Complement-Mediated Glomerulopathies

**Designed for Patients**

- Age ≥16 years for patients with C3G
- With a clinical diagnosis of 1 of 4 complement-mediated glomerulopathies confirmed by renal biopsy (and required measurements performed prior to study participation) but who are not in kidney failure.
  - Immunoglobulin A nephropathy (IgAN)
  - Lupus nephropathy (LN)
  - Primary membranous nephropathy (primary MN)
  - C3G glomerulopathy (C3G)
Complement-Mediated Glomerulopathies

The kidney is prone to uncontrolled hyperactivation of the complement cascade. This hyperactivation happens through activation of one or more of the 3 complement pathways: the classical pathway, the alternative pathway, and the lectin pathway. Each of these pathways leads to the activation of the C3 protein, which is the central component in the complement cascade.

Four types of glomerulopathies have been linked to overactivation of C3. They include IgA nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy (primary MN), and C3 glomerulopathy (C3G), which includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). The resulting inflammatory response can damage the filtering apparatus of the kidney: the glomerulus. This damage can ultimately lead to kidney failure, and even to end-stage renal disease.

In patients with these conditions, deposition of C3 fragments in kidney tissue have been independently associated with poor renal outcomes. These findings suggest that blocking or stopping the activation of C3 could play an important role in altering the course of these diseases.
Role of Complement in IgA Nephropathy (IgAN)

IgA nephropathy is the most common form of primary glomerulopathy. It is a chronic kidney disease that usually first appears during adolescence or young adulthood (age 15 to 35 years). It is 2 to 3 times more common in males than females.¹ Approximately 20% to 25% of patients develop end-stage renal disease over the 20-year period after onset.²

IgAN usually appears after a viral infection of the upper respiratory or gastrointestinal tract. The major symptom is the passing of blood in the urine (hematuria).¹,³ The condition is considered to be an autoimmune disease associated with depositions of IgA immune complexes and C3 fragments in the glomeruli.¹
Role of Complement in Lupus Nephritis (LN)

Systemic lupus erythematosus (SLE) is an autoimmune disease that often affects the kidneys. When SLE attacks the kidneys, the problem is called lupus nephritis (LN). About 50% of SLE patients already have evidence of kidney disease by the time their lupus is diagnosed. Ultimately, 75% of SLE patients will end up with kidney damage from their condition.

LN typically leads to several nonspecific changes in kidney function, such as an increase in serum creatinine level and the presence of protein and blood in the urine. These changes are a result of deposits of immune complexes, along with C3 and C1q, in the glomeruli. The immune complexes trigger the activation of the complement system through the classical complement pathway. The resulting complement activation generates two potent chemoattractants (C3a and C5a), which cause chronic inflammation in the kidney contributing directly to glomerular injury.
Membranous nephropathy (MN) is a kidney disease that can be primary (i.e., occurring by itself) or can be secondary to another disease. Membranous nephropathy is the most common cause of nephrotic syndrome in adults. In 75% of cases, the antigen(s) of the immune complexes cannot be identified.²

MN occurs when antibodies slip through the filtering apparatus of the kidney and bind to antigens on podocytes, which are cells that wrap around the capillaries within the glomerulus. These resulting immune complexes lead to activation of the complement system, through the classical pathway, which promotes the formation of membrane attack complexes (MACs) that attack the podocytes but do not usually kill them. The injured podocytes release material that causes thickening of the basement membrane. When the kidney biopsy specimens are examined with a microscope, uniform granular deposits of IgG antibodies and C3 can be seen in the capillary walls.⁴

The predominant IgG subclass can also activate the alternative and even the lectin pathway.⁵,⁶ Between 25% and 40% of patients with MN eventually develop chronic renal failure, usually in association with persistent proteinuria in the nephrotic range.²
Role of Complement in C3 Glomerulopathy (C3G)

The prevalence of C3G is estimated at 2-3 per 1,000,000 people worldwide.⁷ There are two major forms of C3 glomerulopathy (C3G): dense deposit disease (DDD) and C3 glomerulonephritis. Although both cause similar kidney problems, the features of DDD tend to appear earlier than those of C3 glomerulonephritis (C3GN), usually during adolescence.⁸

C3G is associated with changes in genes that regulate the complement system.⁸,⁹ Abundant C3 and other complement proteins are deposited in the glomerular basement membrane (GBM), which causes progressive damage to the glomeruli, which are small blood vessels in the kidney that filter waste products from the blood. C3 glomerulopathy can also result from the presence of autoantibodies (self-directed) called C3 nephritic factors or C3Nefs that disrupt normal regulation of the complement system, resulting in hyperactivation of the alternative complement pathway.⁷,⁸ As a result, the filtering mechanism of the kidney is impaired, which permits proteins and red and white blood cells to pass into the urine-containing space.⁹

The cumulative effects (or impact) on the kidney in cases of with C3 glomerulopathy tend to worsen over time. Nearly half of affected individuals ultimately develop end-stage renal disease (ESRD) within 10 years after their diagnosis.⁸ The signs and symptoms include blood in the urine (hematuria); dark foamy urine due to the presence of protein (proteinuria); cloudy urine due to presence of white blood cells; edema (swelling), initially of the legs, although any part of the body can be affected; high blood pressure; decreased urine output; and decreased alertness.⁷ These patients will require dialysis or kidney transplantation.⁷
Role of Complement in Glomerulopathy

The underlying mechanisms that trigger complement activation vary from disease to disease; but in general, they involve an imbalance between the activators and regulators of the complement system.6,9

Immune complexes (ICs) containing the antibodies IgG and IgM activate the classical complement pathway and trigger neutrophil infiltration and injury. Classical pathway activation also causes co-deposition of C3 and C4 fragments in lupus nephritis.10

Activation of the lectin pathway contributes to glomerular injury in multiple types of glomerular disease, including lupus nephritis and IgA nephropathy. Activation of this complement pathway is associated with increased severity of disease.10

Spontaneous activation of the complement system followed by amplification via the alternative pathway is a result of poor local regulation of complement. This pathway is responsible for C3 glomerulopathy and is also involved in lupus nephritis and IgA nephropathy. C3b generated by activation of the classical or lectin pathways can secondarily activate the alternative pathway, amplifying the extent of complement activation within tissues.10

Activation of the complement system generates multiple different pro-inflammatory mediators.

• C3a and C5a bind to kidney cells and several immune cells, eliciting a wide range of local and systemic responses including direct injury, vasoactive changes, attraction of inflammatory cells, and modulation of immune response to antigens.

• C5b-9 (the membrane attack complex, MAC) forms pores in the outer membrane of cells and in sufficient quantities causes cell lysis.

• C3b is fixed to the surface of cells and results in further activation of complement on the cell surface.10
What is APL-2?

APL-2 is a PEGylated cyclic peptide inhibitor of complement C3. PEGylation helps keep APL-2 in the body longer, reducing dosing frequency. The peptide portion of APL-2 binds to C3, exerting broad inhibition of the complement cascade and helping to restore normal complement activity.11

Why Evaluate APL-2 in Complement-mediated Glomerulopathies?

By targeting C3 at the point of convergence of all complement activation pathways and upstream of C5, APL-2 can inhibit all 3 principal complement activation pathways.12 By targeting C3, APL-2 can inhibit all 3 of the major complement activation pathways. Thus, APL-2 may be more effective in a broad patient population than partial inhibitors of the complement system would be.13

Primary Objective of the Discovery Clinical Trial

The primary objectives of this study are to establish preliminary efficacy and safety of the investigational drug APL-2 in patients with IgAN, LN, primary MN, and C3G.

Discovery Key Endpoints11

Primary Efficacy Endpoints

- All indications: Proteinuria reduction by 50%, calculated by the change in urinary protein to creatinine ratio from baseline to week 48

Secondary Efficacy Endpoints

- Changes of disease-specific biomarkers:
  - Serum C3 levels
  - AH50 and C3a concentrations

- All indications: Complete clinical remission, defined as urine protein:creatinine ratio <200 mg/g from baseline to week 48

- All indications: Stabilization or improvement in eGFR from baseline to week 48

- Complete renal response: Defined as <200mg/g urine protein:creatinine ratio and stabilization or improvement in eGFR from baseline to week 48

Safety Endpoints

- Physical examination; incidence and severity of adverse events (AE)

- Changes from baseline in laboratory parameters

- Changes from baseline in electrocardiography parameters
**Key Inclusion Criteria**

1. Patients ≥18 years of age (≥16 years in cases of C3G)
2. Diagnosis of IgAN, LN, primary MN, or C3G confirmed by renal biopsy and required measurements performed prior to study participation
3. Proteinuria: urine protein:creatinine ratio >750 mg/g
4. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² calculated by CKD-EPI creatinine equation at screening visit and not currently on dialysis
5. Must have stable renal disease (stable proteinuria, eGFR and blood pressure) on stable and optimized treatment (eg, immunosuppressive agents, anti-hypertensives and/or antiproteinurics) for at least 2 months prior to the first dose of APL-2

**Key Exclusion Criteria**

Subjects will be excluded from the study if there is evidence of any of the following criteria at specified screening and/or treatment visits as appropriate.

1. Platelet count <100,000/mm³ at screening visits
2. Absolute neutrophil count <1000 cells/mm³ at screening visits
3. ALT or AST >3.0 x the upper limit of normal at screening visits
4. Diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or positive serology at screening visits. (Previous HBV or HCV diagnosis cleared by treatment is allowed.)

**Dosing of APL-2**

Subcutaneous (SC) once-daily at-home infusions of 360 mg APL-2 for 48 weeks
Discovery Study Locations
These studies are being conducted at over 100 locations throughout the United States

To Recommend a Patient for This Trial, Email
apellisclinicaltrials@cherryhcc.com
or visit
https://discoveryclinicaltrial.com

References


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