed a fixed amount for that specific weight band. In some embodiments, patients with a body weight of about 10-25 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, patients with a body weight of about 25-50 kg (or under 50 kg) are grouped in the same body weight band and given the same fixed

dose. In some embodiments, patients with a body weight of about 50-75 kg are grouped in the same body weight band and given the same fixed dose. In some embodiments, patients with a body weight of about 75-100 kg (or over 75 kg) are grouped in the same body weight band and given the same fixed dose. In some embodiments, the fixed dose for each weight band is based on the average weight in the weight band (*e.g.*, all patients in the weight band of 50-75 kg are dosed a fixed dose based on the dose for the middle weight – *i.e.*, 62.5 kg for this weight band). In some embodiments, the fixed dose for the weight band 50-75 kg is about 150 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg. In some embodiments, the fixed dose for a weight band is proportional to the fixed dose for the 50-75 kg weight band (*e.g.*, the fixed dose for the weight band 10-25 kg is based on the middle weight of 17.5 kg, which is $17.5 / 62.5 = 28\%$ of the fixed dose for the 50-75 kg weight band).

[0076] Also provided is a method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising: 1) an antibody that specifically binds to complement protein 3d (c3d), wherein the antibody comprises: (a) two heavy chains, each comprising the amino acid sequence of SEQ ID NO: 9; and, (b) two light chains, each comprising the amino acid sequence of SEQ ID NO: 12; and, 2) two complement modulator polypeptides each comprising a biologically active fragment of factor H, wherein each of said complement modulator polypeptide has the amino acid sequence of SEQ ID NO: 15; wherein each said two complement modulator polypeptides is linked to the C-terminus of one of said two heavy chains via a linker having the amino acid sequence of SEQ ID NO: 14; wherein the composition comprising the fusion protein construct is administered to the subject via an initial dose followed by one or more maintenance doses; wherein the initial dose comprises about 1400 mg of the fusion protein construct administered intravenously (IV) to the subject; wherein each of the one or more maintenance doses comprises about 450 mg of the fusion protein constructed administered subcutaneously (SC) to the subject, once every week; and, wherein the first of said one or more maintenance doses is administered about 4 days (*e.g.*, 96 hrs) after the initial dose, such that the AAV in the subject is treated.

[0077] In some embodiments, the subject is an adult (*e.g.*, male or female, over 18 years old) having newly diagnosed or relapsed AAV requiring treatment with RTX (or CYC), such as having GPA or MPA, optionally positive for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) antibody.

[0078] In some embodiments, the subject is further being treated by a SOC (standard of care) treatment for AAV. In some embodiments, the SOC is as described in the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases (KDIGO Glomerular Diseases Work Group 2021, *Kidney Int.* 2021;100(4S):S1-S276, incorporated herein by reference).

[0079] In some embodiments, the subject is further being treated by a B-cell depleting antagonist antibody and/or a glucocorticoid (GC). In some embodiments, B-cell depleting antagonist antibody is an anti-CD20 monoclonal antibody. In some embodiments, the anti-CD20 monoclonal antibody comprises Rituximab (RTX). In some embodiments, the anti-CD20 monoclonal antibody comprises Ofatumumab.

[0080] In some embodiments, the anti-CD20 monoclonal antibody comprises Rituximab (RTX), and the RTX is administered IV as 4 doses of 375 mg/m² body surface area, once weekly for 4 weeks. In another embodiment, about 1000 mg of the RTX is administered IV two weeks apart.

[0081] In some embodiments, the glucocorticoid (GC) comprises methyl prednisolone and/or (oral) prednisolone. In some embodiments, methyl prednisolone is administered intravenously (IV), and/or prednisolone is administered orally. In some embodiments, the GC comprises methyl prednisolone administered intravenously for 0.5-1g daily for a total of no more than 1.5 g, followed by daily oral prednisolone.

[0082] In some embodiments, the subject is further being treated by the B-cell depleting antagonist antibody and the glucocorticoid (GC), wherein the anti-CD20 monoclonal antibody comprises rituximab (RTX) administered IV as 4 doses of 375 mg/m² body surface area, once weekly for 4 weeks, and the GC comprises methyl prednisolone administered intravenously for 0.5-1g daily for a total of no more than 1.5 g, followed by daily oral prednisolone.

[0083] In some embodiments, the method further comprises tapering the amount of (oral) GC (*e.g.*, prednisone or prednisolone) the subject receives over the course of treatment.

[0084] In some embodiments, tapering the amount of (oral) GC begins at 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, or 16 weeks after the administration of the initial IV dose or after Day 1 of switching to oral GC.

[0085] In some embodiments, the amount of GC is tapered to about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or 0%, over the course of 2, 3, 4, 5, 6, 7, or 8 weeks, or up to 20 weeks.

- [0086] In some embodiments, the subject has granulomatosis with polyangiitis (GPA, or Wegener's granulomatosis).
- [0087] In some embodiments, the subject has microscopic polyangiitis (MPA).
- [0088] In some embodiments, the subject has eosinophilic GPA (EGPA, or Churg-Strauss syndrome), such as MPO-ANCA⁺ EGPA and ANCA⁻ EGPA.
- [0089] In some embodiments, the AAV is characterized by the presence of proteinase 3 (PR3)-ANCA in the serum. In some embodiments, the AAV is characterized by the presence of myeloperoxidase (MPO)-ANCA in the serum.
- [0090] In some embodiments, the subject has P-ANCA (perinuclear ANCA).
- [0091] In some embodiments, the subject has C-ANCA (cytoplasmic ANCA).
- [0092] In some embodiments, the subject has ANCA-negative autoimmune vasculitis.
- [0093] In some embodiments, the subject has ANCA glomerulonephritis.
- [0094] In some embodiments, the AAV is characterized by formation of granulomas and inflammation of small arteries, arterioles, venules, and capillaries.
- [0095] In some embodiments, the subject is a nephritic patient, a nephrotic patient, a transplant patient, or a patient with impaired renal function (*e.g.*, moderately increased risk of progression to CKD, high risk of progression to CKD, very high risk of progression to CKD, or highest risk of progression to CKD, *e.g.*, Rapidly Progressive Glomerulonephritis (RPGN)).
- [0096] In some embodiments, the fusion protein is formulated in 12 mM sodium phosphate, 75 mM arginine, 125 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.7.
- [0097] In some embodiments, $\geq 50\%$, 60%, 70%, 80%, 90%, or 95% of the subjects treated by the method of the invention achieve remission (such as defined by a BVAS (Ver. 3) score of 0), after 26 weeks of treatment, and/or up to 52 weeks after treatment (or 26 or 52 weeks, respectively, from the administration of the first dose of the subject fusion protein).
- [0098] BVAS (Birmingham Vasculitis Activity Score) is a comprehensive multisystem clinical assessment used in therapeutic studies of systemic vasculitis. Version 3 of the Birmingham Vasculitis Activity Score (BVAS) helps clinicians assess persistent and new or worse manifestations in patients with system vasculitis.
- [0099] The table below introduces the 9 sections (56 items) of the BVAS score, the maximum points achievable for each section and the points awarded to each item, if present:

Manifestation & Definition	Persistent points	New/Worse points
1. General	Max persistent 2	Max New/Worse 3
Myalgia Pain in the muscles	1	1
Arthralgia or arthritis Pain in the joints or joint inflammation	1	1
Fever $\geq 38^{\circ}\text{C}$ Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5°C	2	2
Weight Loss ≥ 2 kg Loss of dry body weight without dieting	2	2
2. Cutaneous	Max persistent 3	Max New/Worse 6
Infarct Area of tissue necrosis or splinter haemorrhages	1	2
Purpura Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer A disruption in the continuity of the skin	1	4
Gangrene Extensive tissue necrosis	2	6
Other skin vasculitis Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2
3. Mucous Membranes / eyes	Max persistent 3	Max New/Worse 6
Mouth ulcers / granulomata Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers Ulcers on the genitalia or perineum	1	1
Adnexal inflammation Salivary or lacrimal gland inflammation.	2	4
Significant proptosis >2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1

Blurred vision Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss Acute loss of vision	n/a	6
Uveitis Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate (exclude hard exudates) / retinal haemorrhage	2	6
4. ENT	Max persistent 3	Max New/Worse 6
Bloody nasal discharge / crusts / ulcers / granulomata Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6
5. Chest	Max persistent 3	Max New/Worse 6
Wheeze Wheeze on clinical examination	1	2
Nodules or cavities New lesions detected on imaging	n/a	3
Pleural effusion / pleurisy Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate Detected on chest X-ray or CT scan	2	4

Endobronchial involvement Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure The need for artificial ventilation	4	6
6. Cardiovascular	Max persistent 3	Max New/Worse 6
Loss of pulses Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain Typical clinical history of cardiac pain leading to myocardial infarction or angina	2	4
Cardiomyopathy Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure Heart failure by history or clinical examination	3	6
7. Abdominal	Max persistent 4	Max New/Worse 9
Peritonitis Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea Of recent onset	3	9
Ischaemic abdominal pain Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6
8. Renal	Max persistent 6	Max New/Worse 12
Hypertension Diastolic >95 mm Hg	1	4

Proteinuria >1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria 'Moderate' on urinalysis or ≥ 10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 $\mu\text{mol/L}$ At first assessment only	2	4
Serum creatinine 250-499 $\mu\text{mol/L}$ At first assessment only	3	6
Serum creatinine ≥ 500 $\mu\text{mol/L}$ At first assessment only	4	8
>30% rise in creatinine or >25% fall in creatinine clearance Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	n/a	6
9. Nervous system	Max persistent 6	Max New/Worse 9
Headache Unaccustomed & persistent headache	1	1
Meningitis Clinical evidence of meningism	1	3
Organic confusion Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive) Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy Objective sensory deficit in a non-dermatomal distribution	3	6

Mononeuritis multiplex Single or multiple specific motor nerve palsies	3	9
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[0100] Persistent scores can range from 0 to 33 whilst the New/Worse scores can range from 0 to 63. There are several rules for scoring BVAS:

- Disease manifestations are to be scored only when they are attributable to active vasculitis. If there is reasonable evidence a manifestation is likely attributable to another aetiology (e.g. infection, other co-morbidity), it should not be scored.
- Persistent disease scoring should be used for all manifestations due to active (but not new or worsened) vasculitis.
- Specialist opinion, or the results of laboratory or imaging investigations will be required for some items.
- The items of serum creatinine in section 8. “Renal” should be scored only on the first visit.
- There are several items, i.e. Nodules or cavities that are not compatible with persistent disease and can only be scored under new/worse scoring.
- When the BVAS is assessed for the first time in that patient or any of the features have started or deteriorated in the past month, please use the new/worse scoring.
- Features persisting for > 3 months represent damage rather than activity and should be scored on a Vasculitis Damage Index (VDI) form and not on a BVAS form.

[0101] A patient achieves / retains BVAS 0 (*i.e.*, remission) at a time point after commencement of treatment (*e.g.*, 26 weeks after commencement of treatment).

[0102] A patient achieves / retains BVAS 50% when the BVAS value at a time point after treatment (*e.g.*, 26 weeks after commencement of treatment) becomes / remains at least 50% lower than the original BVAS prior to the treatment.

[0103] A patient achieves / retains BVAS 90% when the BVAS value at a time point after treatment (*e.g.*, 26 weeks after commencement of treatment) becomes / remains at least 90% lower than the original BVAS prior to the treatment.

[0104] In some embodiments, the subject has normal renal function, with low risk of progression to CKD (chronic kidney disease), as assessed by, for example, a combined overall relative risk of “0” in the table in FIG. 6 (*i.e.*, estimated glomerular filtration (eGFR) stage G1 (normal or high eGFR at ≥ 90 mL/min) or G2 (mildly decreased eGFR at 60-90 mL/min) / Albuminuria Category A1 (normal to mildly increased urine albumin, at < 3 mg/mmol or <30 mg/g of urine albumin)).

- [0105] In some embodiments, the subject has impaired renal function.
- [0106] In some embodiments, the subject has a moderately increased risk of progression to CKD, as assessed by, for example, a combined overall relative risk of “1” in the table in FIG. 6 (*i.e.*, eGFR stage G3a (mildly to moderately decreased eGFR at 45-59 mL/min) / Albuminuria Category A1; or eGFR stage G1 or G2 / Albuminuria Category A2 (moderately increased urine albumin, at 3-29 mg/mmol or 30-299 mg/g of urine albumin).
- [0107] In some embodiments, the subject has a high risk of progression to CKD, as assessed by, for example, a combined overall relative risk of “2” in the table in FIG. 6 (*i.e.*, eGFR stage G3b (moderately to severely decreased eGFR at 30-44 mL/min) / Albuminuria Category A1; eGFR stage G3a / Albuminuria Category A2; or eGFR stage G1 or G2 / Albuminuria Category A3 (severely increased urine albumin, at ≥ 30 mg/mmol or ≥ 300 mg/g of urine albumin).
- [0108] In some embodiments, the subject has a very high risk of progression to CKD, as assessed by, for example, a combined overall relative risk of “3” in the table in FIG. 6 (*i.e.*, eGFR stage G4 (severely decreased eGFR at 15-29 mL/min) / Albuminuria Category A1; eGFR stage G3b or G4 / Albuminuria Category A2; or eGFR stage G3a or G3b / Albuminuria Category A3).
- [0109] In some embodiments, the subject has highest risk of progression to CKD, as assessed by, for example, a combined overall relative risk of “4” in the table in FIG. 6 (*i.e.*, eGFR stage G5 (kidney failure with eGFR at <15 mL/min) / Albuminuria Category A1, A2, or A3; or eGFR stage G4 / Albuminuria Category A3).
- [0110] As used herein, albuminuria category is assessed / determined by urine albumin-creatinine ratio (uACR).
- [0111] In some embodiments, the subject is an adult (*e.g.*, 18 years and older).
- [0112] In some embodiments, the subject is not an adult (*e.g.*, pediatric patient, or a patient of under 18-year old, under 16-year old, under 14-year old, under 12-year old, under 10-year old, under 5-year old, under 3-year old, under 2-year old, under 1-year old, under 6-month old, or under 3-month old).
- [0113] In some embodiments, the subject is a Caucasian. In some embodiments, the subject is Asian. In some embodiments, the subject is African. In some embodiments, the subject is native American. In some embodiments, the subject is of mixed race or ethnic group.
- [0114] In some embodiments, the subject is biologic male. In some embodiments, the subject is biologic female.

[0115] In some embodiments, the subject has been treated, and/or is being treated with a glucocorticoid (GC) or a corticosteroid.

[0116] In some embodiments, the GC / corticosteroid is administered by IV or/or orally. In some embodiments, the corticosteroid comprises prednisone and/or methylprednisolone (*e.g.*, Medrol, Solumedrol – IV). In some embodiments, the corticosteroid is tapered over time- with a decreasing dose over several months. In some embodiments, the GC comprises 60 mg/day methyl prednisolone, *e.g.*, for daily administration.

[0117] In some embodiments, the subject has been treated, and/or is being treated with an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is Rituximab (Rituxan). In some embodiments, the rituximab is administered intravenously (*e.g.*, as an infusion). In some embodiments, the rituximab is administered as 4 weekly doses, or 2 doses spaced 2 weeks apart. In some embodiments, the rituximab dosing regimen is repeated once every 6 months.

[0118] In some embodiments, the subject is further being treated by or has been treated by a second or additional therapeutic agent effective to treat AAV. In some embodiments, the second / additional therapeutic agent comprises a cyclophosphamide (Cytoxan), methotrexate (MTX), azathioprine (Imuran), trimethoprim-sulfamethoxazole (Bactrim, Septra), plasma exchange, cyclosporine (Sandimmune), intravenous immunoglobulin, monoclonal antibodies, H2-blockers or proton-pump inhibitors, fluconazole (Diflucan), trimethoprim-sulfamethoxazole, and/or Avacopan.

[0119] In some embodiments, the subject has been treated, and/or is being treated with cyclophosphamide (*e.g.*, Cytoxan). In some embodiments, the cyclophosphamide is administered monthly intravenously (*e.g.*, by infusion) or orally (*e.g.*, as a daily pill). In some embodiments, the cyclophosphamide is administered over 3 to 6 months as induction therapy to treat the disease into remission.

[0120] In some embodiments, the subject has been treated, and/or is being treated with Azathioprine (Imuran), which may be administered as part of the maintenance therapy (*e.g.*, after treatment with cyclophosphamide or possibly rituximab).

[0121] In some embodiments, the subject has been treated, and/or is being treated with Plasmapheresis to remove antibodies (such as the ANCA autoantibodies) from the bloodstream. In some embodiments, the Plasmapheresis is performed every 1-2 days for about 2 weeks.

[0122] In some embodiments, the subject achieves remission (BVAS ver. 3 = 0) at Week 26 of treatment; and/or wherein the subject maintains remission at Week 52 of treatment.

[0123] In some embodiments, after 26 weeks of treatment, the subject, compared to control (such as SOC treatment alone), achieves: i) $\geq 30\%$ reduction in uACR (urinary albumin creatinine ratio); ii) 10%, 20%, 30%, 40%, or 50% reduced time to reduction in uACR by $\geq 30\%$; iii) 10%, 20%, 30%, 40%, or 50% reduced time to remission (BVAS = 0); and/or, iv) attains BVAS 50% or BVAS 90% at 26-52 weeks after the administration of the initial IV dose.

[0124] It should be understood that any one embodiment of the invention described herein, including those described only in the examples and claims, can be combined with any other one or more embodiments of the invention, unless such combination is expressly disclaimed or are improper.

[0125] The definitions and methods provided define the present disclosure and guide those of ordinary skill in the art in the practice of the present disclosure. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0126] As used herein, the term “antibody” refers to a protein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region (abbreviated herein as CH). In certain antibodies, *e.g.*, naturally occurring IgG antibodies, the heavy chain constant region is comprised of a hinge and three domains, CH1, CH2 and CH3. In certain antibodies, *e.g.*, naturally occurring IgG antibodies, each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain (abbreviated herein as CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. A heavy chain may have the C-terminal lysine or not. Unless specified otherwise herein, the amino acids in the variable regions are numbered using the Rabat numbering system and those in the constant regions are numbered using the EU system. “Antibody” includes, by way of example, both naturally

occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human and nonhuman antibodies and wholly synthetic antibodies.

[0127] An “IgG antibody”, *e.g.*, a human IgG1, IgG2, IgG3 and IgG4 antibody, as used herein, has, in some embodiments, the structure of a naturally occurring IgG antibody, *i.e.*, it has the same number of heavy and light chains and disulfide bonds as a naturally occurring IgG antibody of the same subclass. For example, an anti-C3d IgG1, IgG2, IgG3 or IgG4 antibody consists of two heavy chains (HCs) and two light chains (LCs), wherein the two heavy chains and light chains are linked by the same number and location of disulfide bridges that occur in naturally occurring IgG1, IgG2, IgG3 and IgG4 antibodies, respectively (unless the antibody has been mutated to modify the disulfide bridges).

[0128] Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K_D) of 10^{-5} to 10^{-11} M or less. Any K_D greater than about 10^{-4} M is generally considered to indicate nonspecific binding.

[0129] In some embodiments, the anti-C3d antibody portion of the fusion protein of the invention specifically binds to C3d (both as free antibody and antibody within the fusion protein), such as binding specifically with a K_D of 10^{-5} to 10^{-11} M or less (*e.g.*, 10^{-5} M or less, 10^{-6} M or less, 10^{-7} M or less, 10^{-8} M or less, 10^{-9} M or less, 10^{-10} M or less, or 10^{-11} M or less).

[0130] In some embodiments, the anti-C3d antibody used or useful for the method described herein binds specifically to C3d (such as human C3d) with a K_D of 10^{-7} M or less, 10^{-8} M or less, 5×10^{-9} M or less, or between 10^{-8} M and 10^{-10} M or less, but does not bind with high affinity to unrelated antigens.

[0131] As used herein, “isotype” refers to the antibody class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE antibody) that is encoded by the heavy chain constant region genes. The IgG isotype is divided in subclasses in certain species: IgG1, IgG2, IgG3 and IgG4 in humans, and IgG1, IgG2a, IgG2b and IgG3 in mice. In some embodiments, the anti-C3d antibodies described herein are of the IgG1 isotype. Immunoglobulins, *e.g.*, IgG1, exist in several allotypes, which differ from each other in at most a few amino acids.

[0132] As used herein, the term “allotype” refers to naturally occurring variants within a specific isotype group, wherein the variants differ in a few amino acids. Anti-C3d antibodies described herein can be of any allotype. As used herein, antibodies referred to as “IgG1f,” “IgG1. If,” or “IgG1.3f” isotype are IgG1, effectorless IgG1.1, and effectorless IgG1.3

antibodies, respectively, of the allotype “f,” *i.e.* having 214R, 356E and 358M according to the EU index as in Kabat.

[0133] The term “antigen-binding portion” of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, human C3d). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term “antigen-binding portion” of an antibody, *e.g.*, an anti-C3d antibody described herein, include (i) a Fab fragment (fragment from papain cleavage) or a similar monovalent fragment consisting of the VL, VH, LC and CH1 domains; (ii) a F(ab')₂ fragment (fragment from pepsin cleavage) or a similar bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a F_d fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment which consists of a VH domain; (vi) an isolated complementarity determining region (CDR) and (vii) a combination of two or more isolated CDRs which can optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv)). Such single chain antibodies are also intended to be encompassed within the term “antigen-binding portion” of an antibody.

[0134] These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

[0135] The term “monoclonal antibody,” as used herein, refers to an antibody from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprised in the population are substantially similar and bind the same epitope(s) (*e.g.*, the antibodies display a single binding specificity and affinity), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

[0136] The term “human monoclonal antibody” refers to an antibody from a population of substantially homogeneous antibodies that display(s) a single binding specificity and

which has variable and optional constant regions derived from human germline immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0137] The term “recombinant human antibody,” as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize particular human germline immunoglobulin sequences are encoded by the germline genes, but include subsequent rearrangements and mutations which occur, for example, during antibody maturation. As known in the art, the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for a foreign antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the foreign antigen. The constant region will change in further response to an antigen (*i.e.*, isotype switch). Therefore, the rearranged and somatically mutated nucleic acid molecules that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen cannot have sequence identity with the original nucleic acid molecules, but instead will be substantially identical or similar (*i.e.*, have at least 80% identity).

[0138] A “human” antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The anti-IL-7R antibodies described herein can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term “human antibody”, as used herein, is not intended to include antibodies in which CDR sequences derived from

the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms “human” antibodies and “fully human” antibodies are used synonymously.

[0139] A “humanized” antibody refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an antibody, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the antibody to bind to a particular antigen. A “humanized” antibody retains an antigenic specificity similar to that of the original antibody.

[0140] A “chimeric antibody” refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

[0141] The phrases “an antibody recognizing an antigen” and “an antibody specific for an antigen” are used interchangeably herein with the term “an antibody which binds specifically to an antigen.”

[0142] An “isolated antibody,” as used herein, is intended to refer to an antibody which is substantially free of other proteins and cellular material.

[0143] An “effector function” refers to the interaction of an antibody Fc region with an Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary “effector functions” include Clq binding, complement dependent cytotoxicity (CDC), Fc receptor binding, FcγR-mediated effector functions such as ADCC and antibody dependent cell-mediated phagocytosis (ADCP), and downregulation of a cell surface receptor (*e.g.*, the B cell receptor; BCR). Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.*, an antibody variable domain).

[0144] An “Fc receptor” or “FcR” is a receptor that binds to the Fc region of an immunoglobulin. FcRs that bind to an IgG antibody comprise receptors of the FcγR family, including allelic variants and alternatively spliced forms of these receptors. The FcγR family consists of three activating (FcγRI, FcγRIII, and FcγRIV in mice; FcRIA, FcRIIA, and FcRIIIA in humans) and one inhibitory (FcγRIIB) receptor. Various properties of human FcγRs are known in the art. The majority of innate effector cell types coexpress one or more

activating Fc γ R and the inhibitory Fc γ RIIB, whereas natural killer (NK) cells selectively express one activating Fc receptor (Fc γ RIII in mice and Fc γ RIIIA in humans) but not the inhibitory Fc γ RIIB in mice and humans. Human IgG1 binds to most human Fc receptors and is considered equivalent to murine IgG2a with respect to the types of activating Fc receptors that it binds to.

[0145] An “Fc region” (fragment crystallizable region) or “Fc domain” or “Fc” refers to the C-terminal region of the heavy chain of an antibody that mediates the binding of the immunoglobulin to host tissues or factors, including binding to Fc receptors located on various cells of the immune system (*e.g.*, effector cells) or to the first component (C1q) of the classical complement system. Thus, an Fc region comprises the constant region of an antibody excluding the first constant region immunoglobulin domain (*e.g.*, CH1 or CF). In IgG, IgA and IgD antibody isotypes, the Fc region comprises two identical protein fragments, derived from the second (CH2) and third (CH3) constant domains of the antibody's two heavy chains; IgM and IgE Fc regions comprise three heavy chain constant domains (CH domains 2-4) in each polypeptide chain. For IgG, the Fc region comprises immunoglobulin domains CH2 and CH3 and the hinge between CH1 and CH2 domains. Although the definition of the boundaries of the Fc region of an immunoglobulin heavy chain might vary, as defined herein, the human IgG heavy chain Fc region is defined to stretch from an amino acid residue D221 for IgG1, V222 for IgG2, F221 for IgG3 and P224 for IgG4 to the carboxy-terminus of the heavy chain, wherein the numbering is according to the EU index as in Kabat. The CH2 domain of a human IgG Fc region extends from amino acid 237 to amino acid 340, and the CH3 domain is positioned on C-terminal side of a CH2 domain in an Fc region, *i.e.*, it extends from amino acid 341 to amino acid 447 or 446 (if the C-terminal lysine residue is absent) or 445 (if the C-terminal glycine and lysine residues are absent) of an IgG. As used herein, the Fc region can be a native sequence Fc, including any allotypic variant, or a variant Fc (*e.g.*, a non-naturally occurring Fc). Fc can also refer to this region in isolation or in the context of an Fc-comprising protein polypeptide such as a “binding protein comprising an Fc region,” also referred to as an “Fc fusion protein” (*e.g.*, an antibody or immunoadhesion).

[0146] A “native sequence Fc region” or “native sequence Fc” comprises an amino acid sequence that is identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region; native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof. Native sequence Fc include the various allotypes of Fcs.

[0147] The term “epitope” or “antigenic determinant” refers to a site on an antigen (*e.g.*, C3d) to which an immunoglobulin or antibody specifically binds, *e.g.*, as defined by the specific method used to identify it. Epitopes can be formed both from contiguous amino acids (usually a linear epitope) or noncontiguous amino acids juxtaposed by tertiary folding of a protein (usually a conformational epitope). Epitopes formed from contiguous amino acids are typically, but not always, retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody (*i.e.*, epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from (*e.g.*, from C3d) are tested for reactivity with a given antibody (*e.g.*, anti-C3d antibody). Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, X-ray crystallography, antigen mutational analysis, 2-dimensional nuclear magnetic resonance and HDX-MS.

[0148] The term “ k_{assoc} ” or “ k_a ”, as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term “ k_{dis} ” or “ k_d ”, as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term “ K_D ”, as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of k_d to k_a (*i.e.*, k_d/k_a) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. Available methods for determining the K_D of an antibody include surface plasmon resonance, a biosensor system such as a BIACORE® system or flow cytometry and Scatchard analysis.

[0149] As used herein, the term “high affinity” for an IgG antibody refers to an antibody having a K_D of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M or less for a target antigen. However, “high affinity” binding can vary for other antibody isotypes. For example, “high affinity” binding for an IgM isotype refers to an antibody having a K_D of 10^{-10} M or less, or 10^{-8} M or less.

[0150] The term “EC50” in the context of an *in vitro* or *in vivo* assay using an antibody or antigen binding fragment thereof, refers to the concentration of an antibody or an antigen-binding portion thereof that induces a response that is 50% of the maximal response, *i.e.*, halfway between the maximal response and the baseline.

[0151] The term “inflammation” or an “inflammatory process,” as used herein, refers to a complex series of events, including dilatation of arterioles, capillaries and venules, with

increased permeability and blood flow, exudation of fluids, including plasma proteins and leukocyte migration into the inflammatory focus. Inflammation may be measured by many methods well known in the art, such as the number of leukocytes, the number of polymorphonuclear neutrophils (PMN), a measure of the degree of PMN activation, such as luminal enhanced-chemiluminescence, or a measure of the amount of proinflammatory cytokines (*e.g.*, IL-6 or TNF- α) present.

[0152] As used herein, the term “regulatory T cells” (Tregs) refer to a population of T cells with the ability to reduce or suppress the induction and proliferation of effector T cells, and thereby, modulate an immune response. In some embodiments, Tregs can suppress an immune response by secreting anti-inflammatory cytokines, such as IL-10, TGF- β , and IL-35, which can interfere with the activation and differentiation of naive T cells into effector T cells. In some embodiments, Tregs can also produce cytolytic molecules, such as Granzyme B, which can induce the apoptosis of effector T cells. In some embodiments, the regulatory T cells are natural regulatory T cells (nTregs) (*i.e.*, developed within the thymus). In some embodiments, the regulatory T cells are induced regulatory T cells (iTregs) (*i.e.*, naive T cells that differentiate into Tregs in the peripheral tissue upon exposure to certain stimuli). Methods for identifying Tregs are known in the art. For example, Tregs express certain phenotypic markers (*e.g.*, CD25, Foxp3, or CD39) that can be measured using flow cytometry. In some embodiments, the Tregs are CD45RA⁻ CD39⁺ T cells.

[0153] As used herein, “administering” refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Different routes of administration for the fusion protein of the invention comprising the anti-C3d antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrastemal injection and infusion, as well as *in vivo* electroporation. Alternatively, an antibody described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0154] The terms “treat,” “treating,” and “treatment,” as used herein, refer to any type of intervention or process performed on, or administering an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down or preventing the progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease or enhancing overall survival. These terms do not include prophylactic intervention.

[0155] The term “prophylactic intervention” refers to treating a subject who does not yet have a disease for preventive purpose.

[0156] The term “effective dose” or “effective dosage” is defined as an amount sufficient to achieve or at least partially achieve a desired effect.

[0157] A “therapeutically effective amount” or “therapeutically effective dosage” of a drug or therapeutic agent (*e.g.*, the subject fusion protein) is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A therapeutically effective amount or dosage of a drug includes a “prophylactically effective amount” or a “prophylactically effective dosage,” which is any amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic agent to promote disease regression or inhibit the development or recurrence of the disease can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials (including the methods described in the examples), in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0158] The term “patient” includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment. In some embodiments, the patient is a human.

[0159] As used herein, the term “subject” includes any human or non-human animal. For example, the methods and compositions described herein can be used to treat a subject having cancer. The term “non-human animal” includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, *etc.*

[0160] The term “weight based” dose or dosing as referred to herein means that a dose that is administered to a patient is calculated based on the weight of the patient. For example, when a patient with 60 kg body weight requires 3 mg/kg of the subject fusion protein, one can calculate and use the appropriate amount of the fusion protein (*i.e.*, 180 mg) for administration.

[0161] Provided are methods for the treatment of AAV using isolated fusion protein as described herein. Representative fusion proteins of the invention, including COMPOUND B, are described in WO2020123662 (the entire contents of which, including sequence listing, are incorporated herein by reference.

[0162] In certain embodiments, the fusion protein construct comprises: 1) an antibody or an antigen binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and, (b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6, and 2) a complement modulator polypeptide, wherein the complement modulator polypeptide comprises factor H or a biologically active fragment thereof.

[0163] The heavy chain CDR region sequences, the light chain CDR sequences, the VH and VL regions encompassing these CDR sequences, as well as the full length antibody sequences, such as those for COMPOUND B, are provided in the table below.

[0164] Amino acid sequences of anti-C3d antibody in COMPOUND B:

SEQ ID NO	SEQ ID NO as in WO2020123662	DESCRIPTION	SEQUENCE
1	29	VH CDR1	GYTFTNYY
2	260	VH CDR2	INPYSGGT
3	31	VHCDR3	SSPY
4	32	VL CDR1	QSLDSDGKTY
5	33	VL CDR2	LVS
6	34	VL CDR3	WQGTTFPRT
7	254	Heavy Chain Variable Region, VH or HCVR	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYYINWVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM

			TVDTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSS
8	258	Light Chain Variable Region, VL or LCVR	DVVMTQSPLSLPVTLGQPASISCKSSQSLLDSDGK TYLNWFQQRPGQSPRRLIYLVSKLDSGVPDRFSGS GSGTDFTLKISRVEAEDVGVIYCWQGTHTFPRTFGG GTKVEIK
9	282	Heavy Chain (HC)	QVQLVQSGAEVKKPGASVKVSKASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVLH EALHSHYTQKSLSLSLG
11	284	Heavy Chain Variable Region + CH1 (VH + CH1)	QVQLVQSGAEVKKPGASVKVSKASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVE SKYG
10	285	Heavy Chain (HC)	QVQLVQSGAEVKKPGASVKVSKASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLG
12	279	Light Chain (LC)	DVVMTQSPLSLPVTLGQPASISCKSSQSLLDSDGK TYLNWFQQRPGQSPRRLIYLVSKLDSGVPDRFSGS GSGTDFTLKISRVEAEDVGVIYCWQGTHTFPRTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC

[0165] In the table above, any of the three HC sequences (*i.e.*, SEQ ID NOs: 9 and 10), or the VH and CH1 sequence of SEQ ID NO: 11 may be present in the fusion protein

construction of the invention. In certain embodiments, the HC sequence is SEQ ID NO: 9 (as in COMPOUND B). In certain embodiments, the HC sequence comprises SEQ ID NO: 11.

In certain embodiments, the HC sequence is SEQ ID NO: 10.

[0166] In certain embodiments, the the fusion protein further comprises: (c) a first linker bound to the C-terminus of the first heavy chain and comprising the amino acid sequence of SEQ ID NO: 14; and (d) a second linker bound to the C-terminus of the second heavy chain and comprising the amino acid sequence of SEQ ID NO: 14.

[0167] SEQ ID NO: 138 as used in WO2020123662 is: GGGGSGGGGS (SEQ ID NO: 14).

[0168] In certain embodiments, the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 72 or 108, as used in WO2020123662:

EDCNELPPRRNTEILTGSWSDQTYPEGTQAIYKCRPGYRSLGNVIMVCRKGEWVALNPLRKC
QKRPCGHPGDTPFGTFTLTGGNVFEYGVKAVYTCNEGYQLLGEINYRECDTDGWTNDIPICE
VVKCLPVTAPENGKIVSSAMEPDREYHFGQAVRFVCNSGYKIEGDEEMHCSDDGFWSKEPKK
CVEISCKSPDVINGSPISQKIIYKENERFQYKCNMGYEYSERGDAVCTESGWRPLPSCEEKS
CDNPYIPNGDYSPLRIKHRTGDEITYQCRNGFYPATRGNTAKCTSTGWIPAPRCTLK (SEQ
ID NO: 15, *i.e.*, SEQ ID NO: 72 as used in WO2020123662 –
soluble factor H 1–5 or fH_{1–5})

EDCNELPPRRNTEILTGSWSDQTYPEGTQAIYKCRPGYRSLGNVIMVCRKGEWVALNPLRKC
QKRPCGHPGDTPFGTFTLTGGNVFEYGVKAVYTCNEGYQLLGEINYRECDTDGWTNDIPICE
VVKCLPVTAPENGKIVSSAMEPDREYHFGQAVRFVCNSGYKIEGDEEMHCSDDGFWSKEPKK
CVEISCKSPDVINGSPISQKIIYKENERFQYKCNMGYEYSERGDAVCTESGWRPLPSCEEKS
CDNPYIPNGDYSPLRIKHRTGDEITYQCRNGFYPATRGNTAKCTSTGWIPAPRCTLKENLYF
QGHHHHHH (SEQ ID NO: 16, *i.e.*, SEQ ID NO: 108 as used in
WO2020123662 – Factor H (1–5) with His₆ tag, and TEV cleavage
site (double underlined)).

[0169] Provided herein are compositions comprising a fusion protein comprising an anti-C3d antibody or antigen-binding portion thereof fused to a complement inhibitor (such as fH fragment) as described herein, having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer.

[0170] Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium

chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

[0171] In a specific embodiment, pharmaceutical compositions comprise a fusion protein as described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In a specific embodiment, pharmaceutical compositions comprise an effective amount of the fusion protein described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In some embodiments, the fusion protein is the only active ingredient included in the pharmaceutical composition. Pharmaceutical compositions described herein can be useful in modulating (e.g., reducing or inhibiting) local / tissue complement activity (e.g., in disease tissue / organs / blood vessels / capillaries where there is complement activity as evidenced by C3d deposit) wherein systemic complement activity remain substantially unaffected.

[0172] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In some embodiments, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, i.e., antibody, immunoconjugate, or bispecific molecule, can be coated in a material to protect the compound from the action of acids and other natural conditions that can inactivate the compound.

[0173] Also provided is a pharmaceutical formulation, which improves the stability of the fusion protein described herein, and thus, allows for their long term storage. In some embodiments, the pharmaceutical formulation disclosed herein comprises: (a) a fusion protein described herein; (b) a buffering agent; (c) a stabilizing agent; (d) a salt; (e) a bulking agent; and/or (f) a surfactant. In some embodiments, the pharmaceutical formulation is stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, at

least 2 years, at least 3 years, at least 5 years or more. In some embodiments, the formulation is stable when stored at 4°C, 25°C, or 40°C.

[0174] Buffering agents can be a weak acid or base used to maintain the acidity (pH) of a solution near a chosen value after the addition of another acid or base. Suitable buffering agents can maximize the stability of the pharmaceutical formulations by maintaining pH control of the formulation. Suitable buffering agents can also ensure physiological compatibility or optimize solubility. Rheology, viscosity and other properties can also dependent on the pH of the formulation. Common buffering agents include, but are not limited to, histidine, citrate, succinate, acetate and phosphate. In some embodiments, a buffering agent comprises histidine (e.g., L-histidine) with isotonicity agents and potentially pH adjustment with an acid or a base known in the art. In some embodiments, the buffering agent is L- histidine. In some embodiments, the pH of the formulation is maintained between about 2 and about 10, or between about 4 and about 8.

[0175] Stabilizing agents are added to a pharmaceutical product in order to stabilize that product. Such agents can stabilize proteins in a number of different ways. Common stabilizing agents include, but are not limited to, amino acids such as glycine, alanine, lysine, arginine, or threonine, carbohydrates such as glucose, sucrose, trehalose, raffinose, or maltose, polyols such as glycerol, mannitol, sorbitol, cyclodextrins or dextrans of any kind and molecular weight, or PEG. In some embodiments, the stabilizing agent is chosen in order to maximize the stability of FIX polypeptide in lyophilized preparations. In some embodiments, the stabilizing agent is sucrose and/or arginine.

[0176] Bulking agents can be added to a pharmaceutical product in order to add volume and mass to the product, thereby facilitating precise metering and handling thereof. Common bulking agents include, but are not limited to, lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, or magnesium stearate.

[0177] Surfactants are amphipathic substances with lyophilic and lyophobic groups. A surfactant can be anionic, cationic, zwitterionic, or nonionic. Examples of nonionic surfactants include, but are not limited to, alkyl ethoxylate, nonylphenol ethoxylate, amine ethoxylate, polyethylene oxide, polypropylene oxide, fatty alcohols such as cetyl alcohol or oleyl alcohol, cocamide MEA, cocamide DEA, polysorbates, or dodecyl dimethylamine oxide. In some embodiments, the surfactant is polysorbate 20 or polysorbate 80.

[0178] In some embodiments, the pharmaceutical formulation comprises the subject fusion protein formulated in 12 mM sodium phosphate, 75 mM arginine, 125 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.7.

[0179] The formulation can further comprise one or more of a buffer system, a preservative, a tonicity agent, a chelating agent, a stabilizer and/or a surfactant, as well as various combinations thereof. The use of preservatives, isotonic agents, chelating agents, stabilizers and surfactants in pharmaceutical compositions is well-known to the skilled person.

[0180] In some embodiments, the pharmaceutical formulation is an aqueous formulation. Such a formulation is typically a solution or a suspension, but may also include colloids, dispersions, emulsions, and multi-phase materials. The term "aqueous formulation" is defined as a formulation comprising at least 50% w/w water. Likewise, the term "aqueous solution" is defined as a solution comprising at least 50 % w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 % w/w water.

[0181] In some embodiments, the pharmaceutical formulation is a freeze-dried formulation, to which the physician or the patient adds solvents and/or diluents prior to use.

[0182] Pharmaceutical compositions described herein also can be administered in combination therapy, *i.e.*, combined with other agents. For example, the combination therapy can include a fusion protein described herein combined with at least one other therapeutic agent. Examples of therapeutic agents that can be used in combination therapy can include other compounds, drugs, and/or agents used for the treatment of a disease or disorder (*e.g.*, an inflammatory disorder such as AAV).

[0183] The pharmaceutical composition described herein can include one or more pharmaceutically acceptable salts.

[0184] A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chlorprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[0185] A pharmaceutical composition described herein can also include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable

antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0186] Examples of suitable aqueous and nonaqueous carriers that can be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0187] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms can be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0188] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions described herein is contemplated. A pharmaceutical composition can comprise a preservative or can be devoid of a preservative. Supplementary active compounds can be incorporated into the compositions.

[0189] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and

suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, the compositions can include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0190] Sterile injectable solutions can be prepared by incorporating the active fusion in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active fusion into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated herein. In the case of sterile powders for the preparation of sterile injectable solutions, some methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0191] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.01 percent to about ninety-nine percent of active ingredient, from about 0.1 percent to about 70 percent, or from about 1 percent to about 30 percent of active ingredient in combination with a pharmaceutically acceptable carrier.

[0192] Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions described herein employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition,

general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0193] A composition described herein can be administered via one or more routes of administration using one or more of a variety of methods taught herein and/or known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration may vary depending upon the desired results. Routes of administration for the fusion protein described herein can include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous (IV), intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous (SC), subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrastemal injection and infusion.

[0194] Alternatively, a fusion protein described herein could potentially be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

[0195] The active compounds / fusion proteins of the invention can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and poly lactic acid. Many methods for the preparation of such formulations are generally known to those skilled in the art.

[0196] Therapeutic compositions can be administered with medical devices known in the art. For example, in a particular embodiment, a therapeutic composition described herein can be administered with a needleless hypodermic injection device. Examples of well-known implants and modules for use with the fusion proteins described herein include an implantable micro-infusion pump for dispensing medication at a controlled rate; a therapeutic device for administering medicaments through the skin; a medication infusion pump for delivering medication at a precise infusion rate; a variable flow implantable infusion apparatus for continuous drug delivery; an osmotic drug delivery system having multi-chamber compartments; and an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

EXAMPLES***Example 1 Phase 1 study evaluating the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of COMPOUND B***

[0197] A randomized, double-blind, placebo-controlled study of COMPOUND B with single ascending and multiple doses to evaluate safety, PK, and PD was performed in healthy participants. Briefly, COMPOUND B was administered in single dose cohorts IV (intravenous) at 0.1-30 mg/kg, or SC (subcutaneous) at 3.75 and 10 mg/kg and in one multiple dose cohort of 450 mg SC QW (once a week) for 5 doses (see FIG. 7A). Safety was evaluated through the review of adverse events, physical examinations, clinical laboratory tests, vital signs and electrocardiograms. Circulating complement alternative pathway (AP) activity, which represents systemic complement AP activity), was measured by Wieslab assay. An exploratory PK/PD model was used to project a dose that maintains circulating drug concentrations in a target range of 0.2 - 3.2 µg/mL.

[0198] Specifically, a total of 56 healthy male and female subjects (49 subjects in Study Part 1, and 7 participants in Study Part 2) were enrolled in this study. Thirty-two received COMPOUND B and 17 received placebo in Part 1 (SAD); 4 subjects received COMPOUND B, and 3 received placebo Part 2 (MAD) (see FIG. 7B). Demographic characteristics were generally similar between placebo and COMPOUND B treated groups in both SAD and MAD cohorts, except that there was higher proportion of female participants in COMPOUND B-treated groups compared to placebo.

[0199] The results showed that COMPOUND B was well tolerated across all dose levels with no clinically significant drug-related safety findings or anti-drug antibodies (ADAs) observed.

[0200] At all doses tested, no deaths occurred, and no serious or ≥ Grade 3 TEAEs (treatment-emergent adverse events) were reported (FIG. 7C). None of the TEAEs led to study drug discontinuation or to withdrawal from the study.

[0201] Four of 24 (16.7%) participants treated with single dose IV, 1 out of 8 (12.5%) treated with single dose SC, and 1 out of 3 (33.3%) treated with 450 mg QW SC of COMPOUND B had treatment-emergent ADA. Titers are ranging from 20-160, which is generally low and at or close to the assay minimal required dilution. The ADA was detected

at the time points when COMPOUND B concentration was below limit of quantification. Therefore, no impact on PK/PD can be evaluated.

[0202] It can be observed in the data in FIG. 7D that mean maximum concentration ($C_{\max}$) in intravenous (IV) administration increased in an approximately dose-proportional manner following 0.1 to 30 mg/kg IV, whereas area under the concentration-time curve (AUC) increased in an approximately dose-proportional manner from 0.1 to 1 mg/kg IV and in a greater than dose-proportional manner from 1 to 30 mg/kg IV.

[0203] In subcutaneous (SC) administration (FIG. 7E), $C_{\max}$ and AUC increased in a greater than dose-proportional manner from 3.75 to 10 mg/kg SC. Following 5 weekly doses of SC administration of 450 mg, mild accumulation was observed. The estimated SC bioavailability was approximately 49.9% using a population PK modeling approach.

[0204] Non-compartmental analysis (NCA)-calculated terminal half-life ($T_{1/2}$) was dose-dependent.

[0205] Dose-dependent reductions in serum alternative pathway (AP) activity were observed after single IV doses of 0.3-30 mg/kg. The highest dose, 30 mg/kg IV of COMPOUND B resulted in AP complement activity at or below the LLOQ (Lower Limit of Quantitation) of the assay (35% of baseline Wieslab activity) at the end of infusion; inhibition of AP activity decreased after 7 days and completely returned to baseline by 14 days post-dose (see FIG. 7F).

[0206] After a single SC injection of 10 mg/kg COMPOUND B, mean serum AP activity decreased from 100% pre-dose to 65% of baseline at 1 day post-dose and then returned to baseline by 7 days post-dose. There was no apparent post-dose changes in mean serum AP activity after a single SC injection of 3.75 mg/kg or 5 SC doses of 450 mg QW (see FIG. 7G).

[0207] No apparent changes were observed in mean serum complement classic pathway (CP) after single doses of IV up to 3 mg/kg or SC up to 10 mg/kg (FIG. 7H), or 5 weekly SC injections of 450 mg COMPOUND B (FIG. 7I). After a single dose of 30 mg/kg IV of COMPOUND B, mean serum CP activity decreased from 100% pre-dose to 61% of baseline at the end of infusion, then started to return to baseline after 1 day, and returned to the baseline level completely by 7 days post-dose (FIG. 7H).

[0208] Monte Carlo simulations were performed using an exploratory PK/PD model. PK and PD of 1,000 participants were predicted using an assumed geometric mean (coefficient of variance [CV]%), body weight of 80 (18.2% CV) kg and a BMI of 27.68 (13.1% CV) kg/m².

Baseline Wieslab AP levels were uniformly sampled with replacement from the distribution of participants enrolled in the Phase 1 study.

[0209] Potential clinical dosing regimens were simulated using 26 SC doses of 450 mg administered weekly (QW) (FIG. 7J). The model predicted 99% subjects achieve greater than 3.2 µg/mL target concentration of C_{trough} at steady state following 450 mg SC QW.

[0210] The estimated concentration of COMPOUND 1 that leads to 50% inhibition of Wieslab AP activity (IC_{50}) is 56.3 µg/mL (FIG. 7K). The estimated median C_{max} at steady state after 450 mg SC QW dosing is 9.62 µg/mL, indicating no apparent AP inhibition is expected at this dose (FIG. 7K).

[0211] In summary, COMPOUND B was well tolerated across all dose levels with no clinically significant drug-related safety findings or ADAs observed. COMPOUND B demonstrated a robust PK/PD relationship with a systemic AP IC_{50} of 56.3 µg/mL. PK/PD simulations projected that 450 mg COMPOUND B SC QW can attain circulating concentrations in the target range for maximal tissue pharmacology in preclinical models, with a $C_{\text{max,ss}}$ ~5-fold below the IC_{50} for systemic AP inhibition.

Example 2 A Phase 2a, Randomized, Double-blind, Placebo-Controlled, Trial of COMPOUND B for the Treatment of ANCA-Associated Vasculitis (AAV)

[0212] COMPOUND B is a fusion protein comprising a fully human, high affinity anti-C3d monoclonal antibody (mAb) fused at the C-termini of its two heavy chains with the factor H fragment fH₁₋₅, each through a flexible (G₄S)₂ linker. COMPOUND B is demonstrated here as an effective treatment for AAV.

[0213] This example demonstrates that COMPOUND B is effective to reduce symptoms of AAV in patients, at least by Week 26 after commencement of treatment based on the dosing regimen described herein. The primary objective of the trial is to show the effect of COMPOUND B with standard of care (SOC) vs SOC alone, to induce disease remission at Week 26 after the commencement of the treatment. Here, the SOC includes a combination therapy using Rituximab (RTX) and glucocorticoid (GC). See the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases (KDIGO Glomerular Diseases Work Group 2021, *Kidney Int.* 2021;100(4S):S1-S276, incorporated herein by reference). The results of this clinical study demonstrate that (1) COMPOUND B, when added to existing SOC therapy, is superior to existing therapy as assessed by either time to achieve remission, or ultimate fraction of patients achieving remission, or both; (2)

COMPOUND B may enable a further reduction in, or elimination of, GC as part of SOC induction of remission therapy; and/or (3) COMPOUND B, when added to existing SOC therapy, is superior at maintaining patients in remission.

[0214] This primary objective is assessed based on the primary endpoint of BVAS (ver.3) at 26 weeks compared with SOC alone (*e.g.*, percentage of patients achieving remission, or BVAS of 0, at Week 26 in the COMPOUND B treatment group vs. the SOC alone group), where effective treatment by COMPOUND B is evidenced by a showing of statistical non-inferiority (with a -25% margin) compared to the SOC alone treatment.

[0215] A detailed study design is provided in FIGs. 1A and 1B. Briefly, the trial includes Parts A and B. Part A is an open label study with 10-12 enrolled patients. The primary intent of the open-label period (Part A) of the study is to provide an opportunity to assess the safety of adding COMPOUND B to SOC therapy in this population. This period also provides an opportunity to characterize the PK and PD profiles of COMPOUND B in patients with AAV in whom AP activation and concomitant features, such as renal impairment, may alter the target sink relative to normal healthy volunteers. Starting from Week 0, about 4 patients in Cohort 1 are given SOC (RTX and GC) with COMPOUND B for 12 weeks (or 13 total doses). Some patients are given tapering doses of GC during the last 4 weeks (4 doses) of this open label period. Part A continues for additional 14 weeks (for a total of 26 weeks) of follow-up period during which no patients are given COMPOUND B, but treatment by SOC (including tapering of GC) continues. Optional biopsy's are obtained from patients at Weeks 0, 12, and 26. Furthermore, at Week 4, safety and PK assessments are conducted. Following review of data from this first sentinel cohort (Part A Cohort 1), including the evaluation of early biomarker data and measures of disease response, Part A Cohort 2 are enrolled. Patients in Part A Cohort 2 receive RTX and COMPOUND B as in the sentinel group but also undergo a more rapid oral GC taper over 4 weeks to examine the potential for steroid sparing with the addition of COMPOUND B to SOC. Histological analyses from pre- and post-treatment kidney biopsies in Part A also provides the potential for early demonstration of proof of mechanism and proof of concept in this population.

[0216] Also at Week 4 of Part A, Part B of the study commences (*i.e.*, Week 0 of Part B) with 3 cohorts of patients. Cohort 1 of about 25 patients are given weekly SOC (RTX & GC) for 26 total weeks (Week 0-26). Cohort 2 of about 15 patients are given SOC and COMPOUND B, including one initial IV dose of about 1400 mg at Week 0 (of Part B), followed by 26 weekly SC maintenance doses of about 450 mg each. Cohort 3 of about 25 patients are given the same treatment as Cohort 2, except that patients in Cohort 3 have

tapering GC dosing starting from Week 2 of Part B. In other words, about 65 total patients are enrolled in Part B, with 2:1:2 randomization into Cohorts 1-3. Part B optionally continues for another 26 weeks to Week 52 through an optional follow-up period during which only SOC is given to each patients in Cohorts 1-3. Optional biopsys are taken at Weeks 0, 26, and 52 of Part B.

[0217] A number of secondary objectives of the trial are also investigated, including:

- change in uACR from baseline
- time to improvement in uACR
- change in BVAS from baselines
- time to remission (BVAS score 0)
- change in eGFR from baseline
- change in urinary MCP1: creatinine ratio from baseline; and time to improvement
- change from baseline in urinary sC5b-9 and time to improvement

[0218] The treatment also has post-treatment duration effect on reducing BVAS in participants with AAV, in that a significant percentage of patients receiving treatment (1) maintain relative percent change from baseline in BVAS score at Week 26 compared with Baseline, and at Week 52, (2) achieve $\geq 50\%$ relative reduction in BVAS score from baseline, at Week 26 compared with Baseline, and at Week 52, and/or (3) have $\geq 50\%$ participants with BVAS score ≤ 5 , 10, 20, 30, and 50, at Week 26, and at Week 52.

[0219] Pharmacokinetics (PK) and immunogenicity of COMPOUND B in treated patients are also characterized to be desirable, based on assays including serum COMPOUND B concentrations based on Schedule of Assessments [SoA], and anti-drug antibody (ADA) rate.

[0220] Finally, the safety and tolerability of COMPOUND B are evaluated, including acceptable numbers or percentages of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) including injection site tolerability, in view of laboratory evaluations, physical examinations, vital signs, and 12-lead electrocardiogram (ECG).

Dose and Frequency (Dosing Regimen)

[0221] Participants are administered either COMPOUND B with SOC, or SOC (RTX + GC) alone.

[0222] COMPOUND B is formulated as 75 mg/mL drug product solution for *s.c.* injection, provided in aseptic filled, sterile, 2R borosilicate glass vials with a Flurotec serum stopper and a matte cap flip-off seal. Each vial contains an extractable volume of 1.5 mL minimum of COMPOUND B. That is, each dose of COMPOUND B contains 112.5 mg of COMPOUND B fusion protein, which is administered as a flat/fixed dose once every week according to the dosing regimen, for a total of one initial IV dose of about 1400 mg COMPOUND B, and 25 SC maintenance doses of about 450 mg each.

[0223] The initial IV dose saturates the COMPOUND B target sink in the circulation, maximize the concentration of COMPOUND B available for homing to tissues, and rapidly initiate clinical benefits mediated by AP inhibition. The initial IV dose achieves faster steady-state status, decreases subject variability, offsets the impact on circulating concentrations by the potential target sink in AAV patients compared to healthy subjects, and maximizes the proportion of patients achieving the target concentration in circulation that is associated with pharmacological activity in the tissue. Furthermore, the benefit of COMPOUND B is strengthened through subsequent SC maintenance dosing (“step-down”) that maintains pharmacological activity in the tissue without inhibiting systemic complement, thereby minimizing the potential risk for infection.

[0224] The initial IV dose of 1,400 mg IV was derived from both preclinical studies and a previous Phase 1 clinical study. Specifically, preclinical pharmacological studies *in vivo* including Cfh^{-/-} mouse PK/PD studies, a rat passive Heymann nephritis (PHN) efficacy model, and a UVB-challenge PK/PD study in cynomolgus monkeys (together verified multiple disease types in multiple organ systems, including kidney, skin, and liver) indicate that the maximal tissue AP inhibition was achieved at circulating systemic concentrations of 0.3 to 3.2 µg/mL. These animal studies (data not shown) collectively demonstrated robust and durable tissue PK/PD (*e.g.*, activity at doses of 1-3 mg/kg, SC or IV; tissue PD EC₉₀ = circulating concentration of 0.3 µg/mL) in the absence of circulating systemic inhibition of complement activity, and supports dosing every 1-2 weeks. For example, the Passive Heymann Nephritis rat model of Human Membranous Nephropathy (HMN) showed robust effect on POM (proof of mechanism) and POC (proof of concept) endpoints, including potent inhibition of proteinuria equivalent to full systemic complement depletion (cobra venom factor); potent inhibition of urine sC5b-9, a non-invasive approach to monitor complement inhibition in kidney; and protection of podocytes, the injury of which is a key driver for protein leakage in various kidney diseases (data not shown).

[0225] Taking 3.2 µg/mL as the conservative end of the plasma concentrations associated with the maximal pharmacological activity in the tissue, and factoring in a 10-fold uncertainty factor due to translation from animal data to human, the circulating concentration resulted in 32 µg/mL as the target threshold for an initial IV dose that includes a loading dose. This serves the function of exploiting sufficient drug concentrations that promptly allocate to the tissue. A clear relationship was observed between plasma COMPOUND B concentrations and Wieslab AP activity. A population PK/PD model derived an estimated IC₅₀ of 56.3 µg/mL. The impact on PK of proteinuria in AAV patients compared with healthy subjects (the original model data) was also considered for selection of an initial IV dose that includes a loading dose. Considering the potential loss of COMPOUND B in the urine, the sensitivity analysis for simulation under conditions of 1.5-fold faster clearance was also conducted (data not shown). Collectively, modeling and simulations predicted 1,400 mg IV maintains the plasma COMPOUND B concentrations above the circulating threshold of 32 µg/mL for 96 hours post dose in >90% of patients.

[0226] An SC dose of 450 mg QW to be continued following the initial IV dose was derived from extensive preclinical studies, and preliminary PK/PD simulation and modeling based on the previous Phase 1 clinical trial. For clinical dose selection, maintenance of plasma concentrations above the target activity threshold throughout dosing is conservatively assumed to be required to sustain tissue penetration, tissue target engagement, and tissue activity. Maintaining plasma COMPOUND B concentrations above 3.2 µg/mL results in maximal tissue PD (≥90% reduction in complement activity), which provides an opportunity for further maximizing and maintaining clinical activity. This target activity threshold was derived from an extensive set of preclinical studies including pharmacology studies in the rat PHN model, PK/PD study in C1H^{-/-} mice, and PK/PD in a monkey UVB skin challenge model. Modeling and simulations of the Phase 1 data predicted 450 mg SC administered QW following a single IV dose of 1,400 mg maintains plasma COMPOUND B minimum concentration at steady state (C_{min,ss}) above the target activity threshold of 3.2 µg/mL in >95% subjects, yet below the model estimated IC₅₀ for serum AP activity in healthy volunteers of 56.3 µg/mL during the SC dosing period. In other words, the mouse, rat and NHP preclinical data provided guidance for drug levels predicted to provide maximal tissue complement inhibition and activity, and about 450 mg SC dosing (*e.g.*, following the initial 1400 mg IV dose) achieved exposures below systemic inhibition and above conservative end of predicted range for clinical activity.

[0227] The initial IV dose and maintenance doses are about 80-fold and 55-fold lower, respectively, than the exposure $C_{\max}$ /AUC at 30 mg/kg IV from previous studies using COMPOUND B, and about 60-fold lower than exposure at NOAEL in 3-month toxicity study with a similar construct ADX-118. Thus the doses provide ample safety margin for patients.

[0228] Indeed, in the previous Phase 1 Study, treatment (COMPOUND B or placebo) has been generally well tolerated in healthy subjects for 8 weeks following a single dose up to 30 mg/kg by IV and approximately 5 weeks following 5 doses of a 450 mg flat dose administered QW by SC. In addition, the maximal systemic AP inhibition as measured by Wieslab assay was achieved up to Day 7 post dose in the majority of subjects after a single dose at 30 mg/kg IV. There was no evidence of COMPOUND B related SAEs across cohorts. The mean $C_{\max}$ and AUC extrapolated to infinity (AUC_{inf}) in COMPOUND B-treated subjects following a single dose of 30 mg/kg were 865 $\mu\text{g/mL}$ and 3500 $\text{day} \cdot \mu\text{g/mL}$, respectively, representing 80-fold and 55-fold higher than the expected exposure $C_{\max, \text{ss}}$ (10.8 $\mu\text{g/mL}$) and $AUC_{\text{tau, ss}}$ (1,530 $\mu\text{g} \cdot \text{h/mL}$) after 450 mg SC QW following a single IV dose of 1,400 mg. Notably, the 450 mg SC dose following the initial IV dose was the dose assessed in the MAD Cohort of Phase 1 clinical study which was tolerated and safe.

[0229] In summary, the Phase 1 study using COMPOUND B in 56 healthy volunteers confirmed that the IV initial dose followed by 450 mg SC doses (a) attained expected dose-dependent PK/PD; (b) the once weekly SC dosing provided desired exposure for predicted complete tissue inhibition with no concomitant systemic inhibition; (c) the PK levels aligned with predicted Wieslab alternative pathway inhibition; (d) there were no serious or severe AEs or discontinuations due to AEs; (e) there were no AEs related to immunogenicity; and (f) there were only minimal anti-drug antibodies (ADA) detected across SAD/MAD groups.

[0230] The formulations are stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with limited access to the authorized personnel until use.

[0231] TEAEs experienced by subjects, standard safety laboratory data and systematic assessment of ADAs are routinely monitored to ensure subject safety and to identify the occurrence of events that meet the criteria for IP discontinuation (see below).

Stopping Criteria

Event	Criteria for IP Discontinuation in Any Subject
Any TEAE	Drug-related TEAE that is Grade ≥ 3
Immunological TEAE	Grade ≥ 3 or serious immunological event of any severity
Lymphocyte counts	Absolute lymphocyte count $\leq 500/\mu\text{L}$ sustained for 2 weeks on repeat testing
Viral reactivation or infection	$\geq$ Grade 3 viral reactivation or serious infection

[0232] The Sponsor conducts blinded periodic safety reviews as the study progresses described in a Safety Monitoring Plan.

[0233] Patients with severe AAV (with renal involvement) who are enrolled in either the first, sentinel group in Part A, or Part B of the study, are treated with SOC as described in the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases (KDIGO Glomerular Diseases Work Group 2021, *supra*). Specifically, all such patients receive induction immunosuppressive therapy with RTX, at the exclusion of CYC for induction, in order to minimize variability within and across treatment arms. RTX is administered IV as 4 doses of 375 mg/m^2 body surface area, once weekly for 4 weeks with appropriate prophylaxis for infusion reactions preceding the first RTX infusion.

[0234] Glucocorticoid therapy commences with IV methylprednisolone, given as 3 daily pulse doses of between 0.5 g and 1 g, with a total dose of no greater than 1.5 g. Any IV methylprednisolone administered within 14 days prior to randomization contributes to this maximum allowable dose. If less than 1.5 g IV methylprednisolone has been administered during this period, participants can receive additional doses over 3 days following randomization to reach a total of no more than 1.5 g. Patients commence the oral GC regimen, given as a single daily dose, on the day following the last IV methylprednisolone dose. In Part A Cohort 2, in which the potential for steroid sparing with adjunctive COMPOUND B treatment is being evaluated, oral GCs are tapered to 0 over a 4-week period following Day 1.

[0235] For patients enrolled in the sentinel group of Part A (Cohort 1), and in Part B, the oral GC regimen is weight-based with 3 weight categories or weight bands, according to the “reduced dose” regimen defined in the PEXIVAS study, which has since been incorporated in the current KDIGO guidelines and includes a programmed taper (KDIGO Glomerular

Diseases Work Group 2021, also see Walsh *et al.*, *N Engl J Med.* 2020;382(7):622-631; all incorporated herein by reference).

Reduced-Dose GC Regimen in the PEXIVAS Study

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50-75 kg	>75 kg
1	50	60	75
2	25	30	40
E	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5
>52	Investigators' local practice		

[0236] For participants receiving SOC therapy, the aim following RTX induction, as per KDIGO guidelines, is for prednisolone to be withdrawn by 6 months with RTX alone continued for maintenance therapy (KDIGO Glomerular Diseases Work Group 2021).

Patient Inclusion Criteria

1. Male or female subjects aged at least 18 years, with new or relapsed AAV where treatment with RTX (or CYC) would be required.
2. Diagnosis of GPA or MPA according to the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria for ANCA-associated vasculitis.
3. Positive for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) at screening.

4. Have at least one “major” item or at least 3 “non-major” items (including renal), or at least 2 renal items on the Birmingham Vasculitis Activity Score (BVAS) version 3.
5. Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m².

Patient Exclusion Criteria

1. Eosinophilic granulomatosis with polyangiitis or other multi-system autoimmune disease besides GPA and MPA.
2. GFR < 45 mL/min/1.73 m².
3. Alveolar hemorrhage with concomitant hypoxia defined as O₂ sats $< 85\%$ on room air, or central nervous system involvement.
4. Received CYC within 12 weeks prior to screening.
5. If on azathioprine, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving RTX (or CYC) dose on Day 1.
6. Received IV glucocorticoids, $> 3,000$ mg methylprednisolone equivalent, within 12 weeks prior to screening.
7. Received an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening.
8. Received RTX or other B-cell antibody within 52 weeks of screening, or 26 weeks provided B cell reconstitution has occurred.
9. Received anti-TNF treatment, abatacept, alemtuzumab, intravenous immunoglobulin, belimumab, or tocilizumab within 12 weeks prior to screening.
10. Previously received an approved or investigational complement therapy.
11. History of allogeneic kidney transplant.
12. Received dialysis or plasma exchange within 12 weeks prior to screening.

Efficacy Analyses

[0237] The efficacy of treatment using COMPOUND B is assessed to demonstrate the primary endpoint that COMPOUND B is safe and tolerable when administered to patients with AAV, and that induction of remission is achieved (*e.g.*, disease remission as measured by BVAS score 0 and no GC at Week 26) in AAV patients in whom COMPOUND B is added to SOC therapy (*e.g.*, RTX plus reduced-dose GC [such as the PEXIVAS regimen]), or as part of a reduced/attenuated GC regimen alongside SOC induction therapy. Use of CYC

for induction is excluded to minimize variability of concomitant medications within, and across, treatment arms.

[0238] A number of secondary endpoints are also evaluated, including time to remission (as measured by (BVAS score 0)), change from baseline in uACR (urine albumin:creatinine ratio) through Week 26, time to improvement in uACR, change from baseline in eGFR through Week 26, time to stabilization/improvement in eGFR, change from baseline in urinary MCP-1: creatinine ratio through Week 26, time to improvement in urinary MCP-1: creatinine ratio, change from baseline in urinary sC5b-9 (soluble complement component 5b-9 (membrane attack complex)) through Week 26, time to improvement in urinary sC5b-9, and/or change from baseline in other complement and non-complement biomarkers in serum and urine through Week 26. While AAV is characterized by a pauci-immune glomerulonephritis, post-treatment kidney biopsies from those patients in whom C3 fragment deposition is observed on their diagnostic biopsy (approximately 40% of patients) are used to evaluate localization of COMPOUND B to sites of complement activation within the kidney, and any associated reduction in C3 fragment deposition.

[0239] A number of exploratory objectives are further evaluated.

[0240] One exploratory objective is to evaluate the local pharmacology of COMPOUND B in patients with AAV. This is evaluated by determining the change from baseline in kidney C3 fragment deposition in patients with C3 fragment deposition present on their diagnostic biopsy, and changes from baseline in other complement and non-complement biomarkers in urine through Week 26.

[0241] Another exploratory objective is to evaluate the localization of COMPOUND B in kidney tissue from AAV patients with C3 fragment deposition on their diagnostic biopsy. This is evaluated by identifying evidence of COMPOUND B localization at sites of complement activation in kidney biopsy tissue.

[0242] Another exploratory objective is to evaluate relapse in AAV patients in whom COMPOUND B is added to SOC, by evaluating relapse after previously achieving BVAS score=0 during the study.

[0243] Another exploratory objective is to investigate the systemic PD effects of COMPOUND B in patients with AAV, by evaluating changes from baseline in serum complement AP activity through Week 26, and changes from baseline in other complement and non-complement biomarkers in serum through Week 26.

[0244] Another exploratory objective is to characterize the immunogenicity of COMPOUND B in patients with AAV, by evaluating incidence and titer of treatment-

emergent anti COMPOUND B antibodies in plasma (anti-drug antibody or ADA), incidence of anti-COMPOUND B NAb (neutralizing antibody) in serum, changes in blood fH levels or anti-fH antibody levels following treatment, and changes in other markers of complement activation, *e.g.*, serum C3 and C4 levels, AH50 (alternative complement pathway functional assay) and CH50 (total complement functional assay).

[0245] Another exploratory objective is to explore the relationships between endpoints in patients with AAV, by evaluating exploratory assessment of the relationships between blood, urine, and tissue PK/PD, ADA, safety, tolerability, and clinical activity, as available.

[0246] Another exploratory objective is to evaluate the effect of treatment with COMPOUND B on health-related quality of life (HRQoL), based on change from baseline in HRQoL through Week 26 (as measured using HRQoL instruments).

Adverse Events of Special Interest

[0247] An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate.

[0248] Following events are considered AESIs for this study and are reported using the same process as for AEs:

- Injection site reactions (will also be recorded on the injection site reaction CRF).
- Infection AEs including viral reactivation infections.
- Lymphopenia CTCAE Grade ≥ 3 ($<500 \mu\text{L}$).

CLAIMS

1. A method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising:
 - 1) an antibody or an antigen binding fragment thereof that specifically binds to complement protein 3d (c3d), wherein the antibody or antigen binding fragment thereof comprises:
 - (a) a heavy chain comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and,
 - (b) a light chain comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6, and
 - 2) a complement modulator polypeptide, wherein the complement modulator polypeptide comprises factor H or a biologically active fragment thereof, wherein the composition comprising the fusion protein construct is administered to the subject to maintain plasma concentration of the fusion protein construct at ≥ 0.3 $\mu\text{g/mL}$, such as ≥ 3.2 $\mu\text{g/mL}$, throughout dosing, such that the AAV is treated in the subject.
2. The method of claim 1, wherein the antibody or antigen binding fragment thereof comprises:
 - (a) a first heavy chain and a second heavy chain, wherein each of the first and the second heavy chain comprises three heavy chain complementarity determining regions (CDR-H1, CDR-H2, CDR-H3), wherein the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 2, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 3, and
 - (b) a first light chain and a second light chain, wherein each of the first and the second light chain comprises three light chain complementarity determining

regions (CDR-L1, CDR-L2, CDR-L3), wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 4, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 5, and the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 6.

3. The method of claim 2, wherein each of the first and the second heavy chain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 7, and wherein each of the first and the second light chain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8.
4. The method of any one of claims 1-3, wherein the first and the second heavy chain each comprises the same amino acid sequence of SEQ ID NO: 9, 10 or 11, and wherein the first and the second light chain each comprises the amino acid sequence of SEQ ID NO: 12.
5. The method of any one of claims 1-4, wherein the fusion protein further comprises:
 - (c) a first linker bound to the C-terminus of the first heavy chain and comprising the amino acid sequence of SEQ ID NO: 14; and
 - (d) a second linker bound to the C-terminus of the second heavy chain and comprising the amino acid sequence of SEQ ID NO: 14.
6. The method of any one of claims 1-5, wherein the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 15 or 16.
7. The method of any one of claims 1-6, wherein the fusion protein construct comprises
 - (a) two heavy chain-containing polypeptides, each comprising, from N- to C-terminal, the amino acid sequence of SEQ ID NO: 9, the amino acid sequence of SEQ ID NO: 14, and the amino acid sequence of SEQ ID NO: 15; and, (b) two light chain-containing polypeptides each comprising the amino acid sequence of SEQ ID NO: 12.
8. The method of any one of claims 1-7, wherein the fusion protein is administered to the subject subcutaneously (*s.c.*), each as a maintenance dose.
9. The method of claim 8, wherein prior to the subcutaneous administration of the maintenance dose(s), the subject is administered an initial IV dose.
10. The method of claim 9, wherein the initial IV dose is administered to the subject at a dose ranging from 3-30 mg/kg, and/or to achieve a target plasma concentration of the

fusion protein construct in the subject at ≥ 0.3 $\mu\text{g/mL}$.

11. The method of claim 9 or 10, wherein the first maintenance dose is administered about 3-4 days (*e.g.*, about 4 days), about 5 days (*e.g.*, about 120 hrs), about 6 days (*e.g.*, about 144 hrs), or no later than about 7 days (*e.g.*, about 168 hrs), after the initial IV dose.
12. The method of any one of claims 9-11, wherein the initial IV dose comprises two or more IV administrations administered QD, Q3D, QW, Q2W, Q3W, or Q4W.
13. The method of claim 12, wherein each IV administration of the initial IV dose comprises about 3-30 mg/kg or about 200-2,000 mg of the fusion protein in order to achieve a plasma concentration of the fusion protein in the subject of ≥ 0.3 $\mu\text{g/mL}$, such as ≥ 32 $\mu\text{g/mL}$, for about 96 hours before the first maintenance dose is administered.
14. The method of any one of claims 8-13, wherein the maintenance doses comprise an infinite number of doses (*e.g.*, for chronic therapy), about 10-60 doses, about 20-55 doses, about 25-51 doses, about 22-28 doses, about 22, 23, 24, 25, 26, 27, or 28 doses, about 50-55 doses, about 50, 51, 52, 53, 54, or 55 doses.
15. The method of claim 14, wherein each maintenance dose comprises about 5 – 1,800 mg or about 0.1 - 20 mg/kg of the fusion protein, in order to maintain a plasma concentration of the fusion protein in the subject of between about 0.3-32 $\mu\text{g/mL}$, such as between about 3.2-32 $\mu\text{g/mL}$ (*e.g.*, after 2, 3, 4, or 5 doses of maintenance doses).
16. The method of claim 15, wherein the maintenance doses are administered BID, QD, Q2D, Q3D, Q4D, Q1W, Q2W, Q3W, Q4W, Q6W, Q8W, Q12W, or intermittent prn.
17. The method of any one of the preceding claims, wherein the fusion protein is administered to the subject at about 5 mg/kg – about 30 mg/kg per dose, about 6 mg/kg – about 28 mg/kg per dose, about 7 mg/kg – about 26 mg/kg per dose, about 8 mg/kg – about 24 mg/kg per dose, about 10 mg/kg – about 22 mg/kg per dose, about 12 mg/kg – about 20 mg/kg per dose, about 16 mg/kg per dose, about 18 mg/kg per dose, about 20 mg/kg per dose, about 22 mg/kg per dose, or about 25 mg/kg per dose.
18. The method of any one of the preceding claims, wherein the fusion protein is administered to the subject at about 1200 mg – about 1600 mg initial IV dose, about

1300 mg – about 1500 mg initial IV dose, or about 1400 mg per initial IV dose.

19. The method of any one of the preceding claims, wherein the fusion protein is administered to the subject at about 100 mg – about 1200 mg per maintenance dose, about 150 mg – about 800 mg per maintenance dose, about 300 mg – about 600 mg per maintenance dose, about 400 mg – about 500 mg per maintenance dose, or about 450 mg per maintenance dose.
20. The method of any one of the preceding claims, wherein the subject is further being treated by a B-cell depleting antagonist antibody (such as an anti-CD20 monoclonal antibody (*e.g.*, rituximab or Ofatumumab)) and/or a glucocorticoid (GC); optionally, the anti-CD20 monoclonal antibody comprises rituximab (RTX) administered IV as 4 doses of 375 mg/m² body surface area, once weekly for 4 weeks, and the GC comprises about 60 mg/day methyl prednisolone administered intravenously for 0.5-1g daily for a total of no more than 1.5 g, followed by daily oral prednisolone.
21. The method of any one of claims 1-20, further comprising tapering the amount of oral GC (*e.g.*, prednisone or prednisolone) over the course of treatment.
22. The method of claim 21, wherein tapering the amount of oral GC begins after Day 1 of switching to oral GC.
23. The method of claim 21 or 22, wherein the amount of oral GC is tapered to 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or 0%, over the course of 2, 3, 4, 5, 6, 7, or 8 weeks, or up to 20 weeks.
24. The method of any one of the preceding claims, wherein the subject has granulomatosis with polyangiitis (GPA, or Wegener's granulomatosis).
25. The method of any one of the preceding claims, wherein the subject has microscopic polyangiitis (MPA).
26. The method of any one of the preceding claims, wherein the AAV is characterized by the presence of proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA in the serum.
27. The method of any one of the preceding claims, wherein the subject is a nephritic patient, a nephrotic patient, a transplant patient, or a patient with impaired renal function (*e.g.*, moderately increased risk of progression to CKD, high risk of progression to CKD, very high risk of progression to CKD, or highest risk of

- progression to CKD, *e.g.*, Rapidly Progressive GlomeruloNephritis (RPGN)).
28. The method of any one of the preceding claims, wherein the fusion protein is formulated in 12 mM sodium phosphate, 75 mM arginine, 125 mM sucrose, and 0.05% (w/v) polysorbate 80 at pH 6.7.
29. The method of any one of the preceding claims, wherein the subject is further treated with an additional therapy, such as cyclophosphamide (Cytoxan), methotrexate (MTX), azathioprine (Imuran), trimethoprim-sulfamethoxazole (Bactrim, Septra), plasma exchange, cyclosporine (Sandimmune), intravenous immunoglobulin, monoclonal antibody, H2-blocker, proton-pump inhibitor, fluconazole (Diflucan), trimethoprim-sulfamethoxazole, and/or Avacopan.
30. The method of any one of the preceding claims, wherein the subject achieves remission (BVAS ver. 3 = 0) at Week 26 of treatment; and/or wherein the subject maintains remission at Week 52 of treatment.
31. The method of any one of the preceding claims, wherein after 26 weeks of treatment, the subject, compared to control, achieves:
- i) $\geq 30\%$ reduction in uACR (urinary albumin creatinine ratio);
 - ii) reduced time to reduction in uACR by $\geq 30\%$;
 - iii) reduced time to remission (BVAS = 0); and/or,
 - iv) attains BVAS 50% or BVAS 90% at 26-52 weeks after the administration of the initial IV dose.
32. A method of treating ANCA-Associated Vasculitis (AAV) in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a fusion protein construct comprising:
- 1) an antibody that specifically binds to complement protein 3d (c3d), wherein the antibody comprises:
 - (a) two heavy chains, each comprising the amino acid sequence of SEQ ID NO: 9; and,
 - (b) two light chains, each comprising the amino acid sequence of SEQ ID NO: 12; and,
 - 2) two complement modulator polypeptides each comprising a biologically active fragment of factor H, wherein each of said complement modulator polypeptide has the amino acid sequence of SEQ ID NO: 15;

wherein each said two complement modulator polypeptides is linked to the C-terminus of one of said two heavy chains via a linker having the amino acid sequence of SEQ ID NO: 14;

wherein the composition comprising the fusion protein construct is administered to the subject via an initial IV dose followed by one or more maintenance doses;

wherein the initial IV dose comprises about 1400 mg of the fusion protein construct administered intravenously (IV) to the subject;

wherein each of the one or more maintenance doses comprises about 450 mg of the fusion protein constructed administered subcutaneously (SC) to the subject, once every week; and,

wherein the first of said one or more maintenance doses is administered about 4 days (*e.g.*, 96 hrs) after the initial IV dose, such that the AAV in the subject is treated.

33. The method of claim 32, wherein the subject is an adult (*e.g.*, male or female, over 18 years old) having newly diagnosed or relapsed AAV requiring treatment with RTX (or CYC), such as having GPA or MPA, optionally positive for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) antibody.