

TREATMENT OF COMPLEMENT-ASSOCIATED RENAL DISEASES

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/546,330, filed on October 30, 2023, and U.S. Provisional No. 63/700,980, 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 "132301-01220.xml" and is 20,934 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] IgA nephropathy (IgAN) is an immune complex-mediated glomerulonephritis characterized by mesangial IgA deposition, activation of complement and glomerular inflammation. IgAN is the most common primary glomerular disease worldwide, although varies widely in its geographic distribution with an estimated incidence of 2 to 28 patients per million population per year. Typically occurring in patients aged between 20 and 30 years, up to 50% of patients progress to ESKD within 20 years of clinical presentation. Patients who undergo transplantation are also at risk of disease recurrence, which occurs in approximately 30% of transplant recipients.

[0004] The role of complement in mediating local tissue injury in IgAN is now widely recognized. Kidney biopsies reveal deposition of complement proteins such as fH, properdin, C4d, mannose-binding lectin (MBL), active C3 fragments and C5b-9, supporting involvement of both the AP and LP. Immune complexes formed from IgG autoantibodies and the altered galactose-deficient IgA1 molecules to which they are directed, together with C3 products, contribute to mesangial proliferation and glomerular inflammation. C3 fragments are found in the same distribution as IgA in up to 90% of cases, with increasing mesangial C3 fragment deposition adversely affecting kidney survival. In contrast, individuals with the protective CFHR3-1 deletion have reduced glomerular C3 fragment deposition, believed to result from the more effective AP regulation in the absence of factor

H (fH) deregulation by complement FHR1 CFHR3. Activation of the LP appears to be associated with more severe disease characterized by greater proteinuria, increased mesangial and extra-capillary proliferation, glomerular sclerosis and reduced kidney survival at 10 years.

[0005] As with other forms of glomerular disease, proteinuria is a recognized risk factor for the progression of IgAN, with time-average proteinuria shown to be the most important predictor of rate of kidney function decline. A quantitative estimate determined that each incremental gram of proteinuria above 1g per day was associated with a 10- to 25-fold more rapid rate of kidney function decline. Reducing proteinuria to below 1g/d is therefore regarded as a treatment target in IgAN, with patients achieving this observed to have a similar rate of disease progression and kidney survival, irrespective of their initial proteinuria and comparable to those whose proteinuria never exceeded 1g/d.

[0006] The SOC (standard of care) for IgAN, as currently described in the Kidney Disease Improving Global Outcomes 2021 guidelines, has consisted of Renin-angiotensin-aldosterone system (RAAS) inhibition as first line therapy to reduce proteinuria and risk of disease progression. However, RAAS inhibition does not affect the underlying disease pathology, with less than half of patients achieving sustained proteinuria levels of < 1g/d (partial remission). The long-term clinical benefit of glucocorticoids has not been established and a 6-month course is only suggested with extreme caution in those at high risk of progressive CKD. Antibody-depleting strategies such as rituximab are also not recommended due to the paucity of evidence for their efficacy and both treatment approaches are associated with significant safety issues.

[0007] Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease in which the most common cause of kidney injury is Lupus Nephritis (LN). Occurring in ~50% of patients with SLE (which affects 10-250 individuals per million population and predominantly women of childbearing age), LN tends to develop early in the disease course with patients presenting at an earlier age than those without LN. Male sex and non-European ancestry accompany younger age as risk factors. With heterogeneous pathophysiology, to which genetic and environmental factors likely contribute, the incidence of LN in the US is higher in black (34%-51%), Hispanic (31%-43%), and Asian (33%-55%) patients, compared with white (14%-23%) patients. The presence of LN increases mortality, with death attributable to renal involvement occurring in 5-25% of patients with proliferative disease (class III, IV, or III/IV + V) within 5 years of onset. Progression to ESKD occurs in 10-30% of those affected by LN, in whom those with proliferative disease are most at risk.

Patients with persistently low isolated C3 hypocomplementemia also have an increased risk of ESKD and death. Critical to renal survival is the attainment of a complete clinical response, associated with 92% kidney survival at 10 years, compared to only 43% in partial responders and 13% in non-responders. Despite the continuing development of immunomodulatory agents and supportive care, the prognosis associated with LN has not improved substantially in the past decade, with ESKD still developing in 5–30% of patients within 10 years of LN diagnosis. In prior studies, repeat biopsies performed after 6 to 8 months of treatment in patients with a complete clinical response showed significant persistent histologic activity in 20% to 50% of cases. Given repeat “protocol” biopsies, performed as part of clinical care, have also shown discrepancies between clinical and histologic findings, the biopsies proposed in our study, particularly after 6 months of treatment, will provide the opportunity to accurately correlate clinical and histological responses.

[0008] Both the innate and adaptive immune systems are implicated in LN pathogenesis. Glomerular immune complex deposition, derived either from the circulation or formed *in situ* from autoantibodies directed against nuclear and cellular antigens, activates complement and engages leucocyte Fc receptors resulting in intrarenal inflammation. The AP has both beneficial (immune complex clearance) and deleterious roles in the setting of lupus, with activation shown to contribute to complement-mediated tissue injury in LN. Immune complex clearance by leukocytes may also be impaired in the presence of additional autoantibodies to C1q and C3b. LN is divided into 6 histopathological classes according to the International Society of Nephrology/Renal Pathology Society system, based on glomerular immune complex deposit location, the extent of glomerular involvement, and whether the injury pattern reflects active or chronic disease. A “full house” pattern is characteristically seen on immunofluorescence, comprising IgG, IgM, IgA, C1q and C3 fragments. IgG subclass staining reveals dominant IgG1 and IgG3, mild IgG2 and minimal IgG4.

[0009] Patient management is determined by disease severity, with non-proliferative forms of LN (with sub-nephrotic range proteinuria and normal GFR) typically treated conservatively with renin-angiotensin system RAAS blockade and immunomodulation with antimalarials (*e.g.*, hydroxychloroquine). Immunosuppression is reserved in these classes for extrarenal manifestations only, while proliferative forms of LN (class III, IV, or III/IV+V) and class V LN with nephrotic syndrome are treated with systemic immunosuppression, combined with high-dose corticosteroids, in an induction phase typically lasting 3 to 6

months. Immunosuppression is continued and gradually reduced in an extended maintenance phase (to reduce the risk of flare), potentially lasting several years. While there have been recent approvals for the treatment of LN (with belimumab and voclosporin), unmet therapeutic need remains. Combination strategies to enhance therapeutic efficacy and enable dosage reduction of individual drugs are being explored in LN. Several clinical trials of novel biological agents and/or targeted small molecules in combination with the SOC in LN are ongoing, including complement therapeutics.

[0010] At present, there's no cure for lupus nephritis. Currently available treatment aims to reduce or eliminate symptoms (remission), to prevent worsening of the disease, to maintain remission, and to avoid the need for dialysis or a kidney transplant. For severe LN, treatment aims to slow or stop the immune system from attacking healthy kidney cells, such as steroids (*e.g.*, prednisone), immunosuppressors (*e.g.*, cyclosporine, Tacrolimus), low dose chemotherapeutic agent (*e.g.*, cyclophosphamide), Azathioprine (Imuran), Mycophenolate (CellCept), Rituximab (Rituxan), and/or Belimumab (Benlysta), *etc.*

[0011] C3 Glomerulopathy (C3G) is a rare kidney disease caused by dysregulation of the complement AP. Comprising 2 major subgroups, dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), it is characterized by C3-dominant glomerular staining by immunofluorescence, of at least 2 orders of intensity greater (on a 0–3+ scale) than any other immune reactant (*e.g.*, immunoglobulins).

[0012] With an estimated incidence of 1-3 patients per million, C3GN is reportedly more common than DDD. DDD tends to be diagnosed at a younger age, predominantly in children and young adults, but has been reported in older adults. Presentation varies from nephritic syndrome, asymptomatic and low-grade proteinuria to nephrotic syndrome, or rapidly progressive glomerulonephritis, with 50% progressing to ESKD within 10 years. Isolated C3 hypocomplementemia is seen in most patients, although more frequently reported in DDD, with accompanying low C4 levels seen only rarely. Acquired partial lipodystrophy and drusen-like macular deposits, similar to those in age-related macular degeneration, have also been reported in association with DDD, but not C3GN.

[0013] Dysregulation can result from genetic mutations in both fluid-phase and surface-bound regulators, or activating proteins, and may also be acquired in the setting of autoantibodies *eg.*, directed against an inhibitor (*e.g.*, factor H) or which stabilize the C3 convertase (C3 nephritic factors). Such autoantibodies are more commonly reported in DDD than C3GN. The uncontrolled AP activation common to all results in glomerular C3 fragment deposition and membrane attack complex formation. Although a

membranoproliferative pattern is most frequently seen, the light microscopic findings can be variable and electron microscopy is required to confirm the electron dense transformation of the GBM (characteristic of DDD), while also distinguishing C3GN from other glomerular diseases. Mass spectrometry of laser micro-dissected glomeruli have demonstrated similar C3 proteomic profiles between DDD and C3GN, with C3dg being the most abundant fragment within deposits in both DDD and C3GN.

[0014] The treatment paradigm for C3G has not been well established. In addition to the standard conservative measures such as RAAS inhibition and blood pressure control, other tested approaches have included immunosuppression, plasma exchange and complement inhibition with varying degrees of success, and significant therapeutic need remains.

[0015] Thus, there is a need to develop effective treatment to alleviate renal diseases characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, such as IgAN, C3G, and LN.

SUMMARY

[0016] Provided is a method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 renal disease is treated in the subject.

[0017] Also provided is a method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 renal disease in the subject is treated.

[0018] 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

[0019] FIG. 1 show the clinical trial scheme for the Phase 2a trial described in Example 2.

[0020] FIG. 2A shows model-predicted plasma COMPOUND B (an anti-C3d antibody fusion with complement inhibitor factor H, see DETAILED DESCRIPTION section below) concentration versus time profile in healthy volunteers following 300 mg SC QW dosing. The solid black line is predicted median, gray area is predicted 95% interval.

[0021] FIG. 2B shows model-predicted plasma COMPOUND B concentration versus time profile in healthy volunteers following 600 mg SC QW dosing. The solid black line is predicted median, gray area is predicted 95% interval.

[0022] FIG. 3 shows IV and SC COMPOUND B inhibit glomerular tissue complement in $CfH^{-/-}$ mice. Abbreviations: Ctrl: control; IV: intravenous; PBS: phosphate buffered saline; RFU: relative fluorescence units; SC: subcutaneous. Kidney tissue was collected 7 days after COMPOUND B administration, and was immunostained with an antibody recognizing C3 fragments and unaffected by the presence of COMPOUND B. Glomerular C3 fragment levels were quantified using image analysis software (Image J). All dose levels tested achieved similar levels of complement inhibition, suggesting that the dose required for maximum complement inhibition is ≤ 1.25 mg/kg, the lowest dose tested.

[0023] FIGs. 4A-4E show characterization of circulating drug exposure and systemic complement inhibition after single dose administration of COMPOUND C (a mouse homolog of COMPOUND B) in $CfH^{-/-}$ mice. Abbreviations: IV: intravenous; mg/kg: milligram per kilogram; PD: pharmacodynamic; PK: pharmacokinetics; SC: subcutaneous. $CfH^{-/-}$ mice were dosed IV or SC with a single dose of COMPOUND C. Serial blood samples were collected at the indicated timepoints. Drug exposure was assessed by an COMPOUND C-specific ELISA; systemic complement inhibition was measured by an ELISA for intact C3 protein. COMPOUND C dosed at 5 mg/kg IV (A) and 25 mg/kg SC (B) achieved C_{max} levels high enough to elicit transient circulating complement inhibition (black lines). Circulating C3 levels return to baseline (indicated by gray bars) by 2-3 days after dosing. COMPOUND C dosed at 5 mg/kg SC (C), 1 mg/kg SC (D), or 0.3 mg/kg SC (E) achieved lower C_{max} that did not lead to appreciable complement inhibition in circulation (increase in circulating C3 levels). Gray bars indicate the mean $\pm$ 1 standard deviation of C3 levels measured in samples where COMPOUND C is no longer present.

[0024] FIG. 5 shows representative immunostaining with anti-fH and anti-C3 fragment antibodies after single-dose administration of COMPOUND C (5 mg/kg, IV) in $CfH^{-/-}$ mice. Abbreviations: mfH: mouse fH; mg/kg: milligram per kilogram. $CfH^{-/-}$ mice were dosed with a single, 5 mg/kg IV dose of COMPOUND C. Kidneys collected at the indicated intervals after dosing were sectioned and immunostained with an antibody recognizing C3 fragments produced by active complement (bottom row) or with an anti-fH antibody to detect drug in the tissue (top row). The left-most panels of each row show representative images from pre-treatment mice: no anti-fH immunostaining was detected and deposition of active C3 fragments was present. Within the first week after dosing (Days 3 and 7), substantial anti-fH immunostaining was evident and little or no active C3 fragment was observed, indicating homing of COMPOUND C to tissue leading to complement inhibition. At later time points (Days 14, 17, and 21), anti-fH immunostaining gradually disappeared while anti-C3 fragment

immunostaining partially returned, indicating gradual clearing of COMPOUND C from tissue and return of complement activity. By Day 28, COMPOUND C was fully cleared from the tissue and active C3 fragment deposition returned to pre-treatment levels.

[0025] FIGs. 6A-6E show tissue (glomerular) drug exposure and C3 complement activation after single-dose administration of COMPOUND C in Cfh^{-/-} mice.

Abbreviations: frag: fragment; IV: intravenous; mg/kg: milligram per kilogram; PD:

pharmacodynamic; PK: pharmacokinetic; RFU: relative fluorescence units; SC:

subcutaneous. Cfh^{-/-} mice were dosed IV or SC with a single- dose of COMPOUND C.

Kidney tissue was collected at the indicated timepoints, sectioned, and immunostained with an anti-fH antibody to measure COMPOUND C exposure and with an anti-C3 active fragment antibody to measure complement activity. The gray bars indicate maximum C3 inhibition, calculated as the mean $\pm$ 1 standard deviation of C3 fragment staining in the 3 highest dosed groups (25 mg/kg SC, 5 mg/kg IV, and 5 mg/kg SC) at the 2-, 3-, and 5-day time points. COMPOUND C dosed at 5 mg/kg IV (FIG. 6A) achieved maximum C3 inhibition (indicated by gray bars) by the time of the earliest tissue collection (8 hours post-dose). Consistent with longer biodistribution times, SC doses took longer to reach maximum inhibition. The 25 mg/kg (FIG. 6B) and 5 mg/kg (FIG. 6C) SC doses reached maximum inhibition by 24 hours after dosing, while 1 mg/kg SC (FIG. 6D) required 2 days to achieve maximum inhibition. Despite this difference in kinetics of distribution, all doses $\geq$ 1 mg/kg achieved the same maximum inhibition, suggesting target saturation at those doses. Dosing with 0.3 mg/kg (FIG. 6E) inhibited tissue C3 but did not reach the same maximum inhibition level as the higher doses, suggesting incomplete target saturation at this dose.

[0026] FIG. 7 shows urine protein:creatinine ratio in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: Ctrl: control; CVF: cobra venom factor; PBS: phosphate buffered saline; fH₁₋₅: First 5 Consensus Repeats of Human Factor H. Anti-Fx1A was injected on Day 0 and Day 1 of study, and elevated urine protein:creatinine ratio (uPCR) was detected by Day 3. COMPOUND B or Fc-fH₁₋₅ were administered by IV injection on Day 3; CVF, a positive control, was administered IV starting one day prior to disease induction (Day 1) and daily until the end of study. Urine was collected daily on Days 2-5 of study and assayed for uPCR levels. As expected, CVF effectively reduced uPCR. All doses of COMPOUND B, as well as Fc-fH₁₋₅, reduced uPCR to a similar degree as CVF. No dose response was observed with COMPOUND B, indicating that the minimum efficacious dose is $\leq$ 1 mg/kg.

[0027] FIG. 8 shows glomerular C3 fragment deposition in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: Ctrl: control; CVF: cobra venom factor; PBS: phosphate buffered saline; RFU: relative fluorescence units. Quantitation of C3 fragment immunostaining in kidney sections. Tissues were collected at end of study (Day 5). Immuno-staining intensities from at least 10 glomeruli per animal were measured, and individual mean values are shown as circles. Group mean values are shown as bars. Anti-Fx1A treatment increased C3 fragment deposition. Prophylactic treatment with CVF reduced C3 fragment immunostaining to levels equivalent to healthy control kidneys. Treatment with 10 or 30 mg/kg COMPOUND B, or with 17 mg/kg Fc-fH₁₋₅ (equimolar to 30 mg/kg COMPOUND B) reduced C3 fragment levels to those of healthy controls. Treatment with 1 or 3 mg/kg COMPOUND B partially inhibited C3 fragment deposition.

[0028] FIG. 9 shows quantitation of COMPOUND B immunostaining in glomeruli in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: CVF: cobra venom factor; NS: not significant; PBS: phosphate buffered saline; RFU: relative fluorescence units. Quantitation of COMPOUND B in glomeruli by anti-fH₁₋₅ immunostaining of kidney sections collected at end of study (Day 5). No fH immunostaining was detected in kidneys of healthy controls, rats treated with anti-Fx1A alone, or rats treated with anti-Fx1A + CVF. No fH immunostaining is detected in kidneys of rats treated with anti-Fx1A + Fc-fH₁₋₅, suggesting that antiproteinuric effects of Fc-fH₁₋₅ are not driven by tissue targeting. Anti-fH immunostaining in 3, 10, and 30 mg/kg groups was similar, suggesting target saturation was reached at the 3 mg/kg dose. A slight but statistically significant reduction in anti-fH immunostaining was evident in the 1 mg/kg group compared to other COMPOUND B dose levels.

[0029] FIG. 10 shows circulating complement activity in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: Ctrl: control; CVF: cobra venom factor; MFI: median fluorescence intensity; PBS: phosphate buffered saline. Circulating serum complement activity was measured by the zymosan assay. As expected, no statistically significant difference in serum complement activity was detected comparing PBS treated anti-Fx1A-injected mice and healthy control mice. CVF treatment reduced circulating complement levels. 30 mg/kg COMPOUND B and equimolar concentration of Fc-fH₁₋₅ inhibited circulating complement activity, suggesting that the anti-proteinuric effect of 30 mg/kg COMPOUND B may have been partially due to inhibiting fluid-phase complement activity. In contrast, no effect on circulating complement activity was observed in the 1, 3, or 10 mg/kg COMPOUND B groups.

[0030] FIGs. 11A-11C show comparison of anti-proteinuria effects of equimolar concentrations of COMPOUND B and Fc-fH₁₋₅ in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: AUC: area under the curve; CVF: cobra venom factor; IV: intravenous; NS: not significant; PBS: phosphate buffered saline; Pro:Cre: protein:creatinine ratio; SC: subcutaneous. Comparison of effects of equimolar doses of COMPOUND B and Fc-fH₁₋₅ on kidney injury (urine protein:creatinine ratio – uPCR) in the PHN model of membranous nephropathy. (FIG. 11A) Treatment of PHN rats with low dose (0.3 mg/kg) COMPOUND B had a non-statistically significant trend towards reduced proteinuria (vs. anti-Fx1A only). Treatment with an equimolar dose of Fc-fH₁₋₅ (0.17 mg/kg) had no effect on uPCR. (FIG. 11B) Treatment of PHN rats with mid-dose (1 mg/kg) COMPOUND B reduced proteinuria vs. anti-Fx1A only ($P < 0.01$). Treatment with an equimolar dose of Fc-fH₁₋₅ (0.57 mg/kg) had no effect on uPCR, indicating the role of C3d targeting in COMPOUND B potency. (FIG. 11C) Treatment of PHN rats with high dose (3 mg/kg) COMPOUND B reduced proteinuria vs. anti-Fx1A only ($P < 0.005$). Treatment with an equimolar dose of Fc-fH₁₋₅ (1.7 mg/kg) reduced uPCR, suggesting that Fc-fH₁₋₅ may have sufficient exposure to inhibit fluid-phase complement at this dose.

[0031] FIGs. 12A-12B show glomerular complement inhibition and drug localization in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: CVF: cobra venom factor; PBS: phosphate buffered saline; SC: subcutaneous; IV: intravenous; RFU: relative fluorescence units. Glomerular complement inhibition and drug localization in the PHN model of membranous nephropathy. (FIG. 12A) Quantitation of glomerular complement (anti-C3c) immunofluorescence in renal tissues collected at end of study (day 7). (FIG. 12B) Quantitation of glomerular drug localization (anti-fH) immunofluorescence in renal tissues collected at end of study (day 7).

[0032] FIGs. 13A-13C show COMPOUND B reduces podocyte foot process effacement in the Passive Heymann Nephritis model of membranous nephropathy. Abbreviations: GBM: glomerular basement membrane; SC: subcutaneous. Transmission electron microscopy on selected samples from the PHN model of membranous nephropathy. (FIG. 13A) Representative TEM image from a healthy control rat collected on Study Day 7 shows clearly differentiated podocyte foot processes (white arrows) along the GBM. (FIG. 13B) In animals treated with anti-Fx1A alone, podocytes along the GBM are significantly effaced (filled arrows). Few or no normal slit diaphragm structures are present. (FIG. 13C) Animals treated with anti-Fx1A + 3 mg/kg (SC) COMPOUND B show significant restoration of podocyte

architecture. Though some effaced podocytes are still evident (black arrows), slit diaphragms are clearly present along the GBM (white arrows).

[0033] FIG. 14 shows Δ uACR at Week 30 in the NZBW/F1 mouse Lupus Nephritis model. Abbreviations: Δ uACR delta: change in urine albumin:creatinine ratio; BB5.1: anti-C5 antibody; PBS: phosphate buffered saline. Change in Δ uACR between Week 22 and Week 30 of a study in NZBW/F1 model of lupus nephritis. Treatment with COMPOUND C, cyclophosphamide, or the anti-C5 antibody BB5.1 reduced Δ uACR but was not a statistically significant change compared to PBS group. No reduction in Δ uACR was detected with Fc-fH1-5 or negative control IgG1 treatment.

[0034] FIG. 15 shows kidney C3 fragment immunostaining in the NZBW/F1 mouse lupus nephritis model. Abbreviations: BB5.1: anti-C5 antibody; PBS: phosphate buffered saline; SEM: standard error of the mean. Semi-quantitative scoring of glomerular immunostaining with an anti-C3 active fragment antibody. Mean staining scores (+ SEM) are shown. Treatment with COMPOUND C or cyclophosphamide led to a reduction in glomerular C3 complement activation ($P = 0.03$), while treatment with Fc-fH1-5, control IgG1, or the anti-C5 antibody BB5.1 had no measurable effect on C3 complement activation.

[0035] FIG. 16 shows histopathology sum scores in the NZBW/F1 mouse Lupus Nephritis model - kidney histopathology in the NZBW/F1 model of lupus nephritis. Sum scores show a statistically significant reduction in kidney histopathology after treatment with COMPOUND C, while treatment with the anti-C5 antibody BB5.1 had no measurable effect.

[0036] FIG. 17A shows the scheme of the Phase 1 trial described in Example 1.

[0037] FIG. 17B 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 $\text{Weight (kg)} / [\text{Height (m)}^2]$.

[0038] FIG. 17C shows the most frequently reported treatment emergent adverse events (TEAEs) (occurred in ≥ 2 subjects). MAD: multiple ascending dose; SAD: single ascending dose.

[0039] FIGs. 17D and 17E show mean (SD) of COMPOUND B plasma concentration-time profiles (semi-logarithmic scale) following single intravenous (IV) doses (FIG. 17D) or single and multiple subcutaneous (SC) doses (FIG. 17E).

[0040] FIG. 17F and 17G show normalized mean (SD) of serum Wieslab alternative pathway (AP) activity over time after single IV doses (FIG. 17F) or single and multiple SC doses (FIG. 17G) 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.

[0041] FIG. 17H and 17I show normalized mean (SD) of serum Wieslab complement classic pathway (CP) activity over time after single IV doses (FIG. 17H) or single and multiple SC doses (FIG. 17I) 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.

[0042] FIGs. 17J and 17K show model-predicted plasma concentrations (FIG. 17J) and Wieslab AP activity (FIG. 17K) 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. 17J: 3.2 µg/mL (dash-dot line); 0.2 µg/mL (solid dark line); Horizontal PD line in FIG. 17K: 50% inhibition of Wieslab activity threshold (thicker dark line) – IC₅₀.

DETAILED DESCRIPTION

[0043] 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.

[0044] 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.

[0045] 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).

[0046] 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.

[0047] 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 the renal diseases characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, such as IgAN, LN, and C3G (including DDD and C3GN).

[0048] Provided is a method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 renal disease is treated in the subject.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] In some embodiments, the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 15 or 16.

[0054] 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.

[0055] In some embodiments, the fusion protein is administered to the subject subcutaneously (*s.c.*), each as a maintenance dose.

[0056] In some embodiments, prior to the subcutaneous administration of the maintenance dose(s), the subject is administered an initial IV dose.

[0057] In certain embodiments, the subject is administered the subcutaneous maintenance doses without the initial IV dose.

[0058] In some embodiments, the initial IV dose (when present) 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 $\mu\text{g/mL}$.

[0059] 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 (when present).

[0060] In some embodiments, the initial IV dose (when present) 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).

[0061] In some embodiments, each IV administration of the initial IV dose (when present) 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.

[0062] In some embodiments, each IV administration of the initial IV dose (when present), 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.

[0063] 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.

[0064] 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.

[0065] 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).

[0066] 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.

[0067] 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 µg/mL, such as between about 3.2-32 µg/mL (*e.g.*, after 2, 3, 4, or 5 doses of maintenance doses).

[0068] 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.

[0069] In some embodiments, the fusion protein is administered to the subject based on a dosing regimen comprising one or more maintenance doses (with or without an initial IV dose administered before the first maintenance dose), 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.

[0070] In some embodiments, the fusion protein is administered to the subject based on a weight-based dosing regimen.

[0071] In some embodiments, the fusion protein is administered to the subject at about 3 mg/kg – about 30 mg/kg initial IV dose (when present), about 5 mg/kg – about 30 mg/kg initial IV dose (when present), about 6 mg/kg – about 28 mg/kg initial IV dose (when present), about 7 mg/kg – about 26 mg/kg initial IV dose (when present), about 8 mg/kg – about 24 mg/kg initial IV dose (when present), about 10 mg/kg – about 22 mg/kg initial IV dose (when present), about 12 mg/kg – about 20 mg/kg initial IV dose (when present), about 16 mg/kg initial IV dose (when present), about 18 mg/kg initial IV dose (when present), about 20 mg/kg initial IV dose (when present), about 22 mg/kg initial IV dose (when present), or about 25 mg/kg initial IV dose (when present).

[0072] 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.

[0073] 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 (when present) and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose (when present) and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose (when present) and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 mg initial IV dose (when present) and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose (when present) and/or about 200 mg –

600 mg SC maintenance dose, or about 1400 mg initial IV dose (when present) and/or about 450 mg SC maintenance dose.

[0074] 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 (when present) and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose (when present) and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose (when present) and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 mg initial IV dose (when present) and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose (when present) and/or about 200 mg - 600 mg SC maintenance dose (*e.g.*, about 300 mg or about 600 mg SC maintenance dose), or about 1400 mg initial IV dose (when present) and/or about 450 mg SC maintenance dose.

[0075] In some embodiments, the BSA dosing is based on Dubois Formula for BSA Dosing, in which $\text{Dose} = \text{BSA Based Dose} \times 0.007184 \times \text{Height (cm)}^{0.725} \times \text{Weight (kg)}^{0.425}$.

[0076] In some embodiments, the BSA dosing is based on Monteller Formula for BSA Dosing, in which $\text{Dose} = \text{BSA Based Dose} \times \text{square root} [(\text{Height (cm)} \times \text{Weight (kg)}) / 3600]$.

[0077] In some embodiments, the fusion protein is administered to the subject based on a fixed / flat dosing regimen.

[0078] 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 (*e.g.*, about 300 mg or about 600 mg SC maintenance dose), about 400 mg – about 500 mg per maintenance dose, or about 450 mg per maintenance dose.

[0079] In some embodiments, the fusion protein is administered to the subject at about 200 mg – about 2000 mg initial IV dose (when present) and/or about 5 mg - 1800 mg SC maintenance dose, about 400 mg – about 1800 mg initial IV dose (when present) and/or about 10 mg - 900 mg SC maintenance dose, about 800 mg – about 1600 mg initial IV dose (when present) and/or about 20 mg - 800 mg SC maintenance dose, about 1200 mg – about 1600 mg initial IV dose (when present) and/or about 50 mg - 700 mg SC maintenance dose, about 1300 mg – about 1500 mg initial IV dose (when present) and/or about 200 mg - 600 mg SC maintenance dose, or about 1400 mg initial IV dose (when present) and/or about 450 mg SC maintenance dose.

[0080] 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).

[0081] Also provided is a method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 one or more maintenance doses; wherein each of the one or more maintenance doses comprises about 300-600 mg (*e.g.*, about 300 mg or about 600 mg) of the fusion protein constructed administered subcutaneously (SC) to the subject, once every week; such that the renal disease in the subject is treated.

[0082] 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.

[0083] In some embodiments, the subject is further being treated by a SOC (standard of care) treatment for the renal disease. In some embodiments, the SOC is or comprises a Renin-angiotensin-aldosterone system (RAAS) inhibitor.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] In some embodiments, the renal disease is Lupus Nephritis (LN).

[0092] In some embodiments, the renal disease is IgA Nephropathy (IgAN).

[0093] In some embodiments, the renal disease is C3 Glomerulopathy (C3G), such as DDD or C3GN.

[0094] In some embodiments, the renal disease is Primary Membranous Nephropathy (MN).

[0095] In some embodiments, the renal disease is IgG4-RD.

[0096] 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)).

[0097] In certain embodiments, the subject: (a) has IgAN, and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, a glucocorticoid, a systemic corticosteroid (*e.g.*, prednisone), and/or an antibody-depleting therapy such as anti-CD20 antibody (*e.g.*, Rituximab); (b) has Lupus Nephritis (LN), and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, an immunomodulatory agent such as an antimalarial agent (*e.g.*, hydroxychloroquine), low dose chemotherapeutic agent (*e.g.*, cyclophosphamide), a Calcineurin inhibitor, Azathioprine (Imuran), Mycophenolate (CellCept), Rituximab (Rituxan), and/or Belimumab (Benlysta), voclosporin, and/or systemic immunosuppression (*e.g.*, cyclosporine, Tacrolimus, mycophenolate mofetil) with optional combination with a (high-dose) corticosteroid (*e.g.*, methylprednisolone, prednisone, or equivalent thereof); or, (c) has C3G (such as DDD or C3GN), and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, a blood pressure reducing agent, corticosteroid, eculizumab, immunosuppression, plasma exchange, and/or complement inhibition.

[0098] In certain embodiments, the subject has IgAN, and has proteinuria below 1g/d at/after about 26 weeks of treatment.

[0099] 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.

[0100] 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 Table A below (*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)).

Table A

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥ 300 mg/g ≥ 30 mg/mmol
GFR Stages	G ₁	Normal or high	≥ 90	0	1	2
	G ₂	Mildly decreased	60-90	0	1	2
	G _{3a}	Mildly to moderately decreased	45-59	1	2	3
	G _{3b}	Moderately to severely decreased	30-44	2	3	3
	G ₄	Severely decreased	15-29	3	3	4
	G ₅	Kidney failure	<15	4	4	4

Key to Figure:

Colors/Numbers: Represents the risk for progression, morbidity and mortality from best to worst.

0- Green: Low Risk (if no other markers of kidney disease, no CKD)

1- Yellow: Moderately Increased Risk

2- Orange: High Risk

3- Red: Very High Risk

4- Deep Red: Highest Risk

[0101] In some embodiments, the subject has impaired renal function.

[0102] 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 Table A (*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).

[0103] 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 Table A (*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).

[0104] 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 Table A (*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).

[0105] 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 Table A (*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).

[0106] As used herein, albuminuria category is assessed / determined by urine albumin-creatinine ratio (uACR).

[0107] In some embodiments, the subject is an adult (*e.g.*, 18 years and older).

[0108] 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).

[0109] 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.

[0110] In some embodiments, the subject is biologic male. In some embodiments, the subject is biologic female.

[0111] In some embodiments, the subject has been treated, and/or is being treated with a glucocorticoid (GC) or a corticosteroid.

[0112] 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.

[0113] 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.

[0114] In some embodiments, the subject is further being treated by or has been treated by a second or additional therapeutic agent effective to treat the renal disease. 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.

[0115] 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.

[0116] 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).

[0117] In some embodiments, the subject has been treated, and/or is being treated with Plasmapheresis to remove antibodies from the bloodstream. In some embodiments, the Plasmapheresis is performed every 1-2 days for about 2 weeks.

[0118] In some embodiments, the subject has been treated, and/or is being treated with a Renin-angiotensin-aldosterone system (RAAS) inhibitor.

[0119] As used herein, “renin-angiotensin-aldosterone system (RAAS) inhibitors” include a group of drugs that act by inhibiting the renin-angiotensin-aldosterone system (RAAS) and include angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-receptor blockers (ARBs), and direct renin inhibitors. ACE inhibitors and ARBs are commonly used in the treatment of patients with hypertension, heart failure with reduced ejection fraction and certain types of chronic kidney disease, as well as patients who have had a myocardial infarction. They are particularly important in the treatment of hypertensive diabetic patients, as they prevent the development of diabetic nephropathy.

[0120] In certain embodiments, the RAAS inhibitor is an angiotensin-converting enzyme inhibitor (ACE inhibitor). Exemplary ACE inhibitors include, without limitation, enalapril, lisinopril, ramipril, captopril, and benazepril.

[0121] In certain embodiments, the RAAS inhibitor is an angiotensin-receptor blocker (ARBs, sartans). Exemplary ARBs include, without limitation, valsartan, candesartan, losartan, and irbesartan.

[0122] In certain embodiments, the RAAS inhibitor is a direct renin inhibitor. Exemplary direct renin inhibitors include, without limitation, aliskiren.

[0123] 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.

[0124] 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.

[0125] 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 Kabat 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.

[0126] 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).

[0127] 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.

[0128] 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).

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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).

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.”

[0141] An “isolated antibody,” as used herein, is intended to refer to an antibody which is substantially free of other proteins and cellular material.

[0142] 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).

[0143] 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 FcγR and the inhibitory FcγRIIB, whereas natural killer (NK) cells selectively express one activating Fc receptor (FcγRIII in mice and FcγRIIIA in humans) but not the inhibitory FcγRIIB 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.

[0144] 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 (Clq) 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).

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] The term “prophylactic intervention” refers to treating a subject who does not yet have a disease for preventive purpose.

[0155] The term “effective dose” or “effective dosage” is defined as an amount sufficient to achieve or at least partially achieve a desired effect.

[0156] 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.

[0157] The term “patient” includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment. In some embodiments, the patient is a human.

[0158] 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.*

[0159] 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.

[0160] Provided are methods for the treatment of the renal diseases characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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.

[0161] 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.

[0162] 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.

[0163] 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	WQGTHTFPRT
7	254	Heavy Chain Variable Region, VH or HCVR	QVQLVQSGAEVKKPGASVKVSCASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDLTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSS
8	258	Light Chain Variable Region, VL or LCVR	DVVMQTQSPPLSLPVTLGQPASISCKSSQSLDSDGK TYLNWFQQRPGQSPRRLIYLVSKLDSGVPDRFSGS GSGTDFTLKISRVEAEDVGYYCQWGTHTFPRTFFGG GTKVEIK
9	282	Heavy Chain (HC)	QVQLVQSGAEVKKPGASVKVSCASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDLTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRV SKYGPPCPAPPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVQLHQLDNLNGKEYKCKVS NKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVLH EALHSHYTQKSLSLSLG
11	284	Heavy Chain Variable Region + CH1 (VH + CH1)	QVQLVQSGAEVKKPGASVKVSCASGYTFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFKGRVTM TVDLTSTSTAYMELSSLRSED TAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTISWNSGALTSGVHTFPAVLQSSGLYS

			LSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVE SKYG
10	285	Heavy Chain (HC)	QVQLVQSGAEVKKPGASVKVSCKASGYFTNYYIN WVRQAPGQGLEWMGVINPYSGGTSYNQKFGRVTM TVDTSTSTAYMELSSLRSEDYAVYFCSSPYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVDVSQEDPEVQFNWYVDGGEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLGLG
12	279	Light Chain (LC)	DVVMTQSPSLPVTLGQPASISCKSSQSLDSDGK TYLNWFQQRPGQSPRRLIYLVSKLDSGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYCWQGTHTFPRTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYEEKHKVYACEVTHQGLSSPV TKSFNRGEC

[0164] 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.

[0165] 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.

[0166] SEQ ID NO: 138 as used in WO2020123662 is: GGGGSGGGGS (SEQ ID NO: 14).

[0167] In certain embodiments, the complement modulator polypeptide comprises an amino acid sequence of SEQ ID NO: 72 or 108, as used in WO2020123662:

EDCNELPPRRNTEILTGSDQTYPEGTQAIYKCRPGYRSLGNVIMVCRKGEWVALNPLRKC
QKRPCGHPGDTFPGTFTLTGGNVFEYGVKAVYTCNEGYQLLGEINYRECDTDGWTNDIPICE
VVKCLPVTAPENGKIVSSAMEPDREYHFGQAVRFVCNSGYKIEGDEEMHCSDDGFWWSKEPK
CVEISCKSPDVINGSPISQKIIYKENERFQYKCNMGYEYSERGDAVCTESGWRPLPSCEEKS
CDNPYIPNGDYSPLRIKHRTGDEITYQCRNGFYPATRGNTAKCTSTGWIPAPRCTLK (SEQ

ID NO: 15, *i.e.*, SEQ ID NO: 72 as used in WO2020123662 – soluble factor H 1–5 or fH₁₋₅)

EDCNELPPRRNTEILTGSWSDQTYPEGTQAIYKCRPGYRSLGNVIMVCRKGEWVALNPLRKC
QKRPCGHPGDTFPGTFTLTGGNVFEYGVKAVYTCNEGYQLLGEINYRECDTDGWTNDIPICE
VVKCLPVTAPENGKIVSSAMEPDREYHFGQAVRFVCNSGYKIEGDEEMHCSDDGFSKEKPK
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)).

[0168] 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.

[0169] 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).

[0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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.*, a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney).

[0182] The pharmaceutical composition described herein can include one or more pharmaceutically acceptable salts.

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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

[0196] 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. 17A). 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.

[0197] 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 the 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. 17B). Demographic characteristics were generally similar between placebo and COMPOUND B treated groups in both SAD and MAD cohorts except there was higher proportion of female participants in COMPOUND B-treated groups compared to placebo.

[0198] COMPOUND B was well tolerated across all dose levels with no clinically significant drug-related safety findings or anti-drug antibodies (ADAs) observed.

[0199] At all doses tested, no deaths occurred, and no serious or $\geq$ Grade 3 TEAEs (treatment-emergent adverse events) were reported (FIG. 17C). None of the TEAEs led to study drug discontinuation or to withdrawal from the study.

[0200] 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.

[0201] It can be observed in the data in FIG. 17D 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.

[0202] In subcutaneous (SC) administration (FIG. 17E), 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.

[0203] Non-compartmental analysis (NCA)-calculated terminal half-life ($T_{1/2}$) was dose-dependent.

[0204] 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. 17F).

[0205] 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. 17G).

[0206] 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. 17H), or 5 weekly SC injections of 450 mg COMPOUND B (FIG. 17I). 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. 17H).

[0207] 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.

[0208] Potential clinical dosing regimens were simulated using 26 SC doses of 450 mg administered weekly (QW) (FIG. 17J). 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.

[0209] The estimated concentration of COMPOUND 1 that leads to 50% inhibition of Wieslab AP activity (IC₅₀) is 56.3 µg/mL (FIG. 17K). 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. 17K).

[0210] 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 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_{max,ss} ~5-fold below the IC₅₀ for systemic AP inhibition.

Example 2 A Phase 2 Study to Evaluate the Safety, Pharmacology, Pharmacokinetics, and Clinical Activity of COMPOUND B Administered Subcutaneously in Male and Female Patients Aged 18 Years or Older with Primary IgA Nephropathy (IgAN), Lupus Nephritis (LN), or C3 Glomerulopathy (C3G)

[0211] 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 the renal diseases characterized by C3d deposit in the kidney, such as primary IgA Nephropathy (IgAN), Lupus Nephritis (LN), or C3 Glomerulopathy (C3G) (collectively in short – “the renal diseases”).

[0212] This example demonstrates that COMPOUND B is effective to reduce symptoms of the renal diseases in patients, at least by Week 26 after commencement of treatment based on the dosing regimen described herein.

[0213] More specifically, the primary objective of the clinical study is to assess the safety and tolerability of COMPOUND B at 2 dose levels (a first does of about 600 mg, and a second dose of either lower (*e.g.* 300 mg) or higher (*e.g.*, 1200 mg), partly depending on the results of the trial in patients receiving the 600 mg dose) in a basket study design over a 26-week treatment period in patients with kidney diseases characterized by dysregulation of the complement system: IgAN, lupus nephritis (LN), and C3 glomerulopathy. Other objectives of this study augment understanding of local and systemic pharmacokinetics (PK) and pharmacodynamics (PD) of COMPOUND B, and characterize its clinical activity in patients with IgAN, LN, and C3G via analysis of paired kidney biopsies and other markers of disease activity.

[0214] The study design was informed by considerations related to the pathophysiology of each disease, the currently understood mechanism of action of COMPOUND B, completed COMPOUND B nonclinical studies, an ongoing Phase 1 FIH (first-in-human) clinical trial, and the high unmet medical need of patients with each disease. Results from the study support clinical development of COMPOUND B in patients with these and potentially other kidney disorders mediated by complement dysregulation.

[0215] The primary objective of this study is to show that COMPOUND B is safe when administered to patients with IgAN, LN, or C3G. Achievement of this objective is measured by incidence of AEs (adverse events).

[0216] A detailed study design is provided in FIG. 1, which depicts a Phase 2 basket study to evaluate the safety, PK, PD, and clinical activity of 2 dose levels of COMPOUND B in patients with IgAN, LN, or C3G.

[0217] While the IgAN and C3G groups are open label, the LN group enrolls participants who are randomly assigned (2:1) to either COMPOUND B + SOC (standard of care), or placebo + SOC in a blinded manner. The total enrollment is for 38 participants (19 participants in Cohort 1 and 19 participants in Cohort 2). Participants in each disease group are permitted to enroll into the study as they successfully pass screening. Accordingly, there may be different proportions of patients in each disease group in each dosing cohort. For each dosing cohort, there are a goal enrollment of at least 3 patients in each disease group. The Sponsor may close enrollment for a given disease group based on recruitment challenges.

[0218] During screening, patients undergo a kidney biopsy to confirm diagnosis of one of the target diseases and accompanying deposition of active C3 fragments. Following the Screening Period of up to 12 weeks, patients are enrolled into the 26-week Treatment Period, and receive a dose of COMPOUND B via SC injection or infusion QW starting on Day 1. Patients already on a RAAS inhibitor when initiating the study should have been on a stable dose for at least 12 weeks prior to dosing on Day 1, and should not change their dose of these agents during the Treatment Period unless deemed medically necessary.

[0219] The COMPOUND B Cohort 1 starting dose is 600 mg (fixed dose equivalent of 8 mg/kg).

[0220] A post-dose kidney biopsy is obtained after the fifth dose (Day 31). The collection of pre- and post-treatment kidney biopsies provides an important opportunity to assess treatment with COMPOUND B. The pre-treatment biopsy is performed as part of standard diagnostic evaluation or clinical care to confirm both the diagnosis and the presence of C3 active fragments reflecting ongoing complement activation. The post-dose kidney biopsy offers the potential to show the presence of COMPOUND B at sites of complement activation and a reduction in local C3 fragment deposition and provides the opportunity for safety monitoring via the assessment for any histologic evidence of immune complex (IC) deposition suggestive of immunogenicity.

[0221] After receiving the fifth dose and associated kidney biopsy, participants are allowed, with guidance from a blinded Safety Review Committee (SRC), to proceed at the same dose level for the remainder of the Treatment Period. The data reviewed by the SRC may includes, but is not limited to, AEs, laboratory results (including urinalysis), vital signs, electrocardiogram (ECG) results, and post-dose kidney biopsies.

[0222] In addition to the SRC, an unblinded Data Monitoring Committee (DMC) has independent oversight of the entirety of the study. The DMC convenes on a recurring basis to review the relevant data for all patients to ensure safety with continued dosing up to 26 weeks. The DMC review a totality of data to assess benefit and risk, including complement biomarkers (*e.g.*, urinary Complement 5b9 [C5b-9]), proteinuria, estimated glomerular filtration rate (eGFR), PK, PD (*e.g.*, systemic AP inhibition), kidney biopsy histology, AEs, laboratory values, vital signs, ECG results, and immunogenicity (including ADA).

[0223] When at least 5 participants in Cohort 1 have completed Week 5 to confirm safety, PK, and pharmacology (magnitude of tissue and systemic AP inhibition), dosing Cohort 2 is opened, and the next 19 participants receive COMPOUND B at a dose that may be higher or lower than the dose level in Cohort 1. If higher than the first dose level, the second dose level is selected from the range of doses determined to be acceptable based on nonclinical and toxicology studies, results from ongoing Phase 1 study, and results from Cohort 1 of this study. The second dose level does not exceed 1200 mg COMPOUND B QW.

[0224] At the end of the Treatment Period (Week 26), participants are offered an additional optional kidney biopsy.

[0225] A number of secondary objectives of the trial are also investigated. One secondary objective is to evaluate the local pharmacology of COMPOUND B in patients with IgAN, LN, or C3G. This secondary objective is measured by the following secondary endpoints:

- Change from baseline in urinary sC5b-9 (soluble Complement 5b9), through Week 26
- Change from baseline in kidney C3 fragment deposition in tissue biopsies at Week 5

[0226] Another secondary objective is to evaluate the localization of COMPOUND B in kidney tissue in patients with IgAN, LN, or C3G. This secondary objective is measured by the following secondary endpoint:

- Evidence of COMPOUND B localization via immunostaining (at sites of complement activation) in the kidney in tissue biopsies at Week 5

[0227] Another secondary objective is to characterize the plasma PK of COMPOUND B in patients with IgAN, LN, or C3G. This secondary objective is measured by the following secondary endpoint: plasma PK of COMPOUND B as evaluated by PPK (population pharmacokinetics) analysis using nonlinear mixed-effects modeling.

[0228] A number of exploratory objectives of the trial are also investigated. One such exploratory objective is to evaluate the clinical activity of COMPOUND B in patients with

IgAN, LN, or C3G. This exploratory objective is measured by the following exploratory endpoints:

- Changes from baseline in proteinuria (urine protein: creatinine ratio, or uPCR) through Week 26
- Changes from baseline in eGFR (estimated glomerular filtration rate) and/or eGFR slope through Week 26

[0229] Another exploratory objective is to characterize the immunogenicity of COMPOUND B in patients with IgAN, LN, or C3G. This exploratory objective is measured by the following exploratory endpoints:

- 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
- Changes in other markers of complement activation: *e.g.*, serum C3 and C4 levels, AH50, and CH50

[0230] Yet another exploratory objective is to investigate the systemic PD effects of COMPOUND B in patients with IgAN, LN, or C3G. This exploratory objective is measured by the following exploratory endpoints:

- Changes from baseline in serum complement AP activity through Week 26
- Changes from baseline in complement and non-complement biomarkers in serum and urine through Week 26

[0231] Still another exploratory objective is to explore the relationships between endpoints in patients with IgAN, LN, or C3G. This exploratory objective is measured by the following exploratory endpoint:

- Exploratory assessment of the relationships between blood, urine, and tissue PK/PD, ADA, safety, tolerability, and clinical activity, as available

[0232] 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)

[0233] The starting dose (Dose 1) for the Phase 2 study is 600 mg SC administered QW, equivalent to an 8 mg/kg dose in a 75 kg subject. Preliminary modeling and simulations of the Phase 1 data (see Example 3) predict that this dosing regimen will maintain plasma COMPOUND B minimum concentration at steady state ($C_{min,ss}$) above the target activity threshold of 3.2 $\mu\text{g/mL}$ (the estimated concentration leading to 90% of maximum effect [EC90] for reduction of glomerular complement activity in a passive Heymann nephritis [PHN] rat model) in >95% of participants, yet below the model-estimated half maximal effective concentrations (EC50) for serum AP activity in healthy volunteers of 72 $\mu\text{g/mL}$. The PD data from the phase 1 healthy participant study show that target activity thresholds are not associated with any appreciable systemic AP inhibition. The assumption is that the PK and PD are similar between healthy and patient populations. PK simulations predict that in patients, nephrotic range proteinuria may impact exposures of COMPOUND B, and that approximately half of the patients will have $C_{min,ss}$ levels exceeding the target activity threshold of 3.2 $\mu\text{g/mL}$ after receiving 600 mg SC QW dosing over 26 weeks. Notably, the proposed starting dose of 600 mg was considered not a substantial leap from 450 mg assessed in MAD Cohort 1 in the Phase 1 healthy participant study based on the following 3 points: 1) A 1.3-fold mathematical increase in dose represents less than a half-log dose increase normally expected in a dose escalation study; 2) The exposure of 600 mg is expected to overlap with the 450 mg exposure in the human population; 3) The steady state at 600 mg SC QW dosing is simulated to be achieved in 2 weeks and no significant accumulation was expected after 26 weeks dosing.

[0234] For clinical dose selection, maintenance of plasma concentrations above the target activity threshold throughout dosing is conservatively assumed to be required in order to sustain tissue penetration, tissue target engagement, and tissue activity. A weekly dosing interval for SC administration is considered a clinically feasible option for patients with kidney diseases, and simulations support the feasibility of weekly dosing to maintain target plasma concentrations. In addition, the half-life of COMPOUND B in the kidney, where complement activation is occurring and the C3d target is deposited, is estimated to be ~7 days (data not shown) based on $\text{CfH}^{-/-}$ mouse data, supporting a weekly dosing interval. The dosing interval can be re-evaluated / adjusted based on evolving understanding of the relationships between blood and tissue pharmacology and exposure/response.

[0235] While baseline body weight was incorporated as fixed exponents of 1.0 on central and peripheral volume of distribution and 0.75 on clearance, intercompartmental clearance and maximum velocity for population PK modeling, weight is not considered to have a meaningful impact on the exposure to COMPOUND B; therefore, a fixed dosing approach is being utilized. Furthermore, fixed dosing has been utilized in the Phase 1 study of COMPOUND B in healthy volunteers and has demonstrated good safety and tolerability to date.

[0236] Subsequent dosages and regimens in the Phase 2 study depend on emerging safety, PK and PD data. The maximal dose level will not exceed 1200 mg COMPOUND B QW. The anticipated maximal exposure $AUC_{\tau,ss}$ would not exceed the AUC_{inf} at 30 mg/kg IV single dose assessed in the Phase 1 study.

[0237] The total duration of study participation for each patient is up to 288 days (approximately 42 weeks). Study periods include:

- Screening Period: between up to 84 prior to Study Day 1 (first dose of study drug);
- Treatment Period: Study Day 1 to Study Day 182 (26 doses of COMPOUND B);
- Follow-up Period: Study Day 183 to Study Day 204.

[0238] Available preclinical data supports dosing of COMPOUND B up to 26 weeks, and 3-months of weekly repeat dosing at 250 mg/kg IV (highest dose tested) was associated with the highest exposure in the study, and is estimated to be > 40-fold of simulated median $AUC_{\tau,ss}$ at 83.3 $\mu\text{g}\cdot\text{days/mL}$ (or 1999.2 $\mu\text{g}\cdot\text{h/mL}$) after 26 weekly doses of COMPOUND B at 600 mg SC.

[0239] COMPOUND B is formulated as 75 mg/mL drug product solution in 12 mM sodium phosphate, 75 mM arginine, 125 mM sucrose, and 0.05% (weight/volume) polysorbate 80 at pH 6.7, 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 2R vials is filled to 1.65 mL, and contains an extractable volume of 1.5 mL minimum of COMPOUND B. That is, each vial of COMPOUND B contains at least 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 26 SC maintenance doses of about 300 mg, 600 mg, or 1200 mg each, as needed.

[0240] The dose level was derived from both preclinical studies and a previous Phase 1 clinical study. Specifically, preclinical pharmacological studies *in vivo* including $\text{CfH}^{-/-}$ 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 $\mu\text{g/mL}$. 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 EC_{90} = circulating concentration of 0.3 $\mu\text{g/mL}$) 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).

[0241] Taking 3.2 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ as the target dose threshold. 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 IC_{50} of 56.3 $\mu\text{g/mL}$. 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 weekly 600 mg SC doses maintain the plasma COMPOUND B concentrations above the circulating threshold of 32 $\mu\text{g/mL}$ for 96 hours post dose in >90% of patients.

[0242] The SC doses was also 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 $\mu\text{g/mL}$ results in maximal tissue PD ($\geq 90\%$ 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

CfH^{-/-} mice, and PK/PD in a monkey UVB skin challenge model. Modeling and simulations of the Phase 1 data predicted 600 mg SC administered QW maintains plasma COMPOUND B minimum concentration at steady state ($C_{min,ss}$) above the target activity threshold of 3.2 $\mu\text{g/mL}$ in >95% subjects, yet below the model estimated IC_{50} for serum AP activity in healthy volunteers of 56.3 $\mu\text{g/mL}$ 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 600 mg SC dosing achieved exposures below systemic inhibition and above conservative end of predicted range for clinical activity.

[0243] The maintenance doses are about 55-fold lower 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 COMPOUND C. Thus the doses provide ample safety margin for patients.

[0244] 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 day* $\mu\text{g/mL}$, respectively, representing 55-fold higher than the expected exposure $C_{max,ss}$ (10.8 $\mu\text{g/mL}$) and $AUC_{tau,ss}$ (1,530 $\mu\text{g}\cdot\text{h/mL}$) after 600 mg SC QW. Notably, the 600mg SC dose was the dose assessed in the MAD Cohort of Phase 1 clinical study which was tolerated and safe.

[0245] In summary, the Phase 1 study using COMPOUND B in 56 healthy volunteers confirmed that the 600 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.

[0246] 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.

[0247] 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

[0248] The Sponsor conducts blinded periodic safety reviews as the study progresses described in a Safety Monitoring Plan.

Patient Inclusion Criteria

[0249] All Participants

- Age 18 years and older
- Biopsy-proven diagnosis (IgAN, LN, or C3G) obtained within 12 weeks of Study Day 1 and evidence of C3 fragment deposition (a score of at least 2+ by immunofluorescence, using a scale of 0-3) on biopsy
- Patients receiving a RAAS (Renin-Angiotensin-Aldosterone System) inhibitor must have been on a stable dose for at least 12 weeks prior to Study Day 1
- All study participants must have vaccinations for *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b. Participants may also be offered ageappropriate immunizations as recommended by regional health authorities prior to dosing, per the Investigator's judgement.

[0250] Participants with IgAN ONLY

- Urine protein $> 1 \text{ g}/24\text{h}$ or urine protein: creatinine ratio (uPCR) $> 1 \text{ g/g}$.
- Screening eGFR $> 30 \text{ mL}/\text{min}/1.73\text{m}^2$ calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-EPI GFR).

[0251] Participants with LN ONLY

- Clinical diagnosis of systemic lupus erythematosus by 2019 American College of Rheumatology and European League Against Rheumatism criteria.
- Diagnosis of active focal or diffuse proliferative LN Class III or IV (+/- class V; may co-exhibit class V disease) according to the 2018 Revised International Society of Nephrology/Renal Pathology Society classification. Clinically active LN at screening, requiring/receiving immunosuppression induction treatment. Participants with *de novo* or relapsing disease may be eligible.
- Urine protein > 1 g/24hr or uPCR > 1 g/g.
- Screening eGFR >30 mL/min/1.73 m² calculated by the CKD-EPI GFR.

[0252] Participants with C3G ONLY

- Biopsy-proven C3G, DDD (dense deposit disease) or C3GN (C3 glomerulonephritis)
- Urine protein > 1 g/24h or uPCR > 1 g/g
- Screening eGFR ≥ 30 mL/min/1.73 m² calculated by the CKD-EPI GFR.

Patient Exclusion Criteria

[0253] All Participants

- Patients without a historic diagnosis who have their diagnostic kidney biopsy performed more than 12 weeks prior to Study Day 1.
- Patients with a historic diagnosis and most recent kidney biopsy more than 12 weeks prior to Study Day 1.
- Patients with ≥ 50% interstitial fibrosis, tubular atrophy, glomerular sclerosis, or crescent formation.
- Patients with urine protein > 3 g/24h or uPCR > 3 g/g.
- Patients with nephrotic syndrome, minimal change nephropathy with IgA deposition, or crescentic nephritis.
- Presence of rapidly progressive glomerulonephritis as defined by 50% decline in eGFR within the last 3 months.
- Concomitant significant renal disease other than IgAN, C3G, or LN.
- Concurrent RAAS inhibition where dosing has not been stable for at least 12 weeks prior to the first dose of study drug.
- Uncontrolled hypertension.

- Kidney, other solid organ, or bone marrow transplantation prior to, or expected, during the study.
- Patients with acute or chronic bacterial or parasitic infectious disease, including a history of recurrent invasive infections caused by encapsulated organisms. Positive hepatitis B virus, hepatitis C virus, or human immunodeficiency virus viral screening test indicative of acute or chronic infection.

- Previously received a complement inhibitor.
- Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose.

[0254] Participants with IgAN ONLY

- Secondary forms of IgAN.
- Patients with mesangial hypercellularity (M), endocapillary hypercellularity (E), and interstitial fibrosis/tubular atrophy (T) scores of M0, E0, and T2 on kidney biopsy, respectively.
- Received systemic corticosteroid therapy (> 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 3 months prior to the first dose of study drug (or within 6 months for rituximab).

[0255] Participants with LN ONLY

- Received any of the following treatments:
 - Cyclophosphamide ≤ 6 months prior to Screening;
 - Calcineurin inhibitors ≤ 3 months prior to Screening;
 - A cumulative dose of intravenous methylprednisolone > 3 g for the current active renal flare;
 - Mycophenolate mofetil > 2 g/day (or equivalent) for ≥ 4 consecutive weeks prior to Screening for the current active renal flare;
 - Prednisone or prednisone equivalent ≥ 0.5 mg/kg/day for ≥ 4 consecutive weeks prior to Screening for the current active renal flare.

[0256] Participants with C3G ONLY

- Patients with anti-factor H (fH) antibodies.
- Evidence of monoclonal gammopathy of unclear significance, infections, malignancy, autoimmune diseases, or other conditions to which C3G is secondary.
- Received systemic corticosteroid therapy (> 10 mg/day of prednisone or equivalent), eculizumab, or any other form of immunosuppressive therapy within 3 months prior to the first dose of study drug (or within 6 months for rituximab).

Efficacy Analyses

[0257] 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 IgAN, LN, or C3G. The primary endpoint includes incidence of AEs.

[0258] A number of secondary endpoints are also evaluated.

[0259] One secondary objective is to evaluate the local pharmacology of COMPOUND B in patients with IgAN, LN, or C3G. This is assessed by secondary endpoints such as change from baseline in urinary sC5b-9, through Week 26, and change from baseline in kidney C3 fragment deposition in tissue biopsies at Week 5.

[0260] Another secondary objective is to evaluate the localization of COMPOUND B in kidney tissue in patients with IgAN, LN, or C3G. This is assessed by secondary endpoints such as identifying evidence of COMPOUND B localization via immunostaining (at sites of complement activation) in the kidney in tissue biopsies at Week 5.

[0261] Yet another secondary objective is to characterize the plasma PK of COMPOUND B in patients with IgAN, LN, or C3G. This is assessed by secondary endpoints such as plasma PK of COMPOUND B as evaluated by PPK analysis using nonlinear mixed-effects modeling.

[0262] A number of exploratory objectives are further evaluated.

[0263] One exploratory objective is to evaluate the clinical activity of COMPOUND B in patients with IgAN, LN, or C3G. This is evaluated by determining the change from baseline in proteinuria (uPCR) through Week 26 (end of treatment), and changes from baseline in eGFR and/or eGFR slope through Week 26.

[0264] Another exploratory objective is to characterize the immunogenicity of COMPOUND B in patients with IgAN, LN, or C3G. This is evaluated by determining incidence and titer of treatment-emergent anti-COMPOUND B antibodies in plasma (ADA), incidence of anti-COMPOUND B NAb 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, and CH50.

[0265] Another exploratory objective is to investigate the systemic PD effects of COMPOUND B in patients with IgAN, LN, or C3G. This is evaluated by changes from baseline in serum complement AP activity through Week 26, and changes from baseline in complement and non-complement biomarkers in serum and urine through Week 26.

[0266] Another exploratory objective is to explore the relationships between endpoints in patients with IgAN, LN, or C3G. This is evaluated by exploratory assessment of the relationships between blood, urine, and tissue PK/PD, ADA, safety, tolerability, and clinical activity, as available.

Adverse Events of Special Interest

[0267] 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.

[0268] 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 ($<500 \mu\text{L}$).

Example 3 Monte Carlo Simulations for Phase 2 Dose Selection - Simulation of 300 mg and 600 mg SC QW in Healthy Volunteers

[0269] Monte Carlo simulations were performed using the established PK/PD model and an assumed geometric mean (CV%) body weight of 68.5 kg (22% CV) to predict PK and Wieslab AP activity in patients with IgA nephropathy, lupus nephritis, and C3 glomerulopathy. These values were based on the healthy volunteer data in from a Phase 1 SAD study. Potential clinical dosing regimens for Phase 2 were simulated, including 300 mg SC QW and 600 mg SC QW for a total of 24 doses, followed by a washout period.

[0270] The model-predicted median steady-state $C_{\min}$ following a dose of 300 or 600 mg SC QW in healthy volunteers is 4.64 $\mu\text{g/mL}$ and 7.01 $\mu\text{g/mL}$, respectively. Key predicted parameters (median and 95% prediction interval) for healthy volunteers are given in table below.

Key Predicted Summary Statistics by Regimen in Healthy Volunteers

	C_{min,ss} (µg/mL)	C_{max,ss} (µg/mL)	Time to SS (days)	Effective AUC Half-life (days)	% of Subjects above 3.2 µg/mL at C_{min,ss}	AUC_{tau,ss} (µg*days/mL)
300 mg QW	4.64 (1.97,8.02)	9.39 (5.24,15.1)	14	4.91 (2.95, 8)	74.5	49.9 (24.8,79.9)
600 mg QW	7.01 (3.3,14.81)	16.6 (9.2,34.2)	14	4.51 (2.82, 6.93)	95	83.3 (43.9,177.8)

- Abbreviations: AUC: area under curve; AUC_{tau,ss}: area under the plasma concentration-time curve over a dosing interval at steady state; C_{max,ss}: maximum concentration at steady state; C_{min,ss}: minimum concentration at steady state; QW: once weekly.

[0271] Simulations suggest that 74.5% and 95% of healthy volunteers would be expected to achieve steady-state C_{min} >3.2 µg/mL following 300 mg and 600 mg SC QW dosing, respectively.

[0272] Predicted concentration versus time profiles for these 2 regimens are provided in FIGs. 2A and 2B. Reference y axis thresholds included:

- 72 µg/mL: the approximate EC50 for Wieslab AP activity reduction from the PK/PD model.
- 42 µg/mL: the EC50 for Wieslab AP activity reduction from the pooled E_{max} model.
- 3.2 µg/mL: the EC90 for reduction of glomerular complement activity in a PHN rat model.
- 0.2 µg/mL: the approximate EC90 for reduction of glomerular complement activity, derived from an estimate of 0.26 µg/mL from a PK/PD analysis of data from a mouse factor H KO model.

[0273] Additional simulations were performed that included (A) sensitivity analyses on 300 mg and 600 mg SC QW to inform potential exposures in the Phase 2 target patient population (data not shown); and (B) simulation of highest COMPOUND B SAD regimen for exposure margin assessment.

[0274] In summary, a preliminary PK/PD model was established to characterize the interim PK and Wieslab AP activity data from healthy volunteers in a Phase 1 study following single IV or SC dosing of COMPOUND B. A parallel elimination mechanism,

consisting of a saturable route and a linear route was characterized. Baseline body weight was incorporated as a covariate on central and peripheral volume of distribution, clearance and $V_{\max}$. No effects of age, serum albumin, body mass index, sex, or race on the PK of COMPOUND B were identified in the current model. Both the PK and PD models were considered fit for the purpose of predicting multiple-dose regimens by the IV and SC route.

[0275] Simulation results for the phase 2 patient population were dependent on assumptions about the impact of increased C3d and proteinuria on elimination. Under worst-case scenario (10-fold increase in $V_{\max}$ and 1.5-fold increase in CL), 47% of patients are predicted to have $C_{\min,ss}$ above the 3.2 $\mu\text{g/mL}$ target activity threshold following 600 mg SC dosing, offering an opportunity for clinical activity.

[0276] In the Phase 1 study, a single dose of 30 mg/kg IV was well tolerated by healthy volunteers, and the simulated exposures following this dose were significantly higher than the predicted $C_{\max,ss}$ and $\text{AUC}_{\tau,ss}$ obtained after 600 mg SC QW (16.6 $\mu\text{g/mL}$ and 83.3 $\mu\text{g}\cdot\text{day/mL}$, respectively). Specifically, the expected exposures were 52-fold higher for $C_{\max,ss}$ and 18.5-fold higher for $\text{AUC}_{\tau,ss}$ for a single 30 mg/kg IV dose compared to the predicted steady state exposures from the 600 mg SC QW dose.

Example 4 In Vivo Target Engagement in Kidney

[0277] Factor H deficient ($\text{CfH}^{-/-}$) mice exhibit elevated levels of complement activation and C3d deposition in the liver and kidneys due to the loss of functional fH protein, and they consequently develop sporadic complement-mediated kidney injury. Kidney and liver complement activation in $\text{CfH}^{-/-}$ mice can be measured using antibodies against C3 split products (C3b and C3d) or against C9, a component of the C5b-9, complement membrane attack complex. Furthermore, because of uncontrolled and excessive AP complement activation, $\text{CfH}^{-/-}$ mice also exhibit reduced plasma levels of intact C3 protein. *In vivo* administration of either exogenous mouse or human fH_{1-5} partially reduces C3 consumption, leading to a transient increase in plasma C3, which can therefore be used as a biomarker to assess inhibition of systemic complement activity. Because of this ability to measure AP complement in tissues (kidney and liver) and in circulation, $\text{CfH}^{-/-}$ mice were used as an *in vivo* model system to evaluate circulating and tissue PK/PD for COMPOUND B and its mouse homolog COMPOUND C.

[0278] COMPOUND B was administered either IV or SC at dose levels ranging from 1.25 to 25 mg/kg. Seven days after dosing, kidney tissue was collected, sectioned, and

immunostained with antibodies recognizing active C3 split products (anti-C3 fragments). Immunostaining was then quantified to measure glomerular anti-C3 fragments in relative fluorescence units (RFU) normalized to total analyzed area (FIG. 3). One week after a single dose of COMPOUND B, complement fragment deposition was inhibited in glomeruli relative to PBS-injected *CfH*^{-/-} mice. This was the case at all dose levels evaluated, suggesting that the minimum dose required to fully inhibit glomerular complement activation is ≤ 1.25 mg/kg, indicating potent and durable *in vivo* tissue target engagement by COMPOUND B.

[0279] The relationship between circulating and tissue PK/PD was further evaluated in a time course study in *CfH*^{-/-} mice. The mouse homolog of COMPOUND B, COMPOUND C, was used to reduce the formation of ADAs. COMPOUND C was delivered IV or SC at doses ranging from 0.3 to 25 mg/kg and plasma and tissue were collected at multiple time points to evaluate circulating and tissue PK/drug exposure and complement activity.

[0280] Circulating drug concentration data are summarized in FIGs. 4A-4E. Twenty-four hours after delivery, a single 25 mg/kg SC dose of COMPOUND C achieved a circulating $C_{\max}$ of about 50 $\mu\text{g/mL}$. A measurable increase in plasma C3 was concomitantly observed, indicating partial inhibition of systemic complement at circulating drug concentrations > 10 $\mu\text{g/mL}$, which occurred over the first 48-72 hours after COMPOUND C administration at this dose. Intravenous delivery of a 5 mg/kg dose of COMPOUND C also resulted in transient elevation of plasma C3 over 1 day, corresponding to drug exposure > 10 $\mu\text{g/mL}$. In contrast, SC delivery of COMPOUND C at 5 mg/kg or less resulted in little or no plasma C3 elevation, consistent with the lower COMPOUND C $C_{\max}$ and overall exposure levels. These data indicate that COMPOUND C administered SC at ≤ 5 mg/kg does not result in circulating drug concentrations sufficient to inhibit systemic complement in *CfH*^{-/-} mice.

[0281] Tissue PK/PD was assessed in *CfH*^{-/-} kidneys collected in a time course of after COMPOUND C dosing. Anti-mfH immunofluorescence was used to measure tissue biodistribution and anti-C3 active fragments (anti-C3c) immunofluorescence used to assess complement activation/PD. Representative images from selected timepoints for the 5 mg/kg IV group are shown in FIG. 5, demonstrating the reciprocal relationship between tissue drug exposure and complement activity in glomeruli. Similar results were obtained with other dose groups.

[0282] Quantitation of immunostaining, measured in RFU normalized to total analyzed area, is shown in FIGs. 6A-6E. COMPOUND C dosed IV at 5 mg/kg was detected in glomeruli by anti-mfH immunofluorescence (FIG. 6A). However, unlike circulating PK or intact C3 in plasma/PD, COMPOUND C remained in tissue for up to 14 days after dosing.

COMPOUND C also inhibited complement in tissue, as active C3 fragments were reduced in glomeruli within 8 hours after delivery. Consistent with glomerular drug exposure, glomerular C3 complement activation remained significantly suppressed 7 days after dosing. In some experiments, approximately 50% complement inhibition could still be detected for up to 14 days after dosing, illustrating the durability of the C3d-targeting approach. Furthermore, because measurement of drug in tissue detects only intact COMPOUND C, the durability in these studies indicates that the anti-C3d-fH fusion protein is quite stable (*i.e.*, the fusion protein is not prone to linker cleavage that would separate fH from the mAb). These data indicate that COMPOUND C distributes to kidney and targets C3d in the glomeruli, showing significantly longer PK and PD in tissue than in circulation.

[0283] Dosing of COMPOUND C at 5 mg/kg by SC administration showed initially slower but overall similar tissue biodistribution as compared to IV administration (FIG. 6C). Importantly, this was achieved with a lower circulating $C_{\max}$ level ($< 2 \mu\text{g/mL}$) that was not associated with systemic complement inhibition as measured by increased circulating intact C3 protein. COMPOUND C dosed SC at 5 mg/kg achieved complement inhibition in the kidney that was comparable to a 25 mg/kg SC dose (FIG. 6B), suggesting full tissue complement inhibition at 5 mg/kg. Near maximal and sub-maximal inhibition of C3 complement activation was observed in the 1 mg/kg and 0.3 mg/kg dose groups, respectively (FIG. 6D, FIG. 6E). Even at these 2 lower doses, target engagement remained evident 5 to 7 days after dosing, when circulating drug levels were at or near the lower limit of quantification (lower limit of quantification; $0.1 \mu\text{g/mL}$) of the PK assay. These data show that COMPOUND C achieves potent and durable target engagement in Cfh^{-/-} kidneys at SC doses $\geq 1 \text{ mg/kg}$, and that doses $\leq 5 \text{ mg/kg}$ do not significantly affect systemic complement activity.

Example 5 *In Vivo Inhibition of Circulating Complement Alternative Pathway Activity in Cynomolgus Monkeys*

[0284] Inhibition of the circulating complement AP by COMPOUND B in cynomolgus monkeys was evaluated using the Wieslab assay in 3 studies: a single-dose PK/PD study, a 28-day non-GLP repeat-dose study, and a 29-day GLP repeat-dose study with a 27-day recovery phase. The Wieslab assay was conducted as usual except the serum was directly obtained from monkeys treated with COMPOUND B *in vivo*.

[0285] After a single-dose SC injection of COMPOUND B at 3, 10, or 30 mg/kg,

circulating AP inhibition was dose-dependent as measured by the extent and duration of inhibition. At 3 mg/kg, a maximum inhibition of approximately 75% was observed within 24 hours, which lasted up to 30 hours after SC administration. The corresponding $C_{\max}$ and AUC extrapolated to infinite time at 3 mg/kg were 22.8 $\mu\text{g/mL}$ and 1670 $\mu\text{g}\cdot\text{h/mL}$, respectively. Greater than 95% inhibition of AP was observed at a dose of ≥ 10 mg/kg which lasted for 72-96 hours after SC injection. Notably, comparable patterns of AP inhibition were observed at 10 mg/kg between SC and IV (data not shown).

[0286] Circulating inhibition of AP was also evaluated in the non-GLP 28-day repeat-dose study of COMPOUND B. This included doses of 60 and 150 mg/kg dosed IV and 150 mg/kg dosed SC on Day 1, then every 3 days starting on Day 8 for 28 days. It also included a dose of 150 mg/kg dosed IV-QW. All groups showed 100% inhibition of AP through Day 11 compared to a maximal inhibition of 14% in the control group at any time point.

COMPOUND B dosed IV or SC at 150 mg/kg, once on Day 1 and then every 3 days starting Day 8, showed a similar maximal duration of inhibition, with both groups achieving 100% inhibition through Day 20, and 6 of 8 total animals achieving 100% inhibition through Day 31. This suggests AP inhibition with repeat COMPOUND B dosing was not impacted by the detected ADA, and any exaggerated pharmacologically-mediated effects can be evaluated under such sustained inhibition of AP by COMPOUND B in this 28-day study.

[0287] Circulating inhibition of AP activity was also assessed in the GLP 29-day repeat-dose study of COMPOUND B. Consistent with the non-GLP study, dose-dependent circulating inhibition of AP activation was observed with COMPOUND B dosed at 3, 10, 30 and 150 mg/kg, with 150 mg/kg revealing the most robust duration of $> 95\%$ inhibition by either SC or IV administration. In contrast, vehicle control treatment did not inhibit AP activity. Notably, the lowest dose tested, 3 mg/kg, revealed $> 80\%$ maximum inhibition of AP activity 24 hours after the first dose as expected. The AP inhibition was gradually reduced to an average of 25% after repeat dosing, likely due to ADA. Similar patterns were observed in the 10 and 30 mg/kg groups. Greater than 95% maximum AP inhibition was achieved after 24 hours of the initial doses and gradually the inhibition was reduced to an average of 60% and greater than 80%, respectively, during the 29-day repeat dosing period. In contrast, 20 out of 22 animals dosed with COMPOUND B at 150 mg/kg by IV or SC administration showed greater than 95% circulating AP inhibition throughout the entire dosing period or prior to necropsy. The exceptions to this were 2 IV animals that lost sustained inhibition starting on Day 20, possibly due to ADA. AP activity returned to baseline after a 27 day dosing-free period for animals in the 150 mg/kg SC and IV groups,

except for one animal (65% of baseline) in the 150 mg/kg SC group and one animal (79% of baseline) in the 150 mg/kg IV group.

Example 6 *In Vivo Efficacy - Passive Heymann Nephritis, a Rat Model of Membranous Nephropathy (MN)*

[0288] Passive Heymann Nephritis is a rat model of MN induced by the administration of sheep nephrotoxic serum raised against a preparation of rat proximal tubules (anti-Fx1A). Two injections of anti-Fx1A on consecutive days leads to the formation of subepithelial immune deposits in the glomerular basement membrane (GBM), podocyte foot process effacement, loss of nephrin expression, and pathological changes in the GBM that are reflected by elevated urine protein levels. The PHN model has been demonstrated to be driven by complement activation, as treatment with either cobra venom factor (CVF), a C3 homolog that depletes endogenous complement, or a small molecule factor B inhibitor effectively inhibits complement activation and disease activity in this model.

[0289] The brief time period of the PHN model (5-7 days of disease induction; 2-4 days of drug treatment) reduces concerns that ADA will affect interpretation of results, allowing testing of the human drug candidate COMPOUND B in a relevant model of kidney disease. Based on data from a natural history study showing that C3d is present in PHN kidney on Day 3, COMPOUND B was dosed on this day.

[0290] Two studies evaluated the effects of COMPOUND B on disease progression in PHN. In the first study, IV doses from 1 to 30 mg/kg were tested to narrow the efficacy range of COMPOUND B. In a follow-up study, lower SC doses (0.3, 1, and 3 mg/kg) were evaluated to identify a minimum efficacious dose more accurately. In the latter study equivalent doses of a non-targeted fH fusion protein (Fc-fH₁₋₅) were also tested to examine the role of anti-C3d targeting in COMPOUND B potency.

[0291] Efficacy of IV COMPOUND B doses ranging from 1 to 30 mg/kg were compared to a prophylactic dose of CVF (delivered daily beginning on Day -1 of study). A non-targeted fH₁₋₅ molecule (Fc-fH₁₋₅) was also tested at a dose equimolar to 30 mg/kg COMPOUND B. Disease was induced by anti-Fx1A injection on Study Days 0 and 1. COMPOUND B and Fc-fH₁₋₅ doses were delivered on Day 3 and tissue samples were collected on Day 5. All test agents reduced proteinuria (measured as uPCR) as early as 24 hours postdosing (FIG. 7) and all differences were statistically significant versus PBS control on Day 5 after disease induction. No dose response was observed among the COMPOUND

B doses tested, suggesting that the lowest dose (1 mg/kg) achieved maximal efficacy.

[0292] Quantitation of glomerular C3 active fragments (anti-C3c) revealed a dose-dependent response with COMPOUND B treatment, with the 1 mg/kg dose demonstrating approximately 40% reduction in C3 complement activation (FIG. 8). These data, combined with the reduction of proteinuria at 1 mg/kg, suggest that 100% complement inhibition in tissue is not required for disease-modifying efficacy.

[0293] The non-targeted Fc-fH₁₋₅ construct also inhibited both proteinuria and C3 fragment deposition. This dose of Fc-fH₁₋₅ (17 mg/kg) was equimolar to the highest tested dose of COMPOUND B (30 mg/kg). These findings suggest that complement inhibition in tissue observed with COMPOUND B at the high dose of 30 mg/kg may have been partially mediated by altering fluid-phase/systemic complement activity in combination with tissue targeting effects. Consistent with the tissue targeting hypothesis, evaluation of COMPOUND B in kidney by immunostaining with an antibody specific for human fH supports its mechanism is related to tissue targeting of C3d. While significant anti-fH signal was detected in COMPOUND B -treated rats, no tissue localized hfH was present in rats dosed with the non-targeted Fc-fH₁₋₅ fusion protein (FIG. 9). In addition, systemic complement inhibition was analyzed in serum samples from the study using a zymosan-coated bead assay. Inhibition of serum complement was observed in the Fc-fH₁₋₅ and 30 mg/kg COMPOUND B treated groups. However, no inhibition of systemic complement was detected in samples from animals treated with 1, 3, or 10 mg/kg doses of COMPOUND B (FIG. 10), indicating that at doses $\leq$ 10 mg/kg, kidney target engagement is driven by tissue-delivered drug.

[0294] Taken together, these data indicate that COMPOUND B reduces kidney injury (measured as urine protein) in the PHN model of MN through tissue-targeted complement inhibition.

[0295] To assess lower SC doses of COMPOUND B and to further explore the importance of tissue targeting and potency in the PHN model, a SC COMPOUND B dose response study was performed that included equimolar concentrations of Fc-fH₁₋₅. COMPOUND B at a dose of 0.3 mg/kg showed a trend toward reducing uPCR and 1 mg/kg significantly reduced uPCR. Notably, 0.57 mg/kg Fc-fH₁₋₅ - a molar-equivalent dose to 1 mg/kg COMPOUND B - had no effect on uPCR levels (FIGs. 11A-11C).

[0296] The efficacy difference of targeted vs. untargeted fusion proteins is also reflected in complement activity in tissue collected at end of study (day 7 after anti-Fx1A, day 4 after fusion protein delivery). While statistically significant reduction in complement activity (anti-C3c immunofluorescence) is evident in glomeruli from the 1 or 3 mg/kg COMPOUND

B groups, treatment with equimolar doses of Fc-fH₁₋₅ has no effect (FIG. 12A). At this same time point, anti-fH immunostaining is detected in COMPOUND B-treated rats, but not in those that received Fc-2fH₁₋₅, indicating no fH localization without the presence of the C3d targeting antibody (FIG. 12B).

[0297] To confirm the correlation of reduced proteinuria with ultrastructural changes in the glomeruli, a subset of samples from selected control rats, animals treated with anti-Fx1A alone, and those treated with anti-Fx1A + 3 mg/kg COMPOUND B were further analyzed by transmission electron microscopy (TEM). Transmission electron microscopy from control glomeruli shows a glomerular filtration barrier with normal podocyte foot process morphology and well differentiated slit diaphragms (white arrows, FIG. 13A). In rats treated with anti-Fx1A alone, podocytes are present on the GBM, but show significant effacement (yellow arrows, FIG. 13B). Treatment of rats with COMPOUND B spares podocyte ultrastructure: as while partially effaced foot processes can be seen along the GBM (yellow arrows, FIG. 13C), a substantial number of normal-appearing slit diaphragms can be observed (white arrows, FIG. 13C).

[0298] Together, these data confirm that COMPOUND B can potently inhibit local complement activation, leading to reduced proteinuria and podocyte injury in the PHN model.

Example 7 In Vivo Efficacy - Mouse Models of Lupus Nephritis

[0299] Systemic lupus erythematosus is an antibody-mediated autoimmune disease where hyperactive helper T-cells drive polyclonal B-cell activation and secretion of pathogenic autoantibodies, leading to IC formation against autoantigens. In the case of LN, circulating immune complexes (CIC) deposit in the kidney mesangium and glomerular subendothelial space, leading to glomerular injury.

[0300] Through its role in clearing ICs from the circulation, the complement system provides critical protection against SLE and LN. Yet complement activation, and particularly the AP, drives local disease pathology: C3 complement split products are deposited at sites of immune complex accumulation and circulating complement has been explored as a biomarker for predicting lupus flares.

[0301] The effect of COMPOUND C was explored in 2 rodent genetic models of LN: NZBW/F1 female mice and the MRL-faslpr mouse strain.

NZBW/F1 female mice

[0302] Female NZBW/F1 mice provide a genetic model of spontaneous LN. These mice develop lymphadenopathy, splenomegaly, serum anti-dsDNA autoantibodies, immune complex-mediated glomerulonephritis, proteinuria, and kidney impairment at approximately 5 to 6 months of age, and these symptoms can subsequently progress to kidney failure and death. These mice also demonstrate systemic and kidney complement activation, including deposition of complement fragments in the glomeruli, by 22 weeks of age. Therapeutic inhibition of the AP complement system or genetic deletion of components of the complement pathway reduces disease pathogenesis in this model, indicating that complement plays a functional role in disease progression.

[0303] The effects of COMPOUND C treatment in female NZBW/F1 mice were evaluated in 2 separate studies. In the first study, mice were dosed intravenously from Week 23 to Week 35 with 50 mg/kg COMPOUND C and outcomes were compared to treatment with cyclophosphamide, anti-C5 antibody (BB5.1), or vehicle control. In the second study, mice were dosed with COMPOUND C either by IV or SC from Week 23 to Week 31 at several dosing concentrations and intervals, and outcomes were compared to treatment with BB5.1 or vehicle control. In both studies, dosing began after onset of proteinuria, which was monitored by measuring urinary albumin to creatinine ratio (uACR). Progression of proteinuria was assessed as the change in uACR (Δ uACR) from treatment initiation to the indicated collection time (*i.e.*, if dosing started at Week 22, Δ uACR at Week 30 was the change in uACR between Week 22 and Week 30). Anti-dsDNA autoantibody titer and body weight were monitored at regular intervals throughout the study. Histopathology was also evaluated in kidneys collected at study termination.

[0304] Collectively, the data indicate that COMPOUND C exhibits *in vivo* activity in female NZBW/F1 mice. In the first study, COMPOUND C decreased the Δ uACR (FIG. 14) to an extent similar to cyclophosphamide treatment. It also showed a statistically significant reduction in kidney tissue complement activation as compared to the vehicle control group (FIG. 15). In the second study, COMPOUND C showed a more modest reduction in Δ uACR and kidney tissue complement activation but showed a statistically significant reduction in disease-related kidney histopathology (FIG. 16). Treatment effects of COMPOUND C were greater than those observed with a comparator complement inhibitor, BB5.1, which was dosed more frequently (20 mg/kg 3 times per week from Weeks 23-31 and then daily Weeks 32-35).

[0305] Notably, these studies also demonstrate that chronic dosing with COMPOUND C does not worsen disease activity as demonstrated by improved rather than worsened

histopathology and reduced Δ uACR in COMPOUND C treated mice. Because of the theoretical potential for a C3d binding protein to accumulate at sites of autoantibody complexes and potentially worsen immune complexes, this finding is important, particularly given the high doses of COMPOUND C used in this study (50 mg/kg weekly). These data provide direct evidence that in a model prone to antigen-antibody complex formation and autoantibody generation, treatment with a mouse homolog fusion protein with the same pharmacological mechanism as COMPOUND B does not further exacerbate disease.

MRL-fas_{lpr} strain (MRL) of mice

[0306] The MRL-fas_{lpr} strain (MRL) of mice develops glomerular, tubulointerstitial, and perivascular kidney disease; arthritis; lymphadenopathy; splenomegaly; and circulating autoantibodies, including antinuclear antibodies and anti-dsDNA antibodies.

[0307] Efficacy of COMPOUND C in MRL mice was evaluated in 2 separate studies. In Study One, IV dosing of 50 mg/kg COMPOUND C was initiated in 12-week-old mice and repeated QW until mice were 21 weeks old. A separate group dosed with 1 mg/kg dexamethasone was included as a positive control. COMPOUND C did not show a reduction in disease endpoints whereas dexamethasone inhibited all readouts. In the COMPOUND C treatment group there was an increased trend ($p=0.16$) in the number of animals that died or were sacrificed and a significant increase in kidney histology scores for glomerular crescents and protein casts but not in glomerular diameter, interstitial inflammation and vasculitis. Given that randomization was solely based on body weight rather than by disease progression, which is highly variable, the relationship of these findings to COMPOUND C is unknown. Study Two was subsequently carried out and MRL mice were randomized at Week 16 based on proteinuria, body weight, and skin and lymph node scores (*i.e.*, normalizing indicators of disease progression across groups at the start of the study). COMPOUND C was delivered as two 50 mg/kg IV doses in Week 16 and IV dosing was repeated at 50 mg/kg every other week from Weeks 17 through 22. Cyclophosphamide at a dose of 15 mg/kg was included as a positive control. No statistically significant reduction in disease endpoints (urine protein, lymphadenopathy, skin lesion, kidney histopathology) was observed with COMPOUND C-treatment, whereas cyclophosphamide inhibited all readouts. COMPOUND C treatment showed no worsening of all histopathology parameters evaluated (glomerular diameter, percent crescents, severity of cortical tubular protein casts, interstitial inflammation and vasculitis) and no effect on survival, but also no specific toxicity.

CLAIMS

1. A method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 renal disease 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 (*e.g.*, about 300 mg or 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 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 the preceding claims, wherein the renal disease is Lupus Nephritis (LN).
22. The method of any one of the preceding claims, wherein the renal disease is IgA Nephropathy (IgAN).
23. The method of any one of the preceding claims, wherein the renal disease is C3 Glomerulopathy (C3G).
24. The method of any one of the preceding claims, wherein the renal disease is Primary Membranous Nephropathy (MN).
25. The method of any one of the preceding claims, wherein the renal disease is IgG4-RD.
26. 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)).
27. 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.
28. The method of any one of the preceding claims, wherein the subject:
- (a) has IgAN, and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, a glucocorticoid, a systemic corticosteroid (*e.g.*, prednisone), and/or an antibody-depleting therapy such as anti-CD20 antibody (*e.g.*, Rituximab);
 - (b) has Lupus Nephritis (LN), and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, an immunomodulatory agent such as an antimalarial agent (*e.g.*, hydroxychloroquine), low dose chemotherapeutic agent (*e.g.*, cyclophosphamide), a Calcineurin inhibitor, Azathioprine (Imuran), Mycophenolate (CellCept), Rituximab (Rituxan), and/or Belimumab (Benlysta), voclosporin, and/or systemic immunosuppression (*e.g.*, cyclosporine, Tacrolimus, mycophenolate mofetil) with optional combination with a (high-dose) corticosteroid (*e.g.*, methylprednisolone, prednisone, or equivalent thereof); or,
 - (c) has C3G (such as DDD or C3GN), and is further or concomitantly treated with a standard of care (SOC) therapy comprising a Renin-angiotensin-aldosterone system (RAAS) inhibitor, a blood pressure reducing agent, corticosteroid, eculizumab, immunosuppression, plasma exchange, and/or complement inhibition.
29. The method of any one of the preceding claims, wherein the subject:
- (a) has IgAN, and has proteinuria below 1g/d at/after about 26 weeks of treatment.
30. A method of treating a renal disease characterized by dysregulation of the complement system and/or characterized by C3d deposit in kidney, 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 one or more maintenance doses;

wherein each of the one or more maintenance doses comprises about 300-600 mg (*e.g.*, about 300 mg or about 600 mg) of the fusion protein constructed administered subcutaneously (SC) to the subject, once every week, such that the renal disease in the subject is treated.

31. The method of claim 30, wherein the subject is an adult (*e.g.*, male or female, over 18 years old), has said renal disease (*e.g.*, IgAN, LN, or C3G) as confirmed by biopsy, evidence of C3 fragment deposition in kidney, urine protein > 1 g/24h or uPCR (urine protein: creatinine ratio) > 1 g/g, and/or eGFR ≥ 30 mL/min/1.73 m² (*e.g.*, as calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine equation or CKD-EPI GFR).
32. The method of claim 31, wherein the subject has clinically active LN, requiring/receiving immunosuppression induction treatment, and active focal or diffuse proliferative LN Class III or IV (+/- class V; may co-exhibit class V disease) according to the 2018 Revised International Society of Nephrology/Renal Pathology Society classification.