Real-World Effectiveness and Safety of Pegcetacoplan in Patients with C3G or Primary IC-MPGN: PRISM-C3, a Multi-Country Phase 4 Study

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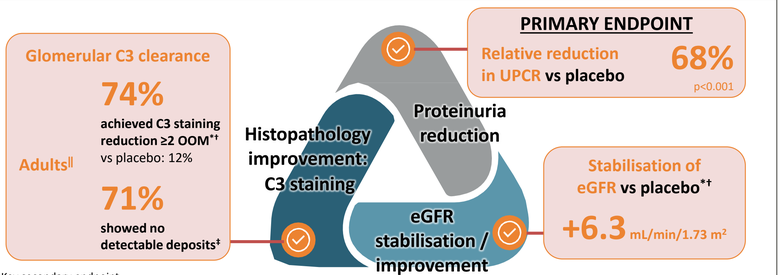
CONCLUSIONS

- The findings of this real-world study will support the long-term evaluation of the benefit–risk profile of pegcetacoplan in a broad population of patients with C3G or primary (idiopathic) IC-MPGN, and may help to optimize evidence-based clinical practice
- Assessing disease-specific biomarkers is a novel and valuable addition to evaluating the real-world effectiveness of pegcetacoplan

INTRODUCTION

- C3G and primary IC-MPGN are two chronic, heterogeneous, rare kidney diseases, driven by C3 dysregulation resulting in progressive kidney damage and a high risk of kidney failure[1–4]
- Pegcetacoplan, a targeted C3/C3b inhibitor, has demonstrated clinical efficacy (proteinuria reduction, estimated glomerular filtration rate stabilization, and clearance of glomerular C3 deposits) and a favorable safety profile in patients with C3G or primary IC-MPGN, in controlled Phase 2 and 3 clinical trials **(Figure 1)**[1,5,6]
- Pegcetacoplan is approved in the EU and the US for the treatment of adult and adolescent patients (aged ≥12 years) with C3G or primary IC-MPGN[7,8]
- To complement clinical trial data, real-world evidence for pegcetacoplan is needed to support clinical decision making[9]

Figure 1. Efficacy of pegcetacoplan in patients with C3G and primary IC-MPGN at 26 weeks[5]



* Key secondary endpoint.
† A fixed sequence testing strategy was used for key secondary endpoints. Key secondary histologic activity score endpoint was not met at week 26; therefore subsequent endpoints including C3 staining reduction and eGFR change were not formally tested and should be interpreted descriptively.
‡ Post-hoc analysis, thus not controlled for type I error.
‖ Biopsy was not mandated in adolescents (aged 12-17 years).

OBJECTIVES

- Here, we describe the design and methodology of PRISM-C3 – a real-world study to evaluate the effectiveness and safety of pegcetacoplan in patients with C3G or primary IC-MPGN,[10] including an assessment of disease-specific biomarkers to better understand disease progression, treatment response, and relapse risk

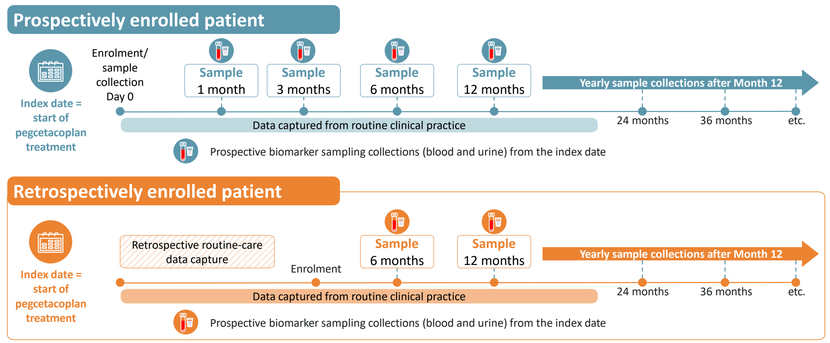
Abbreviations: C3, complement 3 protein; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; EU, European Union; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; OOM, orders of magnitude; PRO, patient-reported outcome; UPCR, urine protein-to-creatinine ratio; UK, United Kingdom; US, United States.

METHODS

Study overview

- PRISM-C3 is an international (ex-US), multicenter, Phase 4 study that will follow patients for ≥2 years **(Figure 2)**
- With an expected 3.5-year recruitment period, the planned prospective study duration for each patient will range from 2 years (for the last patient) to approximately 5.5 years (for the first patient)

Figure 2. Study design



Study population

- Patients who have initiated or plan to initiate pegcetacoplan treatment for C3G or primary IC-MPGN (native or post-transplantation recurrent disease) outside of interventional clinical studies are being recruited; enrolment commenced in August 2026
- Patients are excluded if they have received an investigational treatment for C3G or primary IC-MPGN at the time of pegcetacoplan initiation, or if they have started treatment with pegcetacoplan in an interventional study

Data collection and study endpoints

- Observational part: patient demographics, disease characteristics, medical and treatment (prior or concurrent C3G/primary IC-MPGN related) history, pegcetacoplan treatment details (including start/stop date, dosing regimen, reason for use), clinical outcomes, safety, PROs, and healthcare resource utilization related to C3G/primary IC-MPGN will be collected from medical records both retrospectively and prospectively (through routine clinic visits)
- Low interventional aspect: blood and urine biomarker data will be collected prospectively at scheduled time points relating to the initiation or discontinuation of pegcetacoplan treatment **(Figure 2)** and measured in a central laboratory. Biomarkers to be assessed include disease etiology markers, complement pathway biomarkers, and inflammatory and kidney injury biomarkers. Study endpoints and corresponding data collection measures are outlined in **Table 1**

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Table 1. Summary of study endpoints and data collection to inform study endpoints

Data collection to inform study endpoints	
Category	**Measures**
Renal function	UPCR; serum creatinine (and calculation of eGFR); urinalysis; serum albumin, lipids and lipoproteins; kidney biopsy (including Ig and C3c staining)
Biomarkers	Disease etiology; complement biomarkers; inflammatory and kidney injury
PROs	Peds FACIT-Fatigue and FACIT-Fatigue; TSQM-9; WPAI
Healthcare resource utilization	Number of inpatient/outpatient hospital visits; number of ICU admissions; number of emergency visits; length of hospital stay; length of ICU stay
Safety	AESI (serious/severe infections, malignancies, AKI); SAEs
Study endpoints	
Primary endpoint	
	• Achieving a UPCR of <1 g/g at 6 months after starting pegcetacoplan treatment, summarized at a population level (percentage of patients)
Secondary endpoints	
	• Evaluation of renal function and disease characteristics, including disease progression prior to and during pegcetacoplan treatment • Changes in biomarkers prior to and during pegcetacoplan treatment • PROs during pegcetacoplan treatment • Healthcare resource utilization prior to and during pegcetacoplan treatment
Safety endpoints	
	• Incidence of AESI and SAEs from pegcetacoplan initiation until 8 weeks after the end of treatment

AESI, adverse events of special interest; AKI, acute kidney injury; C3, complement 3; eGFR, estimated glomerular filtration rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; ICU, intensive care unit; Ig, immunoglobulin; Peds FACIT-Fatigue, pediatric FACIT-Fatigue; PRO, patient-reported outcome; SAE, serious adverse event; TSQM-9, Treatment Satisfaction Questionnaire for Medication (9-item version); UPCR, urine protein-to-creatinine ratio; WPAI, Work Productivity and Activity Impairment Questionnaire.

Sample size and data analysis

- The study aims to recruit approximately 150 patients with C3G or primary IC-MPGN, including ≥30 patients with post-transplantation recurrent disease
- Study endpoints will be analyzed for the overall population and for the following subgroups:
  - renal transplant status at the start of pegcetacoplan treatment: disease in native kidney or post-transplantation recurrence
  - age at the start of pegcetacoplan treatment: <18 years or ≥18 years
  - concomitant immunosuppressant use at the start of pegcetacoplan treatment: yes or no
  - primary diagnosis: C3G or primary IC-MPGN
  - UPCR at the start of pegcetacoplan treatment: <3 g/g or ≥3 g/g (nephrotic range)

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