C3 Inhibition With APL-2 Targets the Underlying Disease Process of C3G Complement Hyperactivity and Improves Proteinuria

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Introduction

- C3 glomerulopathy (C3G) is a rare kidney disease with a high unmet need; approximately 50% of patients progress to end-stage kidney disease within 5 to 10 years of diagnosis. Although renal transplantation is an option, up to 50% of patients lose their renal allografts owing to disease recurrence.[1-4]
- C3G is associated with sustained activation of the alternative pathway of complement, most commonly due to the presence of nephritic factors (autoantibodies that stabilize the C3 and C5 convertases) or genetic mutations leading to defective complement regulation. Overactivation of complement leads to excessive deposition of C3 and C5 breakdown products in the glomeruli and may contribute to the damage to the renal parenchyma.
- The clinical manifestations of C3G most commonly include low serum C3, proteinuria, hematuria, hypertension, and decreased glomerular filtration rate (GFR).
- There are currently no available therapies for C3G that target the underlying disease process of C3 activation or that prevent disease progression.
- APL-2 (pegcetacoplan) is a 15–amino acid cyclic peptide conjugated to each end of a linear PEG molecule that binds to C3 and inhibits C3 activation. Additionally, APL-2 binds to and prevents the activity of C3b, a breakdown product of C3.
- Based on its mechanism of action, APL-2 has the potential to address the underlying disease process of C3 overactivation in C3G, and to reduce renal damage.

Objective

- The phase 2 DISCOVERY study (APL2-201; NCT03453619) was designed to evaluate the preliminary efficacy and safety of APL-2 in patients with 4 glomerular diseases: C3G, IgA nephropathy, primary membranous nephropathy, or lupus nephritis. Here we present preliminary data from the C3G cohort of this ongoing study.

Methods

Study Design

- An open-label phase 2 study with a 48-week treatment period with APL-2, followed by a long-term extension option.
- APL-2 was administered by subcutaneous infusion at a dose of 360 mg daily, with transition to 1080 mg twice weekly as early as week 24 of the study.
- Key entry criteria for the C3G cohort:
  - A historical renal biopsy that met the diagnostic criteria for C3G[5]
  - At least 16 years of age
  - Proteinuria >750 mg protein/g creatinine based on a 24-hour urine collection
  - Estimated GFR (eGFR) ≥30 mL/min/1.73 m^2 calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[6]

Endpoints

- The primary endpoint was change in proteinuria, as measured by urine protein-to-creatinine ratio (uPCR) from baseline to week 48. Proteinuria was quantitated with 24-hour urine collection prior to day 1 and again at week 48 (total urine protein and uPCR). At additional time points, proteinuria was quantitated as the mean uPCR from up to 3 spot first-morning urine samples collected on consecutive days.
- Other renal parameters assessed included serum albumin and serum creatinine. eGFR was calculated at all time points using the CKD-EPI equation.[6]
- Complement biomarkers were also assessed, including serum C3 and plasma C5b-9. Of note, serum C3 assays measured a combination of free C3 and C3 bound to APL-2.
- Data reported here are for the C3G cohort through study day 84 (12 weeks), with the exception of plasma C5b-9 levels, for which data are available through day 28.

Results

Baseline Characteristics

- Eight patients (5 female and 3 male) who had a mean age of 22.9 years were enrolled (**Table 1**). Two patients (patient 1 and patient 4) were noncompliant with APL-2 administration and their data are not included in the results for key renal parameters and complement levels.

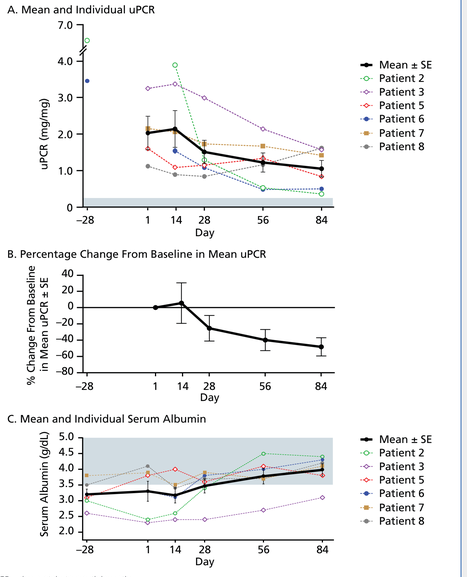
Table 1. Baseline Characteristics

Characteristic	Value (N = 8)
Age, years	
Mean ± SD	22.9 ± 8.9
Median (range)	20.5 (17-44)
Sex	
Female, n (%)	5 (62.5)
Male, n (%)	3 (37.5)
Weight, kg	
Mean ± SD	76.7 ± 15.7
Median (range)	75.7 (49.6-96.3)
Race, n (%)	
White	6 (75)
Black or African	1 (12.5)
Hispanic	1 (12.5)

Key Renal Parameters

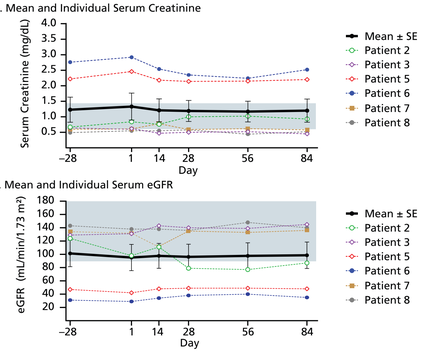
- A downward trend in proteinuria (as measured by mean uPCR) was observed in patients with C3G treated with APL-2. The percentage change from baseline in mean uPCR was 48.23% from baseline to day 84. (**Figure 1A** and **1B**; **Table 2**).
- Mean serum albumin inceased as proteinuria (mean uPCR) decreased. Mean serum albumin was below the lower limit of normal at baseline and increased into the normal range by day 84 (**Figure 1C**; **Table 2**).
- Mean serum creatinine and eGFR levels were stable over 84 days (**Figure 2A** and **2B**; **Table 2**).

Figure 1. Effect of APL-2 on Proteinuria and Serum Albumin



uPCR, urine protein-to-creatinine ratio.
uPCR on days 1 to 84 is the mean of up to 3 first-morning urine samples on 3 consecutive days.
Day –28 uPCR values are from 24-hour urine samples, and are provided for the 2 patients in whom day 1 uPCR results are not available.
Normal ranges, indicated by shading: uPCR (<0.200 mg/mg); serum albumin (3.5-5.5 g/dL).
SE is calculated around the mean for each laboratory parameter.

Figure 2. Serum Creatinine and eGFR Over Time With APL-2 Treatment



Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[6]
Normal ranges, indicated by shading: serum creatinine (0.62-1.44 mg/dL); eGFR (≥90 mL/min/1.73 m^2).
SE is calculated around the mean for each laboratory parameter.

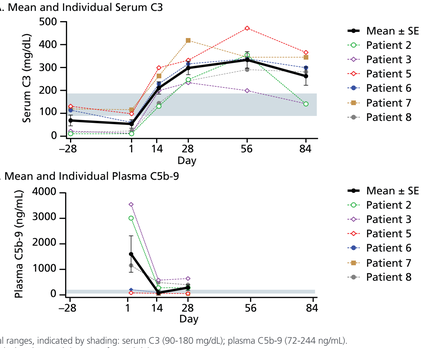
Complement Levels

- All 6 patients had an increase in serum C3 levels following APL-2 administration (**Figure 3A; Table 2**). This level of observed increase is consistent with the known mechanism of action of APL-2. Unpublished data from a target-mediated drug disposition pharmacokinetic model suggests that the binding of APL-2 to C3 substantially decreases the C3 clearance rate, causing an increase in serum C3 level until it reaches a new steady state, without deleterious effects on patients.
- Mean plasma C5b-9 levels decreased in the first 28 days of APL-2 treatment (**Figure 3B; Table 2**), providing evidence that APL-2 is able to modulate the complement hyperactivity of C3G, including at the level of C5.

Tolerability

- A total of 52 treatment-emergent adverse events (TEAEs) were reported in 8 patients (**Table 3**). Fifty percent were judged to be unrelated to study drug.
- All were mild (73.1%) or moderate (26.9%) in severity. There were no study discontinuations due to TEAEs and no serious TEAEs, including no serious TEAEs of infection.

Figure 3. Impact of APL-2 on Complement Protein Levels Over Time in Patients With C3G



Normal ranges, indicated by shading: serum C3 (90-180 mg/dL); plasma C5b-9 (72-244 ng/mL).
SE is calculated around the mean for each laboratory parameter.

Table 3. Overall Incidence of TEAEs

	Patients, n (%) (N = 8)	Events, n (%) (N = 52)
TEAEs	8 (100.0)	52 (100.0)
TEAEs leading to study discontinuation	0	0
Severity*		
Mild	4 (50.0)	38 (73.1)
Moderate	4 (50.0)	14 (26.9)
Severe	0	0
Relatedness*		
Unrelated	0	26 (50.0)
Possibly related	5 (62.5)	22 (42.3)
Probably related	2 (25.0)	3 (5.8)
Related	1 (12.5)	1 (1.9)
Any SAE	0	0

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
All TEAEs reported as of the data cutoff date are presented, including some occurring after day 84.
*Patients were counted only once at worst severity/relatedness.

Table 2. Mean (SE) Values for Key Parameters

Parameter	Day –28	Day 1	Day 14	Day 28	Day 56	Day 84
uPCR, mg/mg	NA	2.03 (0.46)	2.14 (0.50)	1.51 (0.32)	1.22 (0.26)	1.05 (0.23)
Percentage CFB in mean uPCR, with approximate SE	NA	0 (NA)	5.47 (24.87)	–25.38 (15.73)	–39.88 (12.99)	–48.23 (11.22)
Serum albumin, g/dL	3.20 (0.17)	3.30 (0.32)	3.17 (0.24)	3.47 (0.23)	3.78 (0.25)	3.98 (0.20)
Serum creatinine, mg/dL	1.23 (0.41)	1.33 (0.44)	1.21 (0.37)	1.19 (0.34)	1.17 (0.34)	1.20 (0.38)
eGFR, mL/min/1.73 m^2	101 (20)	95 (20)	98 (19)	96 (19)	98 (20)	99 (20)
Serum C3, mg/dL	69 (24)	54 (19)	211 (27)	298 (29)	333 (36)	262 (40)
Plasma C5b-9, ng/mL	NA	1600 (715)	258 (94)	285 (112)	NA	NA

CFB, change from baseline; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI formula;[6] NA, not available; uPCR, urine protein-to-creatinine ratio. Normal range for each of the key disease parameters: first-morning uPCR (<0.200 mg/mg); serum albumin (3.5-5.5 g/dL); serum creatinine (0.62-1.44 mg/dL); serum C3 (90-180 mg/dL); eGFR (≥90 mL/min/1.73 m^2); plasma C5b-9 (72-244 ng/mL).

Conclusions

- These data provide preliminary evidence that APL-2 addresses the underlying disease pathophysiology of C3 activation in C3G, with resulting downstream inhibition of C5. This is supported by the observed increase in serum C3 levels and the decrease in plasma C5b-9 levels.
- During APL-2 treatment, there was a trend towards proteinuria reduction based on decreasing mean uPCR and increasing serum albumin.
- While some patients experienced TEAEs, the TEAEs were not serious and there were no study discontinuations due to TEAEs.
- These preliminary data suggest that APL-2 may be a promising therapy for C3G and support further study of APL-2 in patients with C3G.

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References: 1. Medjeral-Thomas NR, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol*. 2014;9(1):46-53. 2. Zhang Y, et al. Defining the complement biomarker profile of C3 glomerulopathy. *Clin J Am Soc Nephrol*. 2014;9(11):1876-1882. 3. Lu DF, et al. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol*. 2012;27(5):773-781. 4. Servais A, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int*. 2012;82(4):454-464. 5. Pickering MC, et al. C3 glomerulopathy: consensus report. *Kidney Int*. 2013;84(6):1079-1089. 6. Levey AS, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. Acknowledgments: This study was funded by Apellis Pharmaceuticals, Inc. Medical writing support was provided by Rachel Danks of Excel Medical Affairs, Horsham, UK, and funded by Apellis Pharmaceuticals, Inc.

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