C3 inhibition with pegcetacoplan targets the underlying disease process of C3 glomerulopathy.

PO1852

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Introduction

- C3 glomerulopathy (C3G) is a rare renal disease in which sustained activation of the alternative pathway of complement leads to excessive deposition of C3 and C5 breakdown products in the glomeruli[1-3]
  - Clinical manifestations of C3G include low serum C3, proteinuria, hematuria, and renal impairment
  - ~50% of patients with C3G progress to end-stage renal disease within 5 to 10 years of diagnosis[1]
- Pegcetacoplan (APL-2; Apellis Pharmaceuticals, Waltham, MA) is a 15–amino acid cyclic peptide conjugated to each end of a linear polyethylene glycol molecule that binds to C3 and C3b, directly preventing activation of C3, C5, and the alternative pathway
- The phase 2 DISCOVERY study was designed to evaluate the efficacy and safety of pegcetacoplan in patients with glomerular diseases; here, we present the results for the C3G cohort

Objective

- To evaluate the efficacy and safety of pegcetacoplan through week 48 in patients with C3G

Methods

Study design

- This was an open-label, phase 2 study (APL2-201; NCT03453619) with a 48-week treatment period with pegcetacoplan, followed by an optional long-term extension
- Key study inclusion criteria for patients in the C3G cohort
  - Aged ≥16 years
  - C3G diagnosed by historical renal biopsy
  - Proteinuria, defined as a urine protein-to-creatinine ratio (uPCR) >0.750 mg/mg
  - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation[4]
- Pegcetacoplan was administered by subcutaneous infusion at a dose of 360 mg daily, with a transition to 1080 mg twice weekly as early as week 24
- The primary endpoint was change in proteinuria from baseline to week 48, as measured by 24-hour uPCR
  - Proteinuria was evaluated by a 24-hour urine collection prior to day 1 (the first day of study drug administration) and again at week 48
  - Additionally, proteinuria was quantitated as the mean uPCR from 3 first-morning spot urine samples collected on consecutive days and reported at week 46
  - Change from baseline (CFB) in 24-hour uPCR was calculated by determining the CFB for each patient and then by calculating the mean of the individual patient CFB values (mean CFB in 24-hour uPCR)
- Other key laboratory parameters assessed included serum albumin, creatinine, eGFR, serum C3, plasma C5b-9, CH50, and AH50
- 3 patients with interrupted study drug administration or significant self-reported noncompliance were excluded from the efficacy analyses
- Safety outcomes, including treatment emergent adverse events (TEAEs), were monitored throughout the study

Results

Baseline characteristics

- 8 patients with a diagnosis of C3G were enrolled; baseline characteristics are presented in Table 1

Table 1. Baseline characteristics

Characteristic	Patients (N=8)
Sex, n (%)	
Male	3 (37.5)
Female	5 (62.5)
Age, y	
Mean (SD)	22.5 (8.7)
Median (range)	20.5 (17-43)
Weight, kg	
Mean (SD)	76.6 (15.6)
Median (range)	75.7 (49.6-95.6)
Race	
White	6 (75.0)
Black or African American	1 (12.5)
Hispanic or Latino	1 (12.5)
Time since diagnosis, y	
Mean (SD)	8.6 (7.6)

SD, standard deviation.

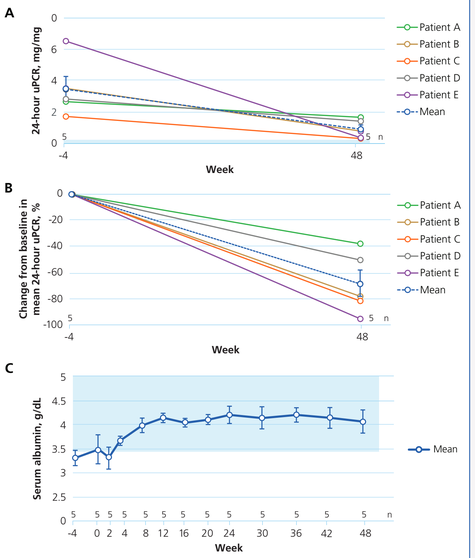
Key renal parameters

- Treatment with pegcetacoplan resulted in proteinuria reduction
  - Mean 24-hour uPCR decreased from 3.48 mg/mg to 0.93 mg/mg from baseline to week 48 (Figure 1A; Table 2)
    - Mean uPCR from triplicate first-morning urine specimens at week 46 was 0.83 mg/mg, concordant with the 24-hour uPCR value at week 48
  - Mean percent CFB in 24-hour uPCR was -67.73% (Figure 1B; Table 2)
  - Following primary data analysis, one additional patient was identified as having a prolonged period of noncompliance; a sensitivity analysis excluding data from this patient demonstrated similar results
- Mean serum albumin was 3.50 g/dL (serum albumin normal range, 3.50-5.50 g/dL) prior to pegcetacoplan administration and increased to >4.0 g/dL at all timepoints from week 8 to week 48 (Figure 1C; Table 2)
- Mean serum creatinine levels and eGFR were stable over 48 weeks (Figure 2; Table 2)

Complement levels

- Levels of key complement biomarkers through week 48 are shown in Table 3
- Mean serum C3 levels increased following administration of pegcetacoplan (Figure 3; Table 3)

Figure 1. (A) Mean and individual 24-hour uPCR, **(B)** mean and individual percentage change from baseline in 24-hour uPCR, and **(C)** mean serum albumin levels



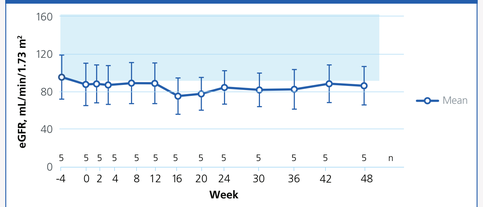
uPCR, urine protein-to-creatinine ratio. Error bars represent standard error. Numbers above each x-axis indicate the number of patients included at each time point. Normal ranges are indicated by shading: uPCR, <0.200 mg/mg; serum albumin, 3.50-5.50 g/dL.

Table 2. Key renal parameters at baseline and week 48

Parameter, mean (SE), [range][a]	Baseline[b] (N=5)	Week 48 (N=5)
24-hour uPCR, mg/mg	3.48 (0.82) [1.74, 6.55]	0.93 (0.27) [0.34, 1.69]
Percentage CFB in 24-hour uPCR	NA	-67.73 (10.50) [-94.12 to -37.31]
Serum albumin, g/dL	3.50 (0.30) [2.40, 4.10]	4.08 (0.24) [3.30, 4.60]
Serum creatinine, mg/dL	1.48 (0.50) [0.55, 2.92]	1.32 (0.38) [0.50, 2.49]
eGFR,[c] mL/min/1.73 m^2	88.00 (22.61) [29.00, 138.00]	86.60 (20.44) [41.00, 142.00]

CFB, change from baseline; eGFR, estimated glomerular filtration rate; SE, standard error; uPCR, urine protein-to-creatinine ratio.
[a]Normal ranges for each of the key disease parameters: first-morning uPCR, <0.200 mg/mg; serum albumin, 3.50-5.50 g/dL; serum creatinine, 0.62-1.44 mg/dL; eGFR, ≥90 mL/min/1.73 m^2. [b]Baseline was the most recent result prior to the first dose. [c]eGFR was calculated using the CKD-EPI creatinine equation.[4]

Figure 2. Mean eGFR



eGFR, estimated glomerular filtration rate. Error bars represent standard error. Numbers above x-axis indicate numbers of patients included at each time point. Normal ranges are indicated by shading: eGFR, ≥90 mL/min/1.73 m^2.

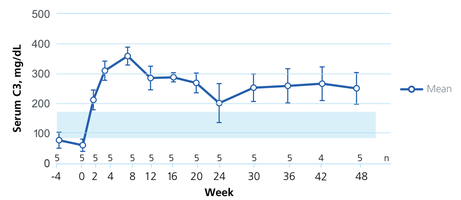
- In contrast, mean serum C3 levels in the 3 patients excluded from efficacy analyses were fluctuating and highly variable, as expected in the absence of consistent study drug administration
- Mean plasma C5b-9 levels decreased from 1113.50 ng/mL at baseline to 385.25 ng/mL at week 48 (Table 3)

Table 3. Complement levels through week 48

Biomarker, mean (SD), [range][a]	Baseline[b]	Week 48
Serum C3, mg/mL	61.60 (20.42) [11.00, 116.00]	252.00 (52.82) [82.00, 407.00]
Serum C4, mg/dL	19.20 (4.22) [5.00, 31.00]	17.75 (2.17) [14.00, 22.00]
CH50, U/mL	183.40 (53.17) [23.00, 298.00]	214.00 (12.52) [190.00, 248.00]
AH50, U/mL	62.00 (25.59) [0.00, 113.00]	60.75 (22.40) [0.00, 96.00]
C5b-9, ng/mL	1113.50 (675.85) [79.00, 3009.00]	385.25 (328.89) [22.00, 1371.00]

SD, standard deviation.
[a]Normal ranges for each of the biomarkers: serum C3, 0.94-1.66 mg/mL; CH50, 176-382 U/mL; AH50, 77-159 U/mL; C5b-9, 72-244 ng/mL.
[b]Baseline was the most recent result prior to the first dose.

Figure 3. Mean serum C3



Error bars represent standard error. Numbers above x-axis indicate numbers of patients included at each time point. Normal ranges are indicated by shading: serum C3, 90-180 mg/dL.

Safety and tolerability

- There were no discontinuations due to TEAEs and no serious or severe adverse events (Table 4)
- The majority of TEAEs were considered unrelated to study drug

Table 4. Incidence of TEAEs

	Patients (N=8)
TEAEs	8 (100)
Severity[a]	
Mild	4 (50.0)
Moderate	4 (50.0)
TEAEs occurring in ≥2 patients	
Vomiting	4 (50.0)
Nausea	3 (37.5)
Headache	3 (37.5)
Sinusitis	3 (37.5)
Diarrhea	2 (25.0)
Fatigue	2 (25.0)
Injection site induration	2 (25.0)
Injection site pruritus	2 (25.0)
Injection site rash	2 (25.0)
Pyrexia	2 (25.0)
Upper respiratory tract infection	2 (25.0)
Migraine	2 (25.0)
Dyspnea	2 (25.0)

TEAE, treatment-emergent adverse event.
[a]Patients were counted only once at worst severity/relatedness to study drug.

Conclusions

- These data provide evidence that pegcetacoplan targets the underlying disease pathophysiology of C3 activation in C3G, resulting in increased serum C3 levels
- Pegcetacoplan treatment resulted in proteinuria reduction, with decreasing mean uPCR, increasing serum albumin levels, and stable renal function
- Pegcetacoplan was generally well tolerated, with no serious TEAEs or discontinuations due to TEAEs
- These data suggest that pegcetacoplan may be a promising therapy for C3G and support further study of pegcetacoplan in patients with C3G

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