11 December 2025
EMADOC-1700519818-2607887
Medicinal Products for Human Use (CHMP)

Assessment report

Aspaveli

International non-proprietary name:

Procedure No. EMEA/H/C/005553/EMAVR0000248937

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

Table of contents

List of abbreviations

ADA	Antidrug antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AH_{50}	50% alternative hemolytic complement pathway activity
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the drug concentration-time curve
AUC_{last}	Area under the plasma-concentration-time curve from time 0 to the time of last quantifiable concentration
$AUC_{0-\infty}$	Area under the concentration-time curve from zero to infinity
AUC_{tau}	Area under the concentration-time curve over the dosing interval
CFB	Change from baseline
CH_{50}	Classical complement pathway hemolytic activity assay
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum concentration
CSF	Cerebrospinal fluid
CSR	Clinical study report
C3G	C3 glomerulopathy
DDD	Dense deposit disease
EBE	empirical Bayesian estimates
eGFR	Estimated glomerular filtration rate
EAIR	Exposure adjusted incidence rate
EMA	European Medicines Agency
EQ-VAS	EuroQol Visual Analogue Score
FDA	Food and Drug Administration (USA)
FMU	First-morning urine
GLOSEN	Spanish Group for the Study of Glomerular Diseases

GLP	Good Laboratory Practice
HLT	High-level term
HR	Hazard ratio
IC50	Half-maximum inhibitory concentration
ICE(s)	Intercurrent Event(s)
ICGN	Immune-complex glomerulonephritis
ICH	International Council for Harmonisation
IC-MPGN	Immune complex Membranoproliferative Glomerulonephritis
Ig	Immunoglobulin
I_{MAX}	maximum proportional treatment effect
IV	Intravenous
KA	Transit absorption rate constant
kDa	Kilodaltons
KDIGO	Kidney Disease Improving Global Outcomes
KEO	Biophase compartment distribution rate constant
kg	Kilogram
LLN	Lower limit of normal
LTE	Long-term extension
LS	Least squares
MAH	Marketing authorization holder
mg	Milligram
mL	Milliliter
MMF	Mycophenolate mofetil
MTT	Mean transit time
Nab(s)	Neutralising antibodie(s)
OECD	Organisation for Economic Co-operation and Development
OLP	Open-label period
PA	Protocol assistance
PD	Pharmacodynamic(s)
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40kDa nominal molecular weight)
PK	Pharmacokinetic(s)
PND	Post Natal Day

PNH	Paroxysmal nocturnal hemoglobinuria
PopPK	Population pharmacokinetic(s)
PopPK/PD	Population pharmacokinetic(s) and pharmacodynamic(s)
PRO	Patient reported outcomes
PT	Preferred term
qd	Once daily
RAASi	Renin-angiotensin-aldosterone-system inhibitors
RaDaR	UK National Registry of Rare Kidney Diseases
RAUC	PND X AUClast/PND28 AUClast, where X=41, 49 or 105
RCP	Randomised controlled period
RP-HPLC	Reverse Phase High-Performance Liquid Chromatography
SAE	Serious adverse event
SC	Subcutaneous
sC5b-9	Soluble C5b-9
SCX-HPLC	Strong Cation Exchange High-Performance Liquid Chromatography
SD	Standard deviation
SE	Standard error
SE-HPLC	Size Exclusion High-Performance Liquid Chromatography
SoC	Standard-of-care
SOC	System organ class
$t_{½}$	Half-life
TK	Toxicokinetics
t_{max}	Time to reach maximum concentration
TTR	Transthyretin
µg	Microgram
uPCR	Urine protein-to-creatinine ratio
VC	Volume of central compartment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 31 January 2025 an application for a variation. The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adults and adolescents aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulopathy (IC-MPGN) for Aspaveli, based on interim results from study APL2-C3G-310; this is a randomised, placebo-controlled, double-blinded, multicenter study to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN and results from Phase 2 study APL2-C3G-204, an open-label, randomised, controlled study to evaluate the efficacy and safety of pegcetacoplan in posttransplant recurrence of C3G or primary IC-MPGN. As a consequence, sections 4.1, 4.2, 4.8, 4.9, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Aspaveli, was designated as an orphan medicinal product EU/3/17/1873 on 22/05/2017 in the following indication: monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. Aspaveli was also designated as an orphan medicinal product EU/3/22/2716 on 10/11/2022 in the following indication: treatment of C3 glomerulopathy with or without immune complexes.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Aspaveli as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:
https://www.ema.europa.eu/en/medicines/human/EPAR/Aspaveli

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0348/2024 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0348/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice/Protocol assistance

The MAH received Scientific Advice from the CHMP in 2019 on the design of the pivotal Phase 3 study for the treatment C3G (EMEA/H/SA/3633/3/2019/PA/SME/II) and for the treatment of IC-MPGN (EMEA/H/SA/3633/4/2019/SME/II), and a follow-up advice in 2023 (EMA/SA/0000145374) also on the design of the pivotal Phase 3 study. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Selma Arapovic Dzakula

Timetable	Actual dates
Submission date	31 January 2025
Start of procedure:	22 February 2025
CHMP Rapporteur's preliminary assessment report circulated on:	24 April 2025
PRAC Rapporteur's preliminary assessment report circulated on:	25 April 2025
CHMP CoRapporteur's preliminary assessment report circulated on:	30 April 2025
PRAC RMP advice and assessment overview adopted by PRAC	8 May 2025
Joint Rapporteur's updated assessment report circulated on:	16 May 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2025
MAH's responses submitted to the CHMP on:	16 July 2025
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 August 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 August 2025
PRAC RMP advice and assessment overview adopted by PRAC	4 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	12 September 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 September 2025
MAH's responses submitted to the CHMP on:	8 October 2025

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 November 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	8 December 2025
CHMP opinion:	11 December 2025
The CHMP adopted a report on similarity of Aspaveli with Fabhalta on date (Appendix 1)	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Complement 3 Glomerulopathy (C3G) is primarily caused by dysregulation of the alternative complement pathway, often due to genetic mutations or acquired factors such as autoantibodies (e.g., C3 nephritic factor), leading to dominant deposition of complement C3 fragments in the glomeruli with minimal or no immunoglobulin deposition. In contrast, the Immune Complex Membranoproliferative Glomerulopathy (IC-MPGN) is typically driven by immune complex formation that activates the classical and/or lectin pathways, resulting in deposition of both immunoglobulins and complement components.

Clinically, both conditions can present with proteinuria, haematuria, reduced kidney function, and progression to end-stage renal disease. Diagnosis relies on kidney biopsy with immunofluorescence and electron microscopy to distinguish between C3-dominant and immune complex–dominant patterns.

The claimed indication, in addition to the approved one, is (*in italics*):

Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Aspaveli is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

Epidemiology

Based on the latest data analysis, the estimated global annual incidence of C3G is between 1 and 3 cases per million people. The risk of progression to kidney failure is high, with up to 30% to 35% of patients with C3G and idiopathic IC-MPGN developing kidney failure within 10 years of diagnosis.

Biologic features

The current classification is based on the pathological composition of glomerular deposits by immunofluorescence (IF) of kidney biopsies classifying the MPGN subtypes into IC-MPGN and C3G.

C3G is further divided into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). C3G is defined by C3 IF staining of ≥2 orders of intensity stronger than any other immune reactant, with little or no Ig deposits, whereas IC-MPGN is characterised by glomerular deposits of immune complexes containing both Ig and complement proteins.

Management

The standard treatment of C3G and IC-MPGN patients is primarily supportive and non-specific, aiming to delay progression to end-stage renal disease. It includes use of: Renin–angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blocker [ARBs]) to reduce proteinuria and preserve kidney function; Sodium-Glucose Cotransporter 2 inhibitors (SGLT2 inhibitors) due to their renoprotective effects in proteinuric kidney disease, though evidence in C3G/IC-MPGN is indirect; Immunosuppressive therapy (corticosteroids, mycophenolate mofetil, cyclophosphamide), particularly in IC-MPGN with clear immune complex involvement.

Furthermore, anti-complement therapies (eculizumab, ravulizumab) are used off-label. Patient care may also include management of complications such as blood pressure control, treatment of dyslipidaemia, and avoidance of nephrotoxic agents.

Of note, at the time of the submission of this application there was no authorised treatment for the targeted indication, but during the evaluation, the medicinal product Fabhalta was approved by the CHMP in the C3G condition.

2.1.2. About the product

Pegcetacoplan is polyethylene glycol (PEG)ylated peptide that binds to complement protein C3 and its activation fragment C3b, thereby regulating cleavage of C3 and the generation of downstream effectors of complement activation. It is authorised as subcutaneous injection in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. The newly proposed dose and regimen in adults are similar to the recommended ones in PNH, and is also intended to reach similar exposures in adolescents as in adults.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

As stated in section 1, several scientific advices were given. In 2019, the CHMP stated that using proteinuria reduction alone, even though measured by triplicate first-morning uPCR, would be insufficient. It was recommended to evaluate clinically meaningful kidney-function endpoints (GFR decline or slope, ESRD events) and to stratify patients by key prognostic factors (baseline proteinuria, eGFR, age, disease subtype). In response, the Phase 3 protocol added a composite secondary endpoint (≥50 % uPCR reduction plus ≤15 % eGFR loss) and collection of histologic data on C3c staining, but it retained uPCR as a sole primary endpoint and did not stratify randomisation by proteinuria level, eGFR category or C3G versus IC-MPGN subtype. The main takeaway was a strong recommendation to blind the pivotal study, which was subsequently done.

In 2023, the CHMP reiterated that a 26-week controlled period was too short to establish a durable benefit, especially in terms of kidney survival, and that retrospective eGFR comparisons were unreliable. It was emphasised that the open-label extension could not substitute for a longer randomised follow-up. The final study design remained a 26-week randomised period followed by an uncontrolled extension, but was justified during the procedure by the MAH (see discussion on

clinical efficacy). The proposed handling of intercurrent events and the lack of detail around estimands was not supported. Although the study employed MMRM and sensitivity analyses, it did not revise its hypothetical strategy for rescue medication or dialysis initiation, nor did it prespecify treatment-policy estimands for all intercurrent events.

2.1.4. General comments on compliance with GLP, GCP

GLP: The dose range-finding juvenile rat study was conducted in accordance with applicable guidelines for good laboratory practice (GLP), from the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Organisation for Economic Co-operation and Development (OECD). All assays were conducted using qualified methods with sufficient sensitivity to meet the respective study objectives. Transthyretin (TTR) analysis in Cerebrospinal Fluid (CSF) was conducted for exploratory purposes only. Analyses for TTR and CSF total protein count, were performed using non-validated assays. Analyses were performed as per Test Site Standard Operating Procedures (SOPs).

During assessment, no issue of GCP non-compliance arose.

2.2. Non-clinical aspects

2.2.1. Introduction

Pharmacology, safety pharmacology, ADME, and toxicology studies with toxicokinetics (TK) conducted on pegcetacoplan were previously performed to support pegcetacoplan as a subcutaneous product for the chronic treatment of PNH. For treatment of C3G or IC-MPGN in children, juvenile toxicity studies were required. A dose-range finding study was completed to determine the tolerability of pegcetacoplan when given *via* SC or IV injection to juvenile Crl:WI(Han) Wistar Han rats, and to provide information for the selection of dose levels to be used in a subsequent pivotal juvenile toxicity study. Pegcetacoplan was given on postnatal days (PND) 21 through 105, and the study was designed to evaluate whether pegcetacoplan would elicit polyethylene glycol (PEG)-related microscopic vacuolation in juvenile rats on PND 50 (main study subset 1) and PND 106 (main study subset 2).

2.2.2. Toxicology

Reproduction toxicity

Studies in which the juvenile animals are dosed and/or further evaluated

Study title: 23CATX001 was a dose-range finding toxicity study of pegcetacoplan (APL-2) by subcutaneous and intravenous (bolus) injection in juvenile rats.

Summary: See Table 1.

Table 1. Summary of DRF juvenile toxicity study with pegcetacoplan

• Study details	**No/Sex /Group**	**Dose** (mg/kg/day)	**Major findings**
23CATX001 (DRF JAS) • Species: Rat, Wistar (PND21) • Duration: ✓ Subset 1: 4 weeks from PND 21-48 (6/sex/group) ✓ Subset 2: 12 weeks from PND 21-105 (6/sex/group) • Route: subcutaneous or intravenous (bolus) • GLP: yes	Main: 12 TK: 12	SC: 0, 28, 140 IV: 10, 30, 100	• Brain, choroid plexus: cytoplasm-vacuolated histiocytes (PND50&106; SC/IV) and epithelial cells (PND106; SC/IV) • Kidney: tubular vacuolation and degeneration/regeneration • Heart, spleen, liver, SC administration site: macrophage vacuolation
Expansion on salient findings • No treatment-related changes on: survival, clinical observations, body weights, food consumption, macroscopic pathology, brain weights, CSF evaluations (PND50: TTR levels; PND106: nucleated cell and RBC counts, or total protein) • Brain: minimal infiltration of chroroid plexus with vacuolated histiocytes (PND50: 140 mg/kg SC, 100 mg/kg IV; PND106: ≥28 mg/kg SC, ≥10 mg/kg IV), minimal to mild cytoplasmic vacuolation of choroid plexus epithelial cells (PND106: 140 mg/kg SC, ≥30 mg/kg IV) • Heart: minimal macrophage vacuolation (PND50: 140 mg/kg SC, 100 mg/kg IV; PND106: 140 mg/kg SC, ≥10 mg/kg IV) • Kidney: minimal tubular vacuolation (PND50:140 mg/kg SC, ≥30 mg/kg; IV: PND106: ≥28 mg/kg SC, ≥10 mg/kg IV), minimal tubular degeneration/regeneration (PND 50&106: 100 mg/kg IV) • Spleen: minimal to moderate macrophage vacuolation (PND50: 140 mg/kg SC, 100 mg/kg IV; PND106: ≥ 28 mg/kg SC, ≥10 mg/kg IV) • Liver: minimal to mild sinusoid macrophage vacuolation (PND106: 140 mg/kg SC, 100 mg/kg IV) • Administration site: minimal to moderate macrophage vacuolation (PND50&106: ≥28 mg/kg SC)			

Design: Pegcetacoplan was administered *via* SC injection at doses of 0, 28 or 140 mg/kg/day or IV injection at doses of 10, 30, or 100 mg/kg/day to 6 rats/sex/group from PND 21 through PND 48 (Subset 1) and 6 rats/sex/group from PND 21 through 105 (Subset 2). All rats assigned to the main study underwent necropsy on PND 50 (Subset 1) or 106 (Subset 2). TK were assessed in satellite groups (12/sex/group, Subset 3), and these rats were euthanised on PND 21, 28, or 106.

Parameters evaluated: mortality, clinical observations, body weights, body weight changes, food consumption, macroscopic and limited microscopic observations. Brain weights were recorded. CSF was collected from all Subset 1 and 2 main study animals *via* the cisterna magna at scheduled euthanasia, and TTR measurements (Subset 1 animals) and CSF interpretation, and measurements of CSF nucleated cells and CSF total protein (Subset 2 animals), were conducted. Plasma samples were collected from rats assigned to Subset 3 at PND 21, 28, 41, 49 and 105, to determine the TK of pegcetacoplan. All PND 50 CSF samples noted as "clear" from the SC groups at 0 and 140 mg/kg/day and IV groups at 30 and 100 mg/kg/day were analysed for TTR.

Results: There were no pegcetacoplan-related deaths, clinical observations, macroscopic findings or pegcetacoplan-related effects on mean body weights, mean body weight gains, mean food consumption, or brain weights in the main study animals at any dose level. Pegcetacoplan, administered either IV or SC, evoked microscopic changes in the brain (choroid plexus), heart, spleen, and kidney at both PND 50 and PND 106, and in liver at PND 106. SC injections also caused microscopic changes at the administration site.

Following IV administration, changes at PND 50, consisted of minimal to mild infiltrates of macro- or micro-vacuolated histiocytes (macrophages) or resident macrophages in the choroid plexus and the interstitium of the heart at 100 mg/kg/day, and red pulp of the spleen, and of minimal vacuolation of renal tubule epithelium with minimal degeneration/regeneration of tubules at 100 mg/kg/day. At PND 106, these infiltrates were seen in the choroid plexus ≥ 10 mg/kg/day, interstitium of the heart, and red pulp of the spleen ≥10 mg/kg/day. The infiltrates were also

observed in the liver at 100 mg/kg/day and in a renal lymph node. In addition, there was minimal to mild vacuolation of the choroid plexus epithelium and minimal vacuolation of renal tubule epithelium with tubular degeneration/regeneration.

Following SC administration, changes at PND 50 consisted of minimal to moderate infiltrates of macro- or micro-vacuolated histiocytes or resident macrophages the choroid plexus at 140 mg/kg/day, interstitium of the heart at 140 mg/kg/day (females only), the red pulp of the spleen at 140 mg/kg/day, and subcutaneous administration site ≥ 28 mg/kg/day. Also seen was minimal vacuolation of renal tubule epithelium in one male. At PND 106, these infiltrates were seen in the choroid plexus ≥ 28 mg/kg/day, interstitium of the heart at 140 mg/kg/day, red pulp of the spleen ≥ 28 mg/kg/day, sinusoids of the liver at 140 mg/kg/day, and SC administration site ≥ 28 mg/kg/day. In addition, there was minimal to mild vacuolation of the epithelium in the choroid plexus epithelium at 140 mg/kg/day and minimal vacuolation of the renal tubule epithelium at ≥ 28 mg/kg/day with tubular degeneration/regeneration in one female. To evaluate the effect of PEG vacuolation on the function of choroid plexus epithelial cells, in accordance with the EMA guideline on the use of PEGylated products in the paediatric population, CSF evaluations were performed, which showed no pegcetacoplan-related findings, *i.e.* CSF nucleated cell and red blood cell counts or CSF total protein changes, in males or females at any dose level on PND 106. TTR was analysed in a total of 26 CSF samples from PND 50, noted as "clear", and data showed no pattern for TTR modulation in rat CSF following pegcetacoplan treatment, and no association of CSF TTR with choroid plexus vacuolation was noted.

Pegcetacoplan was observed in all treated juvenile rats after daily dose of SC or IV injection. The composite AUC_{last} values increased in a dose-proportional manner in both female and male juvenile rats. There were no notable gender differences in exposures. Comparison of the composite AUC_{last} values following multiple dose administration was generally within 2-fold across the study, suggesting no meaningful increase in exposure. One exception to this was that PND 105 exposure values following IV injection in male rats, were close to 2- fold higher relative to PND 28 values.

2.2.3. Ecotoxicity/environmental risk assessment

The MAH provided an updated ERA report (17 Jan 2025) and reflected the cumulative environmental exposures resulting from use of pegcetacoplan for both, PNH and C3G/IC-MPGN indications (see Table 2).

Table 2. Summary of main study results

Substance (INN/Invented Name):	Established name: Pegcetacoplan Other name : [^{3}H]APL-2 Aspaveli		
CAS-number (if available):	CAS No. 2019171-69-6		
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	< -2	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, *refined* *Since pegcetacoplan is to be used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and*	0.028	µg/L	≥ 0.01 threshold: Y

complement 3 glomerulopathy (C3G) and immune-complex-mediated membranoproliferative glomerulonephritis (C3G/IC-MPGN), the calculations of Phase I PECSW are conducted for each indication separately and then summed for a total Phase I PEC_{SW}			

Phase II - Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = *Loam (CA-Hanford)* Soil 2 = *Loam (Iowa-Fayette)* Soil 3 = *Sandy loam (RMN-SL-PF)* Sludge 1 = *New Bedford* Sludge 2 = *Wareham*	OECD 106	 $K_{oc,\ soil\ 1}$ = 89,605 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 23,645 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 26,279 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 3.00 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 4.29 L/kg_{oc}	List all values
Ready Biodegradability Test	OECD 301B	Pegcetacoplan cannot be classified as readily biodegradable	

Phase IIa effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	75,000	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	8,800	µg/L	*Biological parameters: Survival; Reproduction (Total Living Offspring per Surviving Female); Total Body Length* *Reproduction was evaluated using the following endpoints: Total Living Offspring; Total Living Offspring/Surviving Female; Total Living Offspring/Female*
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	10,000	µg/L	Biological parameters: Hatching Success; Live, Normal Larve at Hatch; Survival; Total Body Length; Wet Weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1,000,000	µg/L	respiration

Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	910	mg/kg_{dw}	LOEC; NOEC; EC_{50}

2.2.4. Discussion on non-clinical aspects

A programme of juvenile animal studies (JAS) in rats was initiated to support development in patients from 2 years of age for the treatment of C3G or IC-MPGN. The underlying concern was for any effects on the developing CNS related to a potential for PEG-related vacuolation of choroid plexus epithelial cells in the brain, considering also the high doses of chronically administered PEG. In the context of the present application, the report of the dose range-finding (DRF) study was submitted. The LC-MS/MS and HPLC methods for DRF JAS study have been developed and validated adequately to determine concentrations of pegcetacoplan in rat serum and purity of the active substance/drug product, respectively. Results of study 23CATX-001 were generally consistent with those of the general toxicity studies in rabbits and monkeys performed with pegcetacoplan. In particular, it confirmed the sensitivity of juvenile rats to pegcetacoplan-related cytoplasmic vacuolation of choroid plexus epithelial cells after both SC (140 mg/kg/day) and IV (1/12 at 30 mg/kg/day; 100 mg/kg/day) exposure for 12 weeks. Although the overall data suggest that this represents nonadverse adaptive response to long chain PEG, further confirmation is to be obtained in the ongoing, more powered, definitive juvenile rat study designed to support the use of pegcetacoplan in children aged 2-12 years of age (24CATX-001), which is a part of the agreed PIP. This study is however not seen as critical to support the current extension in patients from 12 years of age considering the coverage provided by general toxicity studies, available clinical data, and the identification in the RMP of potential long-term effects of PEG accumulation as an important potential risk proposed to be monitored in an ongoing long-term PASS in PNH patients. In addition, recommendation for regular renal function monitoring is already included in the SmPC (sec. 4.4) to mitigate potential PEG-related risks.

The updated ERA report was prepared in accordance with the EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev.1 - Corr). The MAH conducted a series of test (see results in section 2.2.3) and these were acceptable to the CHMP. Based on the data provided, no environmental risk was identified and pegcetacoplan is unlikely to pose an environmental risk.

2.2.5. Conclusion on the non-clinical aspects

Overall, the non-clinical package available for pegcetacoplan is considered sufficient to support the marketing authorisation for the extended indication. The updated data submitted in this application lead to a increase in environmental exposure further to the use of pegcetacoplan, however, considering the above data, pegcetacoplan is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3. Available data to support the proposed indication of C3G and primary IC-MPGN (status at submission)

Study and population	Period (Treatment)	Status	Data for extension application
APL2-C3G-310 C3G or primary IC-MPGN in native or transplanted kidney ≥12 years of age	Randomized Controlled Period (26 weeks with pegcetacoplan or placebo)	Complete	Pivotal efficacy data in adults/adolescents, native disease/post-transplant recurrence Safety data
	Open-Label Treatment Period (26 weeks with pegcetacoplan)	Ongoing	Supportive efficacy data as of data cut (20 June 2024) Safety data as of data cut (20 June 2024) Late-breaking safety data (if any)
APL2-C3G-314 C3G or primary IC-MPGN in native or transplanted kidney (who completed APL2-C3G-310) ≥12 years of age	Open-Label Treatment Period (Long-term extension [LTE] with pegcetacoplan for a minimum of 120 weeks)	Ongoing	Supportive efficacy as of data cut (20 June 2024) Safety data (long term) as of data cut (20 June 2024) Late-breaking safety data (if any)
APL2-C3G-204 C3G or primary IC-MPGN in transplanted kidney ≥18 years of age	Part A Randomized Controlled Period (12 weeks with pegcetacoplan or no pegcetacoplan)	Complete	Supportive efficacy data (mechanistic evidence) in post-transplant disease recurrence Safety data (long-term)
	Part A Uncontrolled Period (40 weeks with pegcetacoplan)	Complete	
	Part B (LTE with pegcetacoplan)	Ongoing	Safety data (long-term) as of data cut (13 May 2024) Late-breaking safety data (if any)
APL2-201 C3G in native kidney ≥16 years of age	Part A (48 weeks with pegcetacoplan)	Complete	Supportive efficacy data (long-term; approximately 4 yrs) Safety data (long-term; approximately 4 yrs)
	Part B (LTE with pegcetacoplan)	Complete	

2.3.2. Pharmacokinetics

Concentrations of pegcetacoplan were determined in human serum using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. The bioanalytical methods were developed and validated to perform to the predefined acceptance criteria as per current regulatory requirements in both development programmes (PNH, C3G or primary IC-MPGN). These were accepted by the CHMP.

Population PK model: The purpose of the PK analysis was to develop an integrated PK model for serum pegcetacoplan concentration in healthy adults, adults with renal impairment, adult patients with PNH, and adolescent and adult patients with C3G and IC-MPGN and to develop a model linking serum pegcetacoplan concentrations to uPCR ratio biomarker response. For PK model development, data from new clinical studies APL2-201, APL2-C3G-204, APL2-C3G-310 were pooled with data from previous 11 clinical studies conducted in healthy adults, adults with renal impairment, and adults with PNH used to develop the reference model. Only studies enrolling patients with C3G or IC-MPGN were included in the PK/PD analysis dataset. PK data set from new clinical studies included total of 1217 samples from 133 subjects. Out of 1217 samples, 1173 were quantifiable. Of the patients with C3G or IC-MPGN, 104 (78.2%) had a diagnosis of C3G and 29 (21.8%) had a diagnosis of IC-MPGN. Of the 133, 21 subjects (15.8%) had a history of renal transplantation. Of the 133, 51 (38.3%) were adolescents.

Overall, structural PK model has not changed from previous PK model, and included one compartment model, first-order transit absorption following SC administration, and first-order elimination. Covariate assessment occurred in two stages: 1) baseline (time-invariant) and 2) time-varying (uPCR, eGFR, immunogenicity). Forest plots were generated to facilitate interpretation of the potential impact of covariates. Forest plots for covariate model are presented for CL, the area under the curve over one week at steady-state ($AUC_{wk,ss}$) and minimum concentration at steady-state ($C_{minwk,ss}$). Baseline C3 retained in the final PK model due to mechanistic plausibility of a relationship between C3 and pegcetacoplan CL through target-mediated drug disposition. Weight retained in the final model on CL and Vc, as subjects with lower body weight have tendency to have higher exposure, thus dosage regimen is adjusted by weight.

The final model was further applied to generated empirical Bayesian estimates of steady-state exposure stratified by covariates of special interest (i.e., age, diagnosis, and transplant status), to simulate exposure under overdosing conditions, and to confirm posology for adolescents *via* simulation and exposure-matching to adults.

Final PK model included wight as covariate on CL and Vc, and baseline C3 on CL and Vc, PNH on clearance and formulation on F1. All parameters in the final model were estimated with good precision as RSD(%) were below 30. Comparing to previous model, estimated values of primary PK parameters are similar.

Special populations: In all three studies, out of 133 subjects, 51 subjects were adolescenents (38.3%). Out of 51 subjects, 48 of them were from pivotal Phase 3 study. Based on final popPK model, model-predicted exposure for adolescents with C3G or IC-MPGN was adequately matched to the adult reference by age and weight; therefore, no change to posology from the weight stratified dosing regimens evaluated in APL2-C3G-310 is recommended for adolescents.

Immunogenicity: The potential impact of immunogenicity on pegcetacoplan exposure, serum C3 concentrations (target engagement), and uPCR response (disease biomarker) was also explored. The incidence of anti-peptide immunogenicity among the aggregated modelling data set was 18.0% (23/128). No participants had treatment-boosted anti-peptide immunogenicity. The prevalence of anti-peptide immunogenicity was 17.3%. The frequency of preexisting anti-peptide antibodies at baseline was 1.6%, among evaluable participants with a baseline result. The incidence of anti-PEG immunogenicity among the PK analysis set was 24.2%. The frequency of treatment-emergent anti-PEG immunogenicity was 12.5%. The frequency of treatment-boosted anti-PEG immunogenicity was 11.7%. The prevalence of anti-PEG immunogenicity among the PK analysis set was 61.7%. The frequency of preexisting anti-PEG antibodies at baseline was 61.7%, among evaluable participants with a baseline result. There was no consistent evidence of a temporal association between anti-peptide or anti-PEG immunogenicity, including NAb, and pegcetacoplan serum concentrations or clearance, serum C3 concentrations, or uPCR response in exploratory data analysis at the study, or individual level.

Model-based assessment of the impact of immunogenicity on pegcetacoplan CL and steady-state exposure showed that patients with C3G or primary IC-MPGN and positive anti-peptide antibodies are predicted to have 1.17-fold higher CL than those with negative anti-peptide antibodies.

Participants with C3G or primary IC-MPGN and positive anti-PEG antibodies were predicted to have 0.894-fold (95% CI, 0.823 to 0.964) lower CL than participants with negative anti-PEG antibodies. This covariate effect was determined not to be clinically meaningful based on a 95% CI within the 0.8 to 1.25 bioequivalence range.

Model-based assessment of the impact of immunogenicity on uPCR response to pegcetacoplan showed that participants with C3G or primary IC-MPGN and positive anti-peptide antibodies are predicted to have the half-maximum inhibitory concentration (IC_{50}) of 348 compared to an IC_{50} of 440 µg/mL for participants with negative anti-peptide antibodies. This covariate effect is determined not to be clinically meaningful based on overlapping 95% CIs. Participants with C3G or primary IC-MPGN and positive anti-PEG antibodies are predicted to have an IC_{50} of 401 (95% CI, 193 to 645 µg/mL) compared to an IC_{50} of 475 (95% CI, 251 to 698 µg/mL) for participants with negative anti-PEG antibodies. This covariate effect was determined not to be clinically meaningful based on overlapping 95% CIs.

Since these analyses showed that anti-drug antibodies did not interfere significantly with pegcetacoplan clearance, and that anti-peptide and anti-PEG ADA did not change serum C3 and petgcetacoplan IC_{50}, the CHMP considered the results acceptable.

2.3.3. Pharmacodynamics

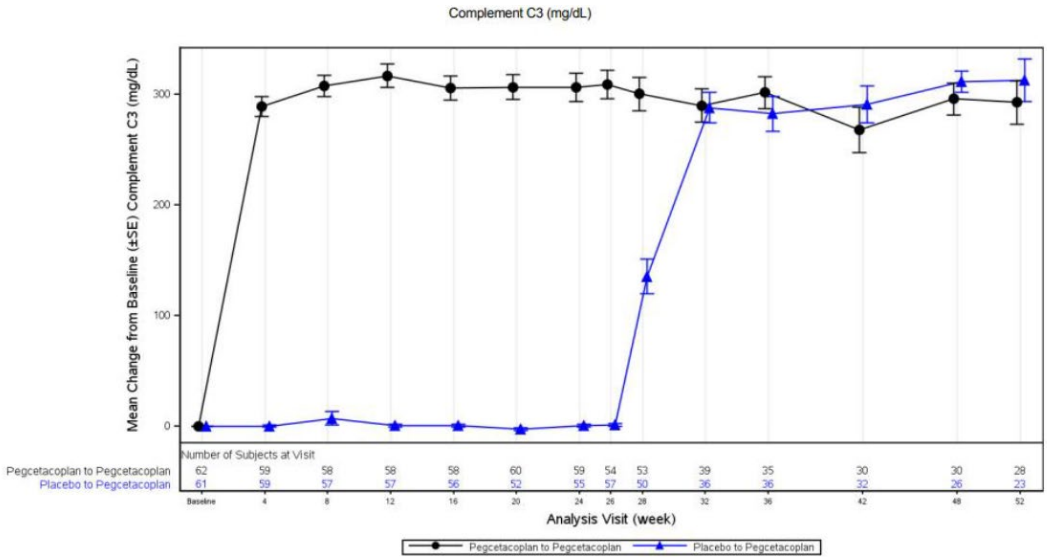
Mechanism of action

Pegcetacoplan is a SC administered PEG-ylated peptide that binds to complement protein C3 and its activation fragment C3b, thereby regulating cleavage of C3 and the generation of downstream effectors of complement activation. The complement dysregulation and overactivation causes deposition of C3 fragments in glomeruli with resultant proteinuria and/or reduced glomerular filtration rate. By targeting both C3 and C3b, pegcetacoplan centrally inhibits complement activation whether the activation was mediated by the classical, lectin, or alternative pathways. Furthermore, by inhibiting C3b, which is a component of both C3 and C5 convertase, pegcetacoplan also inhibits C5 convertase activity and prevents formation of C5b and C5a. By decreasing C3c glomerular deposition, and preventing C5 convertase assembly of C5b-9, pegcetacoplan allows kidney to recover by resolving inflammation and clearing existing deposits.

Primary and secondary pharmacology

Study APL2-C3G-310: Pharmacodynamics parameters were collected in the phase 3 randomised, placebo-controlled, double-blinded, multicentre clinical study, designed to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with C3G or IC-MPGN. The mean (SD) C3 serum levels increased from 62.0 (47.64) mg/dL at baseline to 370.7 (120.37) mg/dL (approximately 6-fold increase from baseline) and mean (SD) sC5b-9 plasma levels decreased from 902.5 (697.97) ng/mL at baseline to 290.2 (248.96) ng/mL (3-fold decrease from baseline) at week 26 in the pegcetacoplan group (Figure 1).

Figure 1. Mean (±SE) plot of change from baseline in serum C3 Over time following pegcetacoplan SC twice weekly (study APL2-C3G-310)



2.3.4. PK/PD modelling

The PK/PD analysis set consisted of 145 participants from studies APL2-C3G-310, APL2-201, and APL2-C3G-204 and 2099 triplicate uPCR samples (first morning urine). The uPCR response to placebo was described among adults and adolescents with C3G or primary IC-MPGN using a linear disease progression model parameterised with the typical progression fixed to zero with interindividual variation around this point estimate, whereas to pegcetacoplan, it was described

using an inhibitory maximal effect model with biophase distribution. Typical model parameter estimates for a 70 kg adult participant with a baseline serum albumin of 3.5 g/dL are presented below (see Table 4).

Table 4. Parameter estimates for the final uPCR model

			Estimate	95% CI	RSE (%)	Shrinkage (%)
Structural Model Parameters						
BASE	θ_1	Baseline uPCR – FMU (mg/g)	1740	1510, 1980	6.74	-
SLOPE	θ_2	Disease Progression Rate (mg/g/hour)	0.00	FIXED	-	-
IMAX	θ_3	Maximum Treatment Effect	0.910	0.783, 1.04	7.14	-
IC50	θ_4	Biphase Compartment Concentration to Achieve 50% IMAX (µg/mL)	493	248, 738	25.4	-
KEO	θ_5	Biophase Distribution Rate Constant (1/hour)	0.00103	0.000663, 0.00139	18.0	-
Covariate Effect Parameters						
ALB~BASE	θ_6	Baseline Albumin on BASE	-2.31	-2.93, -1.69	13.7	-
WT~IC50	θ_7	Baseline Weight on IC50	1.51	0.929, 2.10	19.7	-
ALB~IC50	θ_8	Baseline Albumin on IC50	1.14	0.418, 1.87	32.4	-
Interindividual Variance Parameters						
IIV-BASE	$\Omega_{(1,1)}$	Variance of BASE	0.555 [CV%=86.1]	0.419, 0.691	12.5	3.44
IIV-SLOPE	$\Omega_{(2,2)}$	Variance of SLOPE	0.0405 [SD=0.202 mg/g/hour]	0.0213, 0.0596	24.2	17.6
Residual SD						
uPCR	$\Sigma_{(1,1)}$	Log additive error	0.180	0.168, 0.191	3.37	5.75
OFV		Objective Function Value	-637.672			
CN		Condition Number	57			

Abbreviations: ALB = baseline serum albumin; CI = confidence interval; CN = condition number; CV = coefficient of variation; IC50 = concentration achieving 50% of the maximal response; IIV = inter-individual variability; IMAX = maximum proportional reduction in uPCR with treatment; KEO = biophase (effect) compartment transfer rate constant; OFV = objective function value; uPCR = urine protein-to-creatinine ratio; RSE = relative standard error; SD = standard deviation; WT = baseline body weight

The impact of intrinsic and extrinsic participant factors was evaluated as covariates on uPCR using model-based estimations:

• Age, sex, C3G or primary IC-MPGN diagnosis, serum AST, serum ALT, serum albumin, eGFR, uPCR, and serum C3 at baseline were not deemed to have clinically meaningful impact on uPCR response to pegcetacoplan treatment. There was insufficient evidence to classify the clinical relevance of diagnosis (primary IC-MPGN vs C3G) on uPCR response to pegcetacoplan treatment.

• Baseline uPCR decreases nonlinearly with increasing baseline serum albumin and IC50 increases nonlinearly with increasing baseline serum albumin, leading to higher uPCR at Week 26 with lower baseline serum albumin values and less uPCR change from baseline. Compared to a reference participant with a baseline serum albumin of 3.5 g/dL, Week 26 uPCR and uPCR percentage change from baseline were predicted to be 1.75-fold (95% CI, 1.32, 2.22) and 1.18-fold greater (95% CI, 1.07, 1.32), respectively, in participants at the 5th percentile of baseline serum albumin (2.4 g/dL) and 0.755-fold (95% CI, 0.673, 0.860) and 0.903-fold (95% CI, 0.826, 0.962) lower, respectively, among participants at the 95th percentile of baseline serum albumin (4.2 g/dL). Baseline serum albumin was determined to have a clinically meaningful association with uPCR response to pegcetacoplan treatment.

• The IC_{50} for uPCR response to pegcetacoplan treatment increases nonlinearly with increasing body weight. Compared to a reference 70 kg participant, Week 26 uPCR and uPCR percentage

change from baseline were predicted to be 0.718-fold (95% CI, 0.564, 0.892) lower and 1.24-fold (95% CI, 1.12, 1.36) greater, respectively, in participants at the 5th percentile of body weight (50 kg) and 1.23-fold (95% CI, 1.05, 1.46) greater and 0.797-fold (95% CI, 0.705, 0.897) lower, respectively, in participants at the 95th percentile of body weight (90 kg).

Individual participant EBE of week 26 uPCR and uPCR percentage change from baseline were consistent across covariate strata of special interest including diagnosis, age category, and transplant history; therefore, no changes to posology are needed outside of weight-based dosing for adolescents evaluated in Study APL2-C3G-310. The recommended dosage for the treatment of adult or adolescent participants with C3G or primary IC-MPGN is the dosage used in the pivotal study and is provided in Table 5.

Table 5. Recommended SC dosing regiments for C3G or primary IC-MPGN

Weight	First dose of a twice weekly regimen (infusion volume)	Second dose of a twice weekly regimen (infusion volume)	Subsequent maintenance dosing regimen (infusion volume)
All adult participants, adolescent participants ≥50 kg	1080 mg (20 mL)	1080 mg (20 mL)	1080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Abbreviations: C3G = C3 glomerulopathy; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; s.c. = subcutaneous.

2.3.5. Discussion on clinical pharmacology

Pegcetacoplan is a complement C3 inhibitor. It binds and blocks C3 and its cleavage product C3b, which are central to all three complement pathways (classical, lectin, and alternative) and prevents formation and activity of the C3 convertase that drives the alternative pathway amplification loop. Hence, it halts the ongoing complement activation, reduces generation of downstream effectors such as C5a and the membrane attack complex, and limits further deposition of C3 fragments within the glomeruli. PD endpoints were evaluated in the pivotal Phase 3 study APL-C3G-310. A clear increase of the C3 serum level in the pegcetacoplan group compared to placebo was observed. These PD parameters support the assumed mechanism of action.

Similar dose for adults in this indication is well justified, also by popPK modelling, as the results indicate that age did not have a meaningful effect on the PK of pegcetacoplan. Change of posology for teenage population depending on weight is supported by similar exposures observed by weight range. Changed dosing regimens in population with lower body weight is expected to generate reliable efficacy while being safe and well tolerated. Section 4.2 of the SmPC was accordingly updated. If a dose of pegcetacoplan for treatment of PNH, C3G or primary IC-MPGN is missed, it will be administered as soon as possible. The regular schedule will be resumed even if this results in an interval of less than 3 days between the replacement dose and the subsequent dose.

Results of immunogenicity tests showed that incidence of anti-PEG antibodies was low and modelling found no clinical meaningful effect on PK and PD of pegcetacoplan, as also reflected in the SmPC, section 4.8.

2.3.6. Conclusions on clinical pharmacology

Overall, the CHMP found the clinical pharmacology package acceptable. The proposed posology is considered to result in appropriate exposures and effect and is hence agreed by the CHMP.

2.4. Clinical efficacy

The indication initially applied for in this procedure is:

"the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN)."

Table 6. Summary of the clinical development programme (status at initial submission)

Study, Status	Study design, population	Treatment duration	Age, no. patients enrolled/ Treatments
Primary efficacy			
Study APL2-C3G-310 *RCP Completed* Data cut-off date: 20 June 2024 *OLP Ongoing*	Phase 3 multicenter, randomized, double-blind, parallel arm, placebo-controlled study in patients with c3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis Includes nontransplant and posttransplant	52 weeks planned: 26-week randomised controlled period (RCP) 26-week open-label period (OLP), patients from the placebo arm are switched to pegcetacoplan	Adults and adolescent ≥ 12 years of age N=124: n=63, pegcetacoplan in randomized treatment period n=61, placebo in randomized treatment period
Supportive efficacy			
Study APL2-C3G-204 *Part A Completed* Database lock date: 19 January 2024 *Part B ongoing*	Phase 2 open-label, randomized, placebo controlled study in posttransplant patients with recurrence of c3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis	*Part A:* 12-week randomized controlled period 40-week uncontrolled period, patients from the placebo arm are switched to pegcetacoplan *Part B:* long-term extension	Adults N= 13: n=10, pegcetacoplan in randomized treatment period n=3, placebo in randomized treatment period
Study APL2-C3G-314 *Ongoing* Data cut-off date: 20 June 2024	Phase 3 open-label, single-arm, multicenter, extension study in patients with C3G or primary IC-MPGN who completed participation in Study APL2-C3G-310	Minimum of 120 weeks (approximately 2.5 years)	Adults and adolescent ≥ 12 years of age At the cut-off date, 54 participants who completed 52 weeks of treatment in Study APL2-C3G-310 were enrolled
Study APL2-201 *Completed*	Phase 2 prospective, open-label, single-arm, study in treatment–naive patients with immunoglobulin A nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy (PMN), or C3G.	*Part A:* 48-week *Part B:* long-term extension	Adults and adolescent ≥ 16 years of age N=21: IgAN cohort=6 LN cohort=2 PMN cohort=5 C3G cohort=8

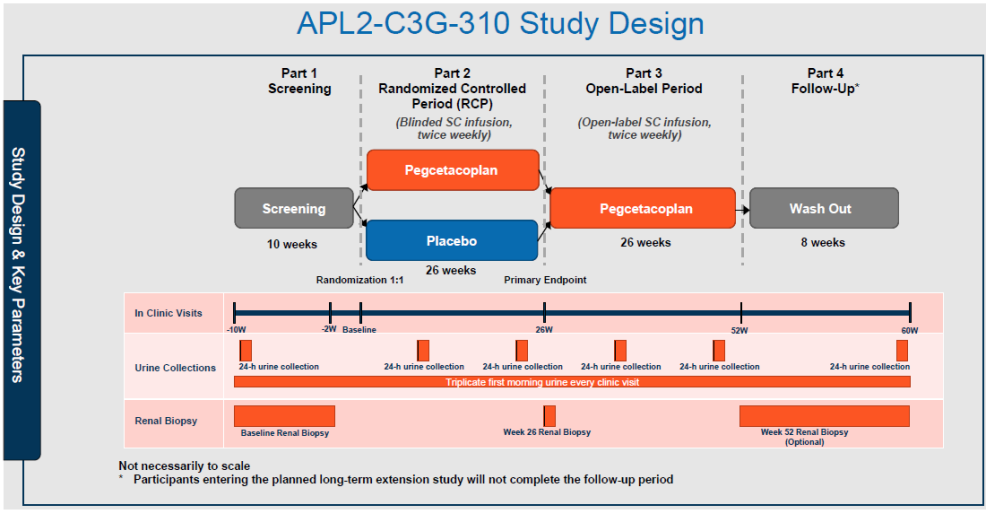
2.4.1. Main study

APL2-C3G-310: A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with C3 Glomerulopathy or Immune-

Complex Membranoproliferative Glomerulonephritis

This phase 3 randomised, placebo-controlled, double-blinded, multicentre clinical study was designed to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with C3G or IC-MPGN. Participants initially screened as adolescents followed adolescent procedures and requirements through the duration of their participation in the study, even if they had passed their 18th birthday while enrolled in the study. This study consisted of 4 parts, see Figure 2:

Figure 2. Study design and schedule of assessments



Abbreviations: SC = subcutaneous; uPCR = urine protein-to-creatinine ratio; W = week.

Methods

Study participants

Key inclusion criteria: Patients ≥18 years and where approved, adolescents (aged 12-17 years) weighing at least 30 kg; diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant); evidence of active renal disease; not more than 50% global glomerulosclerosis or interstitial fibrosis on the baseline biopsy for adult participants or adolescent participants providing a baseline biopsy; at least 1 g/day of proteinuria on a screening 24-hour urine collection and a uPCR of at least 1000 mg/g in at least 2 FMU samples collected during screening; eGFR ≥30 mL/min/1.73 m^2; stable regimen for C3G/IC-MPGN treatment, etc.

Key exclusion criteria: Previous exposure to pegcetacoplan; improving renal disease in 8 weeks *prior* to screening or during the screening period; from a renal transplant participant, evidence of rejection that requires treatment in the baseline renal biopsy collected during screening; C3G/IC-MPGN secondary to another condition; current or prior diagnosis of HIV, hepatitis B, or hepatitis C infection or positive serology; body weight greater than 100 kg at screening; hypersensitivity to pegcetacoplan or excipients; history of meningococcal disease; malignancy; severe infection, etc.

Treatments

All participants: SC infusion of pegcetacoplan/placebo matching volumes 2x weekly, see Table 7.

Table 7. Dosing regimens (pegcetacoplan and placebo)

Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dosing regimen (infusion volume)
All adult participants, adolescent participants ≥50 kg	1080 mg (20 mL)	1080 mg (20 mL)	1080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Participants were on stable doses of all medications relevant to their renal disease for at least 12 weeks prior to randomisation. During the screening period and the RCP, changes to the baseline treatment regimens for C3G/IC-MPGN were minimised. If the participant was in a post-transplant time frame in which immunosuppression or other transplant-related medication adjustments were anticipated, these still occurred, as per centre's standard protocols.

Objectives

The primary objective of the study was to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared with that of placebo in patients with C3G or primary IC-MPGN based on a reduction in proteinuria. The secondary objectives of the study were assessment of the effect of pegcetacoplan on: eGFR and additional C3G/IC-MPGN disease–related parameters, along with the evaluation of safety over 52 weeks of treatment. The exploratory objectives were characterisation of additional clinical, laboratory, and histologic findings of C3G/IC-MPGN in response to treatment.

Outcomes/endpoints

Table 8. Study endpoints

Study endpoints	Week 26
Primary efficacy endpoint	
The log-transformed ratio of uPCR at week 26 compared to baseline	X
Key secondary efficacy endpoints	
The proportion of participants who meet the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.)	X
The proportion of participants with a reduction of at least 50% from baseline in uPCR	X
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score	X
The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline	X
Change from baseline in eGFR	X
Additional secondary efficacy endpoints	
The proportion of participants achieving proteinuria <1 g/day	X
For participants with serum albumin levels below the LLN at baseline, the proportion of participants with normalization of serum albumin levels	X
For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN	X
The change from baseline in the FACIT-Fatigue Scale score	X
The change from baseline in the KDQOL score	X

Sample size

Based on preliminary data from Study APL2 201, a reduction of 60% in uPCR in the pegcetacoplan group at week 26 was assumed *vs* a reduction of 20% in uPCR in the placebo arm, which corresponded to mean log ratio to baseline of −0.92 vs −0.22 respectively, and a standard deviation of 0.88 (on log scale). Based on this assumption, a sample size of 70 participants in total provided at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and impact by COVID-19, at least 78 participants with native kidney disease were planned to be enrolled. A minimum of 63 participants with C3G in native kidneys were planned to be enrolled, which was targeting that at least 80% (*i.e*. 78) of the enrolled participants had native kidney disease.

Randomisation

Participants were randomised to receive pegcetacoplan or placebo in a ratio of 1:1 *via* stratified central permuted block randomisation. To achieve balance between the arms, two stratification factors were applied: a/factor examining participants with post-transplant recurrence *vs* non-transplant participants; b/ followed by examining participants with baseline renal biopsies *vs* participants without baseline renal biopsies.

Blinding

Dosing was double-blinded in the RCP; the OLP was not blinded. Participants, the sponsor, investigators, evaluators and all study site personnel conducting study-related activities remained blinded to treatment allocations during the RCP at least until all participants completed the week 26 assessments and the RCP portion of the database was locked.

Statistical methods

The intent-to-treat (ITT) set included all randomised participants. The per-protocol (PP) set included all participants in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Efficacy analyses, including primary, key secondary, additional secondary, and exploratory analyses, were performed primarily using the ITT set, with participants grouped according to the treatment assigned at randomization. All statistical tests were performed at 2-sided 5% level of significance and all confidence intervals will be two-sided 95% confidence intervals. The following sensitivity analyses were performed: imputation based on missing at random (MAR); tipping point analysis.

Missing data: Imputation for the non-monotone missing pattern was performed *prior* to the multiple imputation for the monotone missing pattern. For the non-monotone missing pattern, missing values between two visits with uPCR measurements were imputed using the MCMC method based on the MAR assumption. Multiple imputation was carried out for the monotone missing pattern. For intercurrent events (ICEs) due to renal replacement therapy (dialysis and/or renal transplant), missing data were imputed based on the worst change of all participants across visits plus a random error.

Analysis of covariance (ANCOVA): Analysis of the C3G histologic index activity score, FACIT-Fatigue score, and KDQOL score, with treatment as a fixed effect, adjusted for baseline score of the endpoint, disease type, and stratification factors. LS means were presented for each treatment group, along with the between-treatment difference and 95% CI.

Mixed effects model for slope analysis of continuous outcomes: For slope analysis of continuous outcomes, a mixed-effects model using the baseline and all postbaseline assessments was used. The model included treatment group, disease type, baseline immunosuppressant, and stratification factors as fixed effects, time, and the time-by-treatment interaction.

Multiplicity adjustment: The primary endpoint of the study was tested at the 2-sided 0.05 level, and if the null hypothesis for the primary endpoint was rejected, the secondary endpoints were tested. The key secondary and additional secondary endpoints were tested sequentially in the order in which they are presented in the SAP.

Estimands: Please see Table 9 below.

Table 9. Estimands and Attributes for Primary, and Key Secondary Endpoints

For all estimands: A. **Population**: participants with C3G or IC-MPGN defined through the study inclusion/exclusion criteria in the ITT Set B. **Treatment regimens of interest:** • Twice-weekly SC doses of pegcetacoplan for 26 weeks of treatment • Twice-weekly SC doses of placebo for 26 weeks of treatment		
C: Variable (or endpoint)	**D: Strategies for addressing ICEs (event†: strategy‡)**	**E: Population-level summary**
Primary Estimand		
Log-transformed ratio of uPCR at week 26 compared to baseline	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of log-transformed uPCR from baseline to week 26 (measured by equal-weighted average over weeks 24, 25, and 26) between the pegcetacoplan group and the placebo group.
Key Secondary Estimands (for comparative endpoints)		
The proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a composite renal endpoint for the pegcetacoplan group to achieving a composite renal endpoint for the placebo group at week 26.
The proportion of participants with a reduction of at least 50% from baseline in uPCR at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a reduction of at least 50% from baseline in uPCR for the pegcetacoplan group to achieving a reduction of at least 50% from baseline in uPCR for the placebo group at week 26.
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score at week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change from baseline to week 26 in activity score between the pegcetacoplan group and the placebo group.

The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of showing decreases in C3c staining for the pegcetacoplan group to showing decreases in C3c staining for the placebo group at week 26.
Change from baseline in eGFR at week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of eGFR from baseline to week 26 between the pegcetacoplan group and the placebo group.

†ICE definitions:

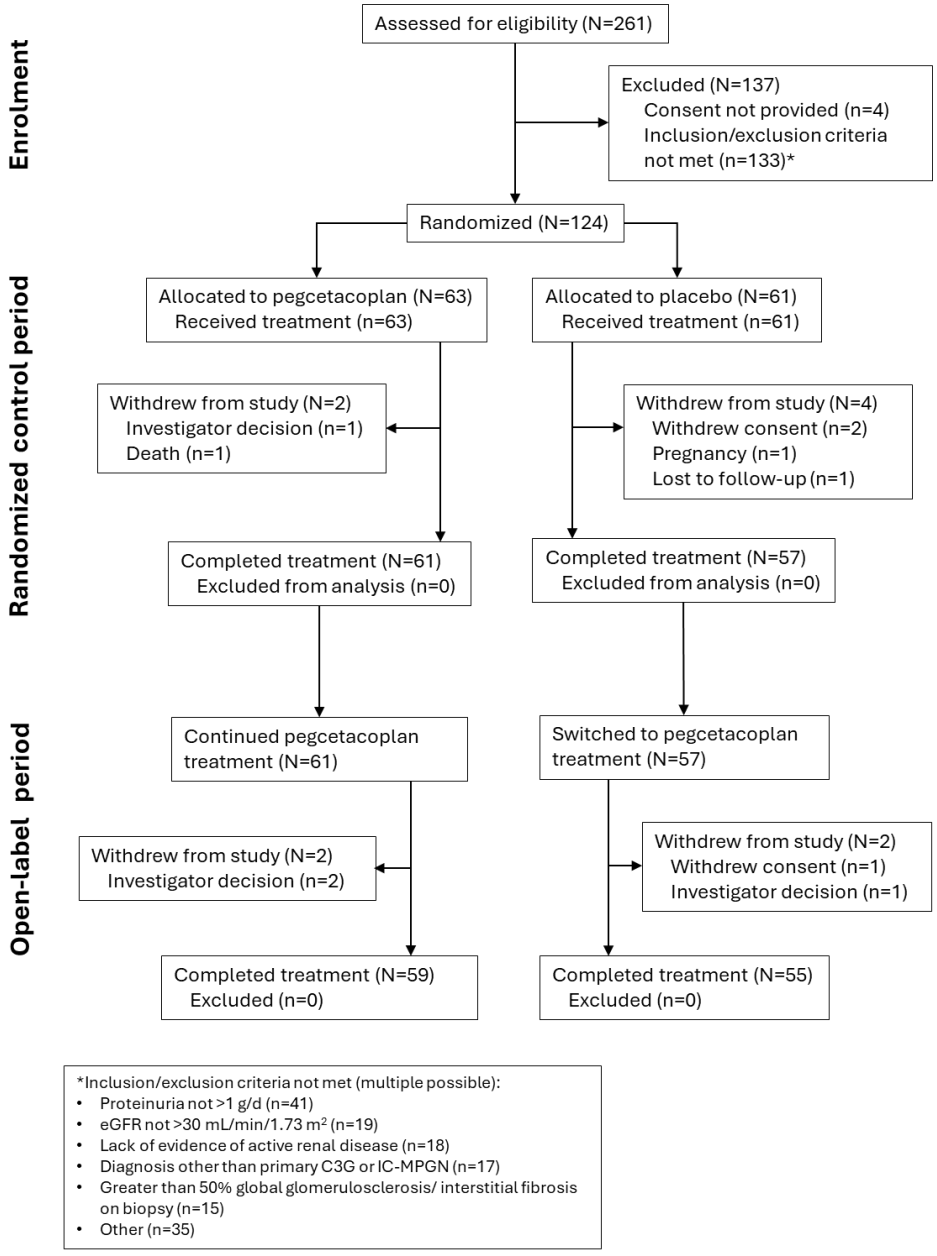
- ProhibiRescue = use of prohibited concomitant medication specified in Protocol Section 8.3.3, or use of rescue therapies defined in Protocol Section 8.3.2
- RenalReplace = start renal replacement therapy (dialysis and/or renal transplant)
- DisctTrt = permanent discontinuation of study treatment

‡Strategies:

- Composite strategy: the endpoint status at or after the initiation of the ICEs will be regarded as non-responder.
- Hypothetical strategy: (for ICEs due to ProhibiRescue) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed using copy reference imputation.
  (for ICEs due to RenalReplace) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed based on the worst change of all participants across visits plus a random error.
- Treatment policy strategy: all measurements after the ICEs will be used as is. Missing data resulting from the ICEs will be imputed using copy reference imputation.

Results

Participant flow



Recruitment

The first patient was enrolled 30 May 2022. The cut-off date was 20 June 2024. At the time of the submission, the RCP was completed and the OLP was ongoing. Subjects were recruited across 122 sites in 19 countries, including 60 sites in Europe. This is reasonable to extrapolate the results to the European population.

Conduct of the study

Among the 4 amendments of the protocol, 2 were made before the recruitment of the first patient to implement feedback from regulatory authorities. In amendment 3, made at FDA's request, the primary endpoint was modified to switch from a binary endpoint to a continuous endpoint assessing change from baseline in uPCR. Considering that there is a loss of information switching from continuous to binary, the change is supported. In amendment 4, the order of the key secondary endpoints was amended to prioritise the histopathologic endpoints over the eGFR endpoint.

Baseline data

Table 10. Baseline Demographics (ITT Set)

	Statistics	Pegcetacoplan (N = 63) n (%)	Placebo (N = 61) n (%)	Overall (N = 124) n (%)
Age at screening (years)	n	63	61	124
	Mean (SD)	28.2 (17.08)	23.6 (14.26)	26.0 (15.86)
	Median	19.0	19.0	19.0
	Q1, Q3	15.0, 45.0	16.0, 26.0	15.0, 27.0
	Min, max	12, 62	12, 74	12, 74
Age group: adolescent (12-17 years)	n (%)	28 (44.4)	27 (44.3)	55 (44.4)
Age group: adult (≥18 years)	n (%)	35 (55.6)	34 (55.7)	69 (55.6)
Sex				
Male	n (%)	26 (41.3)	28 (45.9)	54 (43.5)
Female	n (%)	37 (58.7)	33 (54.1)	70 (56.5)
Race				
White	n (%)	45 (71.4)	46 (75.4)	91 (73.4)
Asian	n (%)	9 (14.3)	9 (14.8)	18 (14.5)
Black or African American	n (%)	1 (1.6)	0	1 (0.8)
American Indian or Alaskan Native	n (%)	1 (1.6)	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
Other	n (%)	7 (11.1)	6 (9.8)	13 (10.5)
Ethnicity				
Hispanic	n (%)	15 (23.8)	10 (16.4)	25 (20.2)
Not Hispanic or Latino	n (%)	41 (65.1)	47 (77.0)	88 (71.0)
Not reported[a]	n (%)	6 (9.5)	2 (3.3)	8 (6.5)
Unknown	n (%)	1 (1.6)	2 (3.3)	3 (2.4)

Abbreviation: ITT = intent-to-treat.
[a] Some participants with ethnicity not reported because some countries do not allow the collection of ethnicities.

Baseline disease characteristics for the C3G and IC-MPGN subgroups in the pivotal study 310: were generally similar to those in the overall ITT set. Baseline eGFR was slightly higher in the pegcetacoplan group for IC-MPGN; this was not observed in the overall ITT set.

Of the 96 participants with C3G disease type, 51 participants in the pegcetacoplan group, and 45 participants in the placebo group had C3G underlying disease based on screening biopsy. Of the participants with C3G on screening biopsy, indication per disease-specific medical history form was C3G for 88.2% in the pegcetacoplan and 93.3% in the placebo group. For IC-MPGN per disease-specific medical history form, it was 11.8% in the pegcetacoplan and 6.7% in the placebo group. Baseline proteinuria was slightly higher in the pegcetacoplan than in the placebo group, and mean baseline eGFR was slightly lower in the pegcetacoplan than the placebo group. Baseline serum C3 was slightly higher in the pegcetacoplan compared to the placebo group.

Of the 28 participants with IC-MPGN disease type, 12 (100%) in the pegcetacoplan group and 16 (100%) in the placebo group had IC-MPGN underlying disease based on screening biopsy. Of the

participants categorised as having IC-MPGN on screening biopsy, indication per disease-specific medical history form was C3G 16.7% in the pegcetacoplan and 37.5% participants in the placebo group. For IC-MPGN per disease-specific medical history form, it was 83.3% in the pegcetacoplan and 62.5% participants in the placebo group. Baseline proteinuria was slightly higher in the pegcetacoplan than in the placebo group, mean (SD) baseline eGFR was similar in both groups pegcetacoplan groups, as was the mean (SD) baseline serum C3.

Baseline disease characteristics for the post-transplant and nontransplant subgroups were generally similar to those reported for the overall ITT set.

Numbers analysed

Table 11. Analysis populations for the RCP (screened set)

	Statistics	Pegcetacoplan to pegcetacoplan	Placebo to pegcetacoplan	Overall (N = 261)
Screened set	n			261
Screen failure	n			137
ITT set	n (%)	63 (100)	61 (100)	124 (100)
Safety set	n (%)	63 (100)	61 (100)	124 (100)
PP set	n (%)	63 (100)	59 (96.7)	122 (98.4)
PK set	n (%)	61 (96.8)	48 (78.7)	109 (87.9)
PD set	n (%)	62 (98.4)	61 (100)	123 (99.2)
Week 52 set	n (%)	29 (46.0)	28 (45.9)	57 (46.0)
OLP set	n (%)	59 (93.7)	57 (93.4)	116 (93.5)

Abbreviations: ITT = intent-to-treat; OLP = open-label period; PD = pharmacodynamic; PK = pharmacokinetic; PP = per-protocol; RCP = randomized controlled period.

Notes: The screened set included all participants who had provided written informed consent. The ITT set included all participants who had been randomly assigned. The safety set included all participants who had received at least 1 dose of pegcetacoplan or placebo. The PP set included all participants in the ITT set who had not violated any inclusion or exclusion criteria and with RCP drug compliance ≥80%. The PK set includes all participants in safety set who had at least 1 quantifiable postdose concentration of pegcetacoplan (even with value of below the limit of quantification). The PD set included all participants in the safety set who had at least 1 quantifiable post-dose PD endpoint evaluated. The week 52 set included all participants in the ITT set who had the opportunity to complete their week 52 assessments. The OLP set included all participants in the ITT set who had entered into the OLP.

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint, the log-transformed ratio of uPCR at week 26 compared to baseline, was met, see Table 12.

Table 12. Analysis of CFB in log-transformed FMU uPCR with MMRM for RCP (ITT set)

Week	Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Week 24-25-26[c]	**Estimated/comparisons[a]**		
	LS mean (SE)	−1.115 (0.1356)	0.029 (0.0606)
	95% CI of LS mean	(−1.381 to −0.849)	(−0.090 to 0.148)
	Difference (95% CI) in LS mean (pegcetacoplan vs placebo)	−1.144 (−1.437 to −0.851)	
	P value (pegcetacoplan vs placebo)	<.0001	
	Geometric means (95% CI)[b]	0.328 (0.251-0.428)	1.029 (0.914-1.159)
	Geometric means ratios (95% CI) (pegcetacoplan vs placebo)[b]	0.319 (0.238-0.427)	

Abbreviations: FMU = first-morning spot urine; LS = least-square; ITT = intent-to-treat; MMRM = mixed-effect model for repeated measures; PP = per-protocol; uPCR = urine protein-to-creatinine ratio

[a] An MMRM including fixed categorical effect for treatment group, visit, disease type, baseline immunosuppressants use, stratification factors, and the visit-by-treatment group interactions as well as the continuous, fixed covariate of baseline log-transformed uPCR, was utilized to analyze the log-transformed ratio of uPCR at week 26 compared to baseline. Use of prohibited medications or rescue therapies or start of renal replacement therapy was handled by hypothetical strategy; discontinuation of treatment was handled by treatment policy strategy.

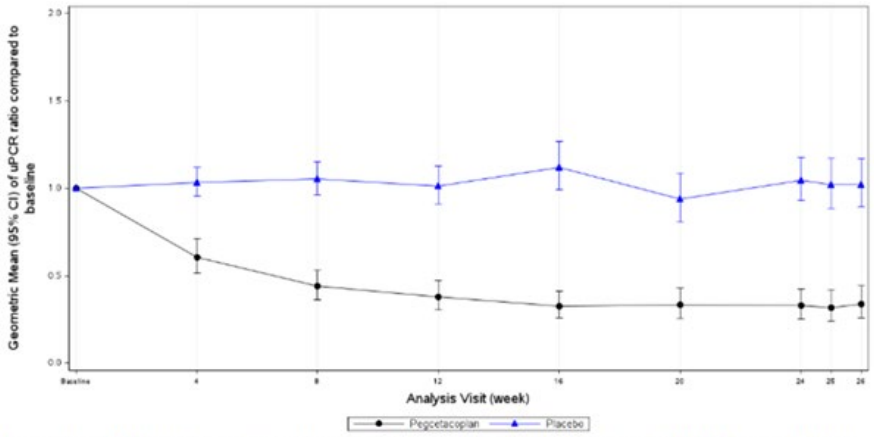
[b] Geometric means and ratios were estimated by the exponentiated LS means and differences.

[c] The LS mean of week 24-25-26 was estimated using a composite contrast of equal-weighted average over week 24, 25, and 26.

Note: Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive.

The geometric mean of uPCR ratio compared to baseline over the course of the 26-week RCP is presented in Figure 3.

Figure 3. Geometric mean (95% CI) of uPCR ratio compared to baseline for RCP (ITT)



Abbreviations: FMU = first-morning spot urine; ITT = intent-to-treat; LS = least-square; MMRM = mixed-effect model for repeated measures; uPCR = urine protein-to-creatinine ratio.

Key secondary endpoints

Any participant met the requirements of the composite renal endpoint at week 26 if they:

a/ Had a stable or improved eGFR at week 26 compared to baseline (≤15% reduction in eGFR), and b/ Had a ≥50% reduction in uPCR at week 26 compared to baseline.

Table 13. Analysis of proportion of participants who met criteria for achieving a composite renal endpoint at week 26 with logistic model by treatment group (ITT set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Participants who achieved the composite renal endpoint, n (%)	31 (49.21)	2 (3.28)
Participants with stable or improved eGFR compared to baseline (≤15% reduction in eGFR), n (%)	43 (68.25)	36 (59.02)
Participants with ≥ 50% reduction in uPCR compared to baseline, n (%)	38 (60.32)	3 (4.92)
Estimates/comparisons at week 26		
Proportion (SE)	0.490 (0.1352)	0.034 (0.0280)
95% CI of proportion	(0.250-0.735)	(0.006-0.158)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.456 (0.212-0.700)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	27.479 (6.097-123.846)	
P value (pegcetacoplan vs placebo)	<.0001	

Abbreviations: eGFR = estimated glomerular filtration rate; FMU = first-morning spot urine; ITT = intent-to-treat; uPCR = urine protein-to-creatine ratio.

Notes: Baseline eGFR value was calculated using the last nonmissing assessment prior to first dose. Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. Week 26 eGFR value was calculated based on the week 26 assessment result. Week 26 uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26. Participants who met criteria for achieving a composite renal endpoint were defined as: (1) a stable or improved eGFR compared to baseline (≤15% reduction in eGFR), and (2) a ≥50% reduction in uPCR compared to baseline. The logistic model included treatment group as independent variable and adjusted for baseline eGFR values, baseline log-transformed uPCR values, disease type, and stratification factors. A composite strategy was used where the composite renal endpoint status at or after the occurrence of any of the ICEs were regarded as nonresponder. Participants with missing eGFR and/or uPCR values at week 26 for reasons other than ICEs were regarded as nonresponder.

Table 14. Analysis of proportion of participants who achieved a reduction of ≥50% from baseline in FMU uPCR at week 26 with logistic model by treatment group (ITT set)

Parameter	Pegcetacoplan (N = 63)	Placebo (N = 61)
Participants with ≥50% reduction in uPCR compared to baseline (n [%])	38 (60.32)	3 (4.92)
Estimates/comparisons at week 26		
Proportion (SE)	0.568 (0.1336)	0.041 (0.0305)
95% CI of proportion	(0.312-0.793)	(0.009-0.164)
Difference (95% CI) in proportion (pegcetacoplan vs placebo)	0.527 (0.292-0.762)	
Odds ratio (95% CI) of responder (pegcetacoplan vs placebo)	30.901 (8.393-113.772)	
P value (pegcetacoplan vs placebo)	<.0001	

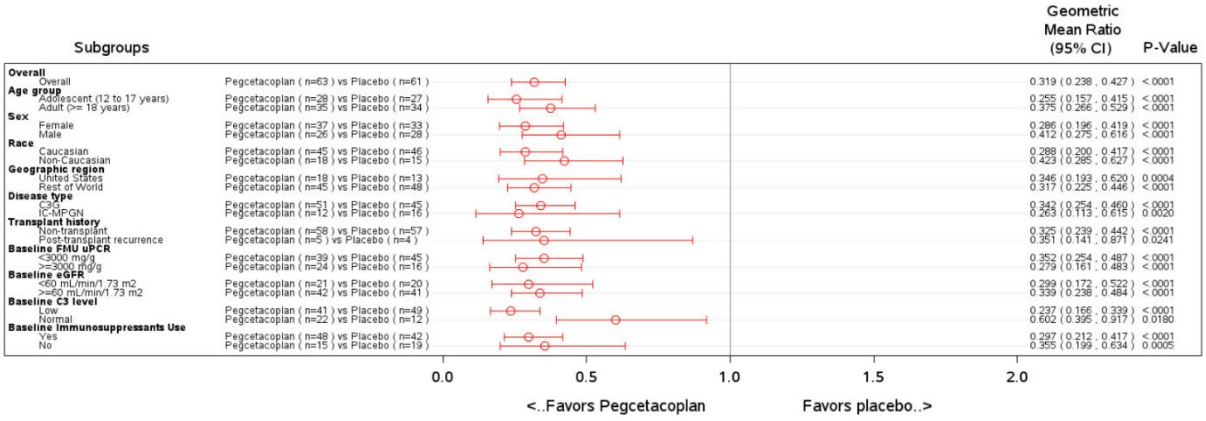
Abbreviations: FMU = first-morning spot urine; ITT = intent-to-treat; uPCR = urine protein-to-creatine ratio.

Notes: Baseline uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. Week 26 uPCR value was calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26. The logistic model included treatment group as an independent variable and adjusted for baseline log-transformed uPCR values, disease type, and stratification factors. A composite strategy was used where the responding status at or after the occurrence of any of the ICEs was regarded as nonresponder. Participants with missing uPCR values at week 26 for reasons other than ICEs were regarded as nonresponder.

Ancillary analyses

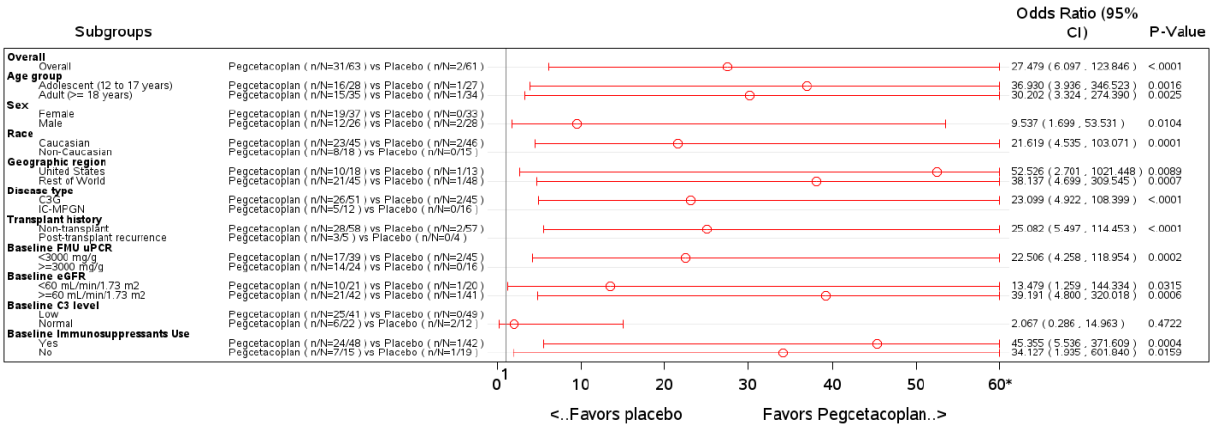
Analyses of the primary efficacy endpoint, log-transformed ratio of uPCR at week 26 compared to baseline, by subgroup are presented in the below Figure 4.

Figure 4. LS Mean (95% CI) treatment difference at week 26 in the change from baseline in log-transformed FMU uPCR (mg/g) by treatment group from MMRM model by subgroups for randomized controlled period ITT set



The proportion of participants achieving the composite renal endpoint by subgroups is presented below.

Figure 5. Odds ratio (95% CI) of responder for achieving a composite renal endpoint at week 26 with logistic model by treatment group by subgroups for randomized controlled period ITT set



Change from baseline in EQ-5D-5L at Week 26: Among the participants with available data (n = 71), there was no difference observed in the change from baseline in the EuroQol visual analogue score (EQ-VAS) for the pegcetacoplan group compared to the placebo group.

Concomitant medication

Table 15. Concomitant medications as standard of care (C3G or IC-MPGN) during the RCP

	Pegcetacoplan (N = 63) n (%)	Placebo (N = 61) n (%)	Overall (N = 124) n (%)
ACEI/ARB	57 (90.5)	56 (91.8)	113 (91.1)
Immunosuppressants	47 (74.6)	42 (68.9)	89 (71.8)
Mycophenolate mofetil	36 (57.1)	34 (55.7)	70 (56.5)
Mycophenolate sodium	2 (3.2)	4 (6.6)	6 (4.8)
Mycophenolic acid	4 (6.3)	1 (1.6)	5 (4.0)
Tacrolimus	12 (19.0)	11 (18.0)	23 (18.5)
Tacrolimus monohydrate	0	1 (1.6)	1 (0.8)
Ciclosporin	0	1 (1.6)	1 (0.8)
Tocilizumab	1 (1.6)	0	1 (0.8)
Corticosteroids for systemic use	25 (39.7)	24 (39.3)	49 (39.5)
Prednisone	17 (27.0)	16 (26.2)	33 (26.6)
Prednisolone	8 (12.7)	5 (8.2)	13 (10.5)
Deflazacort	0	1 (1.6)	1 (0.8)
Hydrocortisone	0	1 (1.6)	1 (0.8)
Meprednisone	0	1 (1.6)	1 (0.8)
Methylprednisolone	0	1 (1.6)	1 (0.8)
Prednisolone hemisuccinate	0	1 (1.6)	1 (0.8)
SGLT2 inhibitors	7 (11.1)	6 (9.8)	13 (10.5)
Dapagliflozin	3 (4.8)	4 (6.6)	7 (5.6)
Dapagliflozin propanediol monohydrate	4 (6.3)	1 (1.6)	5 (4.0)
Empagliflozin	0	1 (1.6)	1 (0.8)

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; RCP = randomized controlled period; SGLT2 = sodium-glucose cotransporter-2.

Immunogenicity

Of the 123 participants exposed to pegcetacoplan, 102 (82.9%) participants were classified as ADA negative for anti–pegcetacoplan peptide antibodies at week 52. Twenty (16.3%) participants developed a positive treatment-emergent response, and 5 (4.0%) participants developed anti-pegcetacoplan peptide neutralizing antibodies.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of efficacy for trial APL2-C3G-310

Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis			
Study identifier	**APL2-C3G-310**		
Design	This was a phase 3, randomised, placebo-controlled, double-blinded, multicenter study to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN. Approximately 80 to 100 participants, including patients with disease in native kidney or posttransplant, were planned to be randomized 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm. Treatment regimen (pegcetacoplan or placebo) was twice-weekly SC infusion, with the dose amount dependent on the age and body weight. All adult participants (regardless of weight), and adolescent participants who weighed at least 50 kg, were to receive 1080 mg (20 mL) SC infusions. Adolescent participants who weighed at least 35 kg but less than 50 kg were to receive a reduced infusion volume (648 mg [12 mL] for the first infusion and 810 mg [15 mL] for each infusion thereafter). Adolescent participants who weighed at least 30 kg but less than 35 kg were to receive a further reduced infusion volume (540 mg [10 mL] for the first 2 infusions and 648 mg [12 mL] twice weekly thereafter). The planned duration of participation in the study for each participant was a maximum of approximately 70 weeks. The study consisted of 4 parts: • Part 1: 10-week screening period • Part 2: 26-week randomized controlled period • Part 3: 26-week open-label period • Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study) During the open-label period, all participants were treated with pegcetacoplan.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks not applicable 26 weeks
Hypothesis	Superiority		
Treatments groups	Pegcetacoplan		Pegcetacoplan, 26 weeks, 63
	Placebo		Placebo, 26 weeks, 61
Endpoints and definitions	Primary endpoint	uPCR	Log-Transformed Ratio of uPCR at Week 26 Compared to Baseline

	Secondary endpoint	Composite endpoint (uPCR and eGFR)	Proportion of participants achieving the composite renal endpoint at Week 26
	Secondary endpoint	% uPCR	Proportion of participants with ≥50% reduction in uPCR at Week 26
	Secondary endpoint	C3G histologic index score	Change in the activity score of the C3G histologic index score from baseline at Week 26
	Secondary endpoint	% C3c staining on renal biopsy	Proportion of participants showing decreases in C3c staining on renal biopsy from baseline at Week 26
	Secondary endpoint	eGFR	Change in eGFR from baseline at Week 26

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Week 24-25-26 (primary endpoint) Week 26 (key secondary endpoints)			
Descriptive statistics and estimate variability	Treatment group	Pegcetacoplan	Placebo	
	Number of subject	63	61	
	uPCR LS mean 95% CI	-1.115 (-1.381 to -0.849)	0.029 (-0.090 to 0.148)	
	Composite endpoint (uPCR and eGFR) Proportion 95% CI	0.490 (0.250;0.735)	0.034 (0.006;0.158)	
	% uPCR Proportion 95% CI	0.568 (0.312;0.793)	0.041 (0.009;0.164)	

	C3G histologic index score LS mean 95% CI	-3.482 (-4.721 to -2.244)	-2.480 (-3.775 to -1.186)	
	% C3c staining on renal biopsy Proportion 95% CI	0.908 (0.651;0.981)	0.265 (0.079;0.602)	
	eGFR LS mean 95% CI	-1.497 (-5.892 to 2.899)	-7.808 (-11.570 to -4.047)	

Effect estimate per comparison	Primary endpoint uPCR	Comparison groups	Pegcetacoplan - Placebo
		Difference in LS mean	-1.144
		95% CI	(-1.437 to -0.851)
		P-value	<.0001
	Secondary endpoint Composite endpoint (uPCR and eGFR)	Comparison groups	Pegcetacoplan - Placebo
		Difference in proportion	0.456
		95% CI	(0.212, 0.700)
		P-value	<.0001
	Secondary endpoint % uPCR	Comparison groups	Pegcetacoplan - Placebo
		Difference in proportion	0.527
		95% CI	(0.292, 0.762)
		P-value	<.0001
	Secondary endpoint C3G histologic index score	Comparison groups	Pegcetacoplan - Placebo
		Difference in LS mean	-1.002
		95% CI	(-2.803, 0.798)
		P-value	.2753
	Secondary endpoint % C3c staining on renal biopsy	Comparison groups	Pegcetacoplan - Placebo
		Difference in proportion	0.643
		95% CI	(0.414, 0.872)

		P-value	<.0001
	Secondary endpoint eGFR	Comparison groups	Pegcetacoplan - Placebo
		Difference in LS mean	6.312
		95% CI	(0.501-12.122)
		P-value	.0333
Analysis description	**Secondary analysis**		
	Hierarchical testing was stopped after the third key secondary endpoint (C3G histologic index activity score).		

Supportive studies

APL2-C3G-204: an open-label, randomised, controlled, phase 2 study in participants who had posttransplant recurrence of C3G or primary IC-MPGN. Participants were randomised 3:1 to group 1 (pegcetacoplan treatment for 52 weeks) or group 2 (no pegcetacoplan treatment for the first 12 weeks followed by pegcetacoplan treatment for the remaining 40 weeks). There were 2 parts: Part A, the core study and Part B, a long-term extension to continue receiving pegcetacoplan until it is commercially available for the disease under study.

Key inclusion criteria were age ≥18 years at screening; clinical and pathologic evidence of recurrent C3G or IC-MPGN; stable (not improving) or worsening kidney disease in the 2 months before the first dose of pegcetacoplan; stable and optimised treatment of recurrent C3G/IC-MPGN for at least 4 weeks *prior* to the screening; eGFR ≥15 mL/min/1.73 m^2. Primary objective was to evaluate efficacy of pegcetacoplan in improving the underlying pathophysiology of C3G/IC-MPGN after 12 weeks of treatment.

A total of 13 participants were enrolled (10 in group 1; 3 in group 2) and all completed the controlled portion. Reduction in C3c staining at week 12 (primary endpoint) was observed in 50% of the participants in pegcetacoplan group and in 33.3% of the participants in placebo group. On the overall controlled and non-controlled periods, mean (SD) eGFR changed from 52.3 (12.11) mL/min/1.73 m^2 at baseline to 57.3 (25.12) mL/min/1.73 m^2 at week 52, and median eGFR changed from 50.5 mL/min/1.73 m^2 at baseline to 58.5 mL/min/1.73 m^2 at week 52. No particular trend can be observed across two groups from baseline to week 12. From Week 12 to Week 40 (all patients on pegcetacoplan), the values seem stable over the time.

APL2-C3G-314: an open-label, single-arm, multicentre study to evaluate the long-term safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with C3G or IC-MPGN who had completed participation in APL2-C3G-310 and who had experienced clinical benefit from treatment. Enrolment was for a minimum of 120 weeks (53 patients). Data from study APL2-C3G-310 were pooled and summarised by the treatment group assigned ("pegcetacoplan to pegcetacoplan" or "placebo to pegcetacoplan"). The efficacy analysis was mainly performed based on the 314 ITT set, but some analyses were also conducted using the 310 ITT set and the re-aligned ITT/safety set in order to show efficacy trends for all patients receiving treatment. Proteinuria was stable beyond week 26 in patients from the RCP pegcetacoplan group. In patients from the RCP placebo group and switched on pegcetacoplan during the OLP, the curve draws near the RCP pegcetacoplan group beyond Week 26. Regarding eGFR, the renal function seems stable over time.

APL2-201: a prospective, open-label, single-arm trial to evaluate safety and efficacy of pegcetacoplan in treatment–naive patients with IgAN, LN, PMN or C3G. It consisted of 2 parts: Part A was a 48-week treatment period; Part B was a long-term extension study. Key inclusion criteria for the C3G cohort were age ≥16 years at screening; diagnosis of C3G; proteinuria, defined as a 24-hour uPCR >750 mg/g; eGFR ≥30 mL/min per 1.73 m^2; stable or worsening kidney disease while on stable/optimised treatment for ≥2 months prior to first dose of pegcetacoplan. The primary efficacy endpoint was proteinuria reduction from baseline to week 48 based on uPCR. The secondary efficacy endpoints for part A of the study were changes from baseline in disease biomarkers, complete clinical remission, stabilisation/improvement in eGFR. In total, 21 subjects entered the study. The reduction in proteinuria (SE) from baseline to Week 48 appears consistent with the results of the phase 3, while the magnitude of the effect at week 26 is smaller. Based on change in eGFR, renal function seems quite stable over the 1-year period.

2.4.2. Discussion on clinical efficacy

The claimed indication is:

"the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN)."

This indication was revised by the CHMP in course of the evaluation, as discussed below.

Design and conduct of clinical studies

Study APL2-C3G-310: pivotal phase 3 study, a randomised, placebo-controlled, double-blinded, multicenter trial conducted in patient with C3G or IC-MPGN. The overall features of the design are acceptable. Considering the rarity of the diseases, the demonstration of the efficacy based on a single pivotal study could be acceptable, as described in the *Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation application (EMA/CHMP/458061/2024)*.

The study consists of 4 periods, of which the key part is the RCP of 26 weeks' duration. There was then an OLP of 26 weeks (interim data up to week 52). The study population was adults and adolescents (≥12 years, ≥30 kg) with primary C3G or IC-MPGN, including those with a history of renal transplantation. The inclusion of adolescents is in line with the granted PIP. Participants showed evidence of active kidney disease, either through renal biopsy with ≥2+ C3c staining or, for adolescents without biopsy, alternative markers like low serum C3, high sC5b-9, active urinary sediment, or presence of C3 nephritic factor. Eligible individuals also had proteinuria ≥1 g/day, and eGFR ≥30 mL/min/1.73 m^2, indicating mild or moderate kidney damage; patients with severe renal impairment were excluded. Participants could be on a stable dose of ACE inhibitor, ARB and/or SGLT2 inhibitor. Overall, the selection criteria were considered acceptable, however, the CHMP noted that IC-MPGN is characterised by glomerular deposits of immune complexes containing both Ig and complement proteins; in some patients, dominant immune drivers may be immunoglobulins, with weaker C3 staining. Low C3 staining (<2+) does not exclude active or severe IC-MPGN. In the trials, two participants with low/absent C3c intensity showed response to pegcetacoplan despite minimal biopsy staining. The MAH reported in one case uPCR decreasing by 46% after 40 weeks despite C3c 1+ on biopsy and in the other case, a rapid uPCR reduction after treatment initiation even when C3c was 0 and serum C3 remained low. Mechanistic rationale was clearly described supporting efficacy in low-C3 patients, acknowledging the small sample size. The choice of the placebo as comparator is acceptable.

The proposed dose in adults is 1080 mg administered SC twice weekly, resulting in systemic exposures of pegcetacoplan similar to those seen in study APL2-201 and studies in PNH. Modelling-based simulations were performed for adolescents using an adult PK model from 10 clinical studies and demonstrated that model-predicted exposure matched the adult reference when adjusted for age and weight. The posology section of the SmPC was updated to reflect this dosing regimen.

Patients were allowed to remain on all medications relevant to their renal disease during the study if on stable dose for at least 12 weeks prior to randomisation. This is agreed, in particular in the context of a study *versus* placebo. However, the MAH was requested to discuss how the available data support the originally claimed stand-alone indication rather than an on-top treatment. Following the receipt of the responses, it was clarified that since RAS inhibitors were used concomitantly in 91.1% of patients in Study APL2-C3G-310 and 100% in Study APL2-C3G-204, the indication should be appropriately limited co-medication wording to RAS inhibitors, without reference to immunosuppressants. Data on stand-alone indication were scarce, and therefore, the MAH did not claim it anymore. The indication wording was revised accordingly to accurately reflect the study population:

"treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated"

The primary endpoint was the log-transformed ratio of uPCR at week 26 compared to baseline. According to the guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016), the recommended primary endpoint is the GFR and reduction in proteinuria is a surrogate marker not yet a fully validated predictor of long-term outcome. However, the 52-week data show good stabilisation of eGFR and in addition, there is sufficient literature reporting on increasing body of real-world evidence that proteinuria reduction in patients with C3G or primary IC-MPGN is associated with a reduction in the risk of developing kidney failure. Based on the provided overall body of clinical evidence from other efficacy endpoints, literature references, as well as 1-year data suggesting a maintenance of the effect over the time, and also considering the rarity of the conditions, the primary clinical efficacy findings are accepted and agreed by the CHMP. Furthermore, Study APL2 C3G 314 will evaluate the long-term safety and efficacy of pegcetacoplan in subjects with C3G or primary IC-MPGN, as reflected in the RMP.

The key secondary endpoints were the proportion of subjects with ≥50% reduction in uPCR, the change from baseline in the activity score of the C3G histologic index score (for participants with evaluable renal biopsies), change in eGFR from baseline, and the proportion of participants showing decreases in C3c staining on renal biopsy. The inclusion of these endpoints is fully supported. The MAH has provided the results of analysis of the primary endpoint in uPCR and the secondary endpoints in eGFR using an estimand with all ICEs addressed with treatment policy strategy. Overall, the results are consistent with the original analysis and supportive of the indication and treatment of pegcetacoplan in C3G and IC-MPGN.

The sample size calculated to provide 90% power at 1-sided significance level of 0.025 is acceptable. The hypothesis was assuming a reduction of 60% in uPCR in the pegcetacoplan group at week 26 *vs* a reduction of 20% in uPCR in the placebo arm based on the phase 2 APL-201 study. The method of randomisation and the 1:1 ratio are acceptable, as was the blinding strategy. Primary and key secondary analysis were conducted in the ITT population; PP population was used providing supplemental analyses. An approach using the concept of estimands was well established, including for the primary and key secondary analysis. ICEs (use of prohibited rescue

medication, initiation of renal replacement therapy, permanent discontinuation of study treatment) and strategies addressing them is acceptable. For key secondary responder analysis, a composite strategy was used to address ICEs; the endpoint status at or after initiation of the ICEs were regarded as non-responder. This is agreed.

Regarding the active treatment, participants with monotone missing data due to prohibited medication, rescue therapies, or treatment discontinuation had missing data imputed based on the placebo arm; this is acceptable. The monotone missing data were imputed assuming MNAR using reference-based methods. The intermediate non-monotone missing data were imputed under MAR, as MNAR imputation at intermediate visits would not be scientifically justified due to surrounding observed data. The robustness of primary endpoint was supported by treating all missing week 26 values as non-responders in the key secondary endpoint (≥50% uPCR reduction). The missing data was hence addressed, with reasonable imputation strategies and sensitivity analyses.

The conduct of the study did not raise important issues and demographic characteristics were well balanced across the two arms. About 77.4% of participants had C3G and 22.6% had IC-MPGN.

Efficacy data and additional analyses

Pivotal phase 3 study APL2-C3G-310: Among the 124 participants enrolled, 116 have completed the 26-weeks RCP (59 in the pegcetacoplan ram and 57 in the placebo arm: 6 subjects have discontinued the study treatment (2 in the pegcetacoplan group and 4 in the placebo group), and 6 subjects have discontinued the study (also respectively 2 and 4). All patients enrolled in the study (n=124) were included in the ITT set. The primary endpoint was met. The difference in LS mean of log-transformed uPCR between pegcetacoplan and placebo was -1.144 (95% CI: -1.437 to -0.851]; P <.0001). The LS mean was (SE) -1.115 (0.1356) in the pegcetacoplan group and 0.029 (0.0606) in the placebo group. Overall, the supplemental and sensitivity analysis were consistent with the primary analysis. This corresponds to a 67.2% proteinuria reduction at week 26 in the pegcetacoplan group and a 2.9% increase in the placebo group compared to baseline. Regarding the validity, while 67.2% reduction in the pegcetacoplan group is consistent with the hypothesis used for the sample size calculation, a larger difference was seen for placebo. Hence, the MAH provided plots illustrating individual urine creatinine levels as changes from baseline, measured in the first morning void in the RCP of APL2-C3G-310 for both treatment groups. The urine creatinine levels remain overall stable in the majority of the subjects. Additionally, the MAH relies on the analysis in the creatinine-independent absolute proteinuria levels, which are consistent with the primary result, which is reassuring.

The first key secondary endpoint was met. 49.21% of the patients in the pegcetacoplan group achieved the composite renal endpoint (stable or improved eGFR [≤ 15% reduction in eGFR] and a ≥50% reduction in uPCR at Week 26) vs 3.28% in the placebo group. The difference in proportion was 45.6% (95% CI: 21.2;70.0, p < .0001). The proportion of participants who achieved a ≥50% reduction in uPCR at Week 26 was 60.32% in the pegcetacoplan group vs 4.92% in the placebo group. The difference in proportion was 52.7% (95% CI: 29.2;0.762, p < .0001). The difference appears quite large and is supportive of the findings from the primary endpoints. The study failed to show a statistically significant difference in change C3G Histologic Index Score from baseline at Week 26. The LS mean (SE) was -3.482 (0.6317) in the pegcetacoplan and -2.480 (0.6602) in the placebo group; the difference (95% CI) in LS mean (pegcetacoplan *vs* placebo) -1.002 (95%CI: -2.803;0.798, p=0.2753). The MAH explained that this endpoint may not be suitable for measuring longitudinal treatment effects and the subsequent results are seen as exploratory only.

Regarding the decrease in C3c staining on kidney biopsy, the proportion of participants who had a reduction in C3c staining on kidney biopsy of at least 2 orders of magnitude of intensity of immunofluorescence from baseline at Week 26 was 74.29% in the pegcetacoplan group vs 11.76% in the placebo group. The difference (95% CI) in proportion between the two groups was 64.3% (41.4;87.2). This is supportive of the pharmacodynamics effects seen in increase of C3 serum level and decrease in sC5b-9 plasma level. No significant difference was observed in the change from baseline in the EQ-VAS score at week 26.

Of the 123 participants exposed to pegcetacoplan, 5 (4.0%) participants developed anti-pegcetacoplan peptide neutralizing antibodies (NAbs), which is quite limited. In their answer to the CHMP's request, the MAH provided the individual data of these patients, and these do not suggest an impact of the NAbs on the efficacy.

Supportive studies: Overall, the results, even with some limitations, were consistent with the Phase 3 study APL2-C3G-310. Study APL2-C3G-204 had different eligibility cut-offs compared to APL2-C3G-310. Study APL2-C3G-310 had a higher baseline eGFR cutoff of ≥30 mL/min/1.73 m^2, including participants with at least 1 g/day of proteinuria and a uPCR ≥1000 mg/g in 2 FMU samples. Therefore, participants likely had significant kidney damage. Study APL2-C3G-204 allowed for a lower eGFR cutoff of ≥15 mL/min/1.73 m^2, however enrolled participants had baseline eGFR ranging from 30 to 72 mL/min/1.73 m^2, also reflecting a population with an impaired kidney function and a broader range of proteinuria severity.

The currently limited long-term efficacy data will be complemented in post-authorisation by the extension APL2-C3G-314 study (cat. 3 in the RMP) evaluating the long-term safety and efficacy of pegcetacoplan in patients who had completed participation in the phase 3 study APL2-C3G-310 (beyond Week 52).

Analysis across trials: Pooled analyses of efficacy were not performed due to the heterogeneity of clinical studies, which is endorsed. However, descriptive comparisons for several endpoints are presented and assessed. Proteinuria decreased with pegcetacoplan in studies 310 (RCP and OLE), LTE Study 314 and in the phase 2 Study 204. The effect was sustained across subgroups (C3G or primary IC-MPGN, adults or adolescents, native disease or post-transplant recurrent disease, baseline immunosuppressant use present or absent). Those receiving pegcetacoplan show a smaller magnitude of eGFR decrease over time compared to participants on placebo. This decrease sustained over time, after reaching a maximum at around 12 weeks of treatment.

2.4.3. Conclusions on the clinical efficacy

Demonstration of efficacy is based on a single pivotal randomised, parallel, placebo-controlled, double blind phase 3 study and three supportive studies. Considering the clinical efficacy data obtained, namely the statistically significant effect observed on primary efficacy endpoint of the log-transformed ratio of uPCR at week 26 compared to baseline, and on majority of the secondary key efficacy endpoints. Hence, the clinical efficacy of pegcetacoplan is considered established. As for the long-term data, these are expected to be collected *via* the post-authorisation follow up; besides the ongoing long-term extension studies APL2-C3G-204 and APL2-C3G-314 (in the RMP), the MAH is conducting a phase 4 multi-country study to monitor real-world effectiveness, safety, patient-reported outcomes, and biomarkers. The MAH will report all findings in the regular PSURs and post-authorisation measures reports. The relevant efficacy data are reflected in the updated SmPC, which was agreed by the CHMP.

2.5. Clinical safety

Introduction

At the time of initial approval of pegcetacoplan for the treatment of patients with PNH in Europe, there was a limited database of patients exposed and the duration of exposure, especially in chronic use. The most prominent AEs were diarrhoea and infusion site reactions. Immunogenicity is an important potential risk in the EU RMP and is included as a safety concern monitored in the PASS. Serious infections are an important potential risk in the RMP with additional risk mitigation measure using registry data. Malignancies and haematological abnormalities are also important potential risks in the RMP and are monitored in PSURs and PASS.

The safety of pegcetacoplan in patients with C3G and primary IC-MPGN was investigated in pivotal study APL2 C3G 310 and 3 supportive studies APL2 C3G 314, APL2 C3G 204, and APL2 201.

Patient exposure

Table 17. Available data to support the proposed indication (status at initial submission)

Study and Population	Period (Treatment)	Status	Date of Safety Data
APL2-C3G-310 C3G or primary IC-MPGN in native or transplant kidney ≥12 years of age	RCP: 26 wks with pegcetacoplan or placebo	Complete	Safety data as of 20 June 2024
	OLP: 26 wks with pegcetacoplan	Ongoing	Safety data as of 20 June 2024[a]
			Late-breaking safety data as of 20 September 2024
APL2-C3G-314 C3G or primary IC-MPGN in native or transplant kidney (who completed APL2-C3G-310) ≥12 years of age	LTE with pegcetacoplan for a minimum of 120 wks	Ongoing	Safety data (LTE) as of data cut 20 June 2024[a]
			Late-breaking safety data as of 20 September 2024
APL2-C3G-204 C3G or primary IC-MPGN in transplant kidney ≥18 years of age	Part A controlled period:12 wks with pegcetacoplan or no pegcetacoplan	Complete	Safety data (LTE) as of 19 January 2024
	Part A uncontrolled period: 40 wks with pegcetacoplan	Complete	
	Part B: LTE with pegcetacoplan	Ongoing	Safety data (LTE) as of 13 May 2024
			Late-breaking safety data as of 20 September 2024
APL2-201 C3G in native kidney ≥16 years of age	Part A: 48 wks with pegcetacoplan	Complete	Safety data (LTE; approximately 4 yrs)
	Part B: LTE with pegcetacoplan	Complete	

Abbreviations: C3G = C3 glomerulopathy; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; LTE = long-term extension; OLP = open-label period, RCP = randomized controlled period; wks = weeks.

[a] The data cutoff date for Studies APL2-C3G-310 and APL2-C3G-314 was 20 June 2024; however, for 4 participants, additional data from Study APL2-C3G-310 out to 26 June 2024 was also included.

Study APL2-C3G-310: During the RCP, a total of 124 participants received at least 1 dose of study drug during the RCP. Sixty-three participants received pegcetacoplan and 61 participants received placebo. The mean durations of treatment were similar between treatment groups: 181.9 days in the pegcetacoplan group (range: 1 to 207 days) and 176.1 days in the placebo group (range: 60 to 204 days). During the OLP, a total of 116 participants received at least one dose of study drug during the OLP up to the reported analysis cutoff date. Fifty-three participants continued from the RCP pegcetacoplan group and maintained their pegcetacoplan treatment, while 48 participants

continued from the RCP placebo group and began receiving pegcetacoplan for the first time. During the OLP, the mean duration of treatment with pegcetacoplan was similar between treatment groups and was an additional 111.6 days in the pegcetacoplan-to-pegcetacoplan group and 103.1 days in the placebo-to-pegcetacoplan groups.

Study APL2-C3G-314: For the 120 participants in the re-aligned safety set, the median duration of treatment was 242.5 days since the first dose of pegcetacoplan; 118 (98.3%) participants received at least one infusion.

Study APL2-C3G-204: In group 1, the mean total dose administered was 24,840.0 (2693.99) mg, and the mean duration of treatment was 80.3 days. All participants in group 1 received at least 1 infusion, with 3 participants missing at least 1 infusion, 1 participant having 1 or more incomplete infusions, and 3 participants having at least 1 interrupted infusion. Group 2 was consistent with the protocol and did not have any IP exposure.

Study APL2- 201: For total dose administered, all subjects (n = 21) received doses of 360 mg daily; 12 subjects (5 subjects in the IgAN cohort and 7 subjects in the C3G cohort) received at least one dose of 1080 mg twice weekly.

Additional safety data: Adolescents were included in trials APL2 C3G 310 and APL2 201; patients with post-transplant disease recurrence were included in trials APL2 C3G 310 and APL2 C3G 204.

Prior and concomitant medications: These were medicines taken on or after the first administration of IP, especially immunosuppressives, angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARB), systemic corticosteroids, and sodium glucose cotransporter 2 inhibitors. Over 90% of participants across all studies received ACEIs, ARBs. Most participants across studies received immunosuppressants, and >30% of participants received corticosteroids.

Adverse events

Table 18. Overview of Safety Data for Study APL2-C3G-310 (safety population)

	Study APL2-C3G-310		
Category of AE, n (%)	**26-week RCP**		**Total OLP[a]**
	Placebo	**Pegcetacoplan**	**Pegcetacoplan**
	(N = 61)	**(N = 63)**	**(N = 116)**
All AEs	57 (93.4)	53 (84.1)	70 (60.3)
Treatment-related AEs	26 (42.6)	25 (39.7)	24 (20.7)
Infusion-related AEs	16 (26.2)	21 (33.3)	15 (12.9)
SAEs	6 (9.8)	6 (9.5)	7 (6.0)
Maximum severity of AEs			
Mild	26 (42.6)	27 (42.9)	40 (34.5)
Moderate	27 (44.3)	23 (36.5)	24 (20.7)
Severe	4 (6.6)	3 (4.8)	6 (5.2)

	(N = 61)	(N = 63)	(N = 116)
AE leading to treatment withdrawn	2 (3.3)	2 (3.2)	1 (0.9)
AEs leading to dose interruption	12 (19.7)	7 (11.1)	12 (10.3)
AEs leading to study discontinuation	1 (1.6)	1 (1.6)	1 (0.9)
AEs leading to death	0	1 (1.6)	0
Rejection episodes	0	0	0
Graft loss (renal transplant)	0	0	0

Abbreviations: AE = adverse event; n = number of unique participants in statistic; N = number of participants in study group; OLP = open-label period; RCP = randomized controlled period; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Total OLP refers to only participants enrolled in OLP and does not include events happening during RCP.

Notes: A TEAE was defined as any new AE that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count, and the event was counted only once in the total unique events count. All occurrences were counted in the total events count. A treatment related AE was defined as a TEAE with a relationship to study drug of definitely related or possibly related. Any AEs with missing or unknown relationship were considered as related to study drug. Rejection episodes and graft loss (renal transplant) were summarized for participants with posttransplant disease recurrence only. The percentage was based on participant population with posttransplant disease recurrence. TEAEs were referred to as AEs in this table.

Treatment Emergent Adverse Events (TEAE)

Study APL2-C3G-310, RCP

TEAEs by age group

Adolescents: The number of participants who had a TEAE during the RCP was similar: 23 (82.1%) in the pegcetacoplan and 26 (96.3%) participants in the placebo group; most were mild or moderate. Adults: The number of participants who had a TEAE during the RCP was similar: 30 (85.7%) participants in the pegcetacoplan group and 31 (91.2%) participants in the placebo group. See Table 19 below for the overview of reported TEAEs *per* age group.

Table 19. Overall summary of TEAEs by age group during the RCP (safety set)

Adolescents (12 to 17 years) **Events**	**Pegcetacoplan** **(N = 28)** **n (%)**	**Placebo** **(N = 27)** **n (%)**
Any TEAE	23 (82.1)	26 (96.3)
Treatment-related TEAE	13 (46.4)	11 (40.7)
Infusion related TEAEs	9 (32.1)	7 (25.9)
Serious TEAE	3 (10.7)	3 (11.1)
Maximum severity of TEAEs		
Mild	12 (42.9)	11 (40.7)
Moderate	9 (32.1)	14 (51.9)
Severe	2 (7.1)	1 (3.7)
Infusion site reaction	8 (28.6)	7 (25.9)
TEAE leading to treatment withdrawn	1 (3.6)	2 (7.4)
TEAE leading to dose interruption	2 (7.1)	6 (22.2)
TEAE leading to study discontinuation	0	1 (3.7)
TEAE leading to death	0	0
Rejection episodes	0	0
Graft loss	0	0

Adults ≥18 years Events	Pegcetacoplan (N = 35) n (%)	Placebo (N = 34) n (%)
Any TEAE	30 (85.7)	31 (91.2)
Treatment-related TEAE	12 (34.3)	15 (44.1)
Infusion related TEAEs	12 (34.3)	9 (26.5)
Serious TEAE	3 (8.6)	3 (8.8)
Maximum severity of TEAEs		
Mild	15 (42.9)	15 (44.1)
Moderate	14 (40.0)	13 (38.2)
Severe	1 (2.9)	3 (8.8)
Infusion site reaction	10 (28.6)	10 (29.4)
TEAE leading to treatment withdrawn	1 (2.9)	0
TEAE leading to dose interruption	5 (14.3)	6 (17.6)
TEAE leading to study discontinuation	1 (2.9)	0
TEAE leading to death	1 (2.9)	
Rejection episodes	0	0
Graft loss	0	0

Abbreviation: n = number of participants; TEAE = treatment-emergent adverse event.
Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. A treatment-related AE was defined as a TEAE with a relationship to study drug of definitely related, or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug. Rejection episodes and graft loss were summarized for posttransplant participant only. Percentage was based on posttransplant participant.

TEAEs by transplant history

Nontransplant: The number of participants who had a TEAE during the RCP was similar: 48 (82.8%) in the pegcetacoplan and 53 (93.0%) in the placebo group; most were mild or moderate. Posttransplant: The number of participants who had a TEAE during the RCP was similar: 5 (100%) in the pegcetacoplan and 4 (100%) in the placebo group. See Table 20 below for the overview of reported TEAEs *per tr*ansplant history.

Table 20. Overall Summary of TEAEs by Transplant History During the RCP (Safety Set)

Posttransplant Events	Pegcetacoplan (N = 5) n (%)	Placebo (N = 4) n (%)
Any TEAE number of participants	5 (100)	4 (100)
Treatment-related TEAE	1 (20.0)	2 (50.0)
Infusion related TEAEs	1 (20.0)	0
Serious TEAE	0	2 (50.0)
Maximum severity of TEAEs		
Mild	3 (60.0)	1 (25.0)
Moderate	2 (40.0)	2 (50.0)
Severe	0	1 (25.0)
Infusion site reaction	1 (20.0)	0
TEAE leading to treatment withdrawn	0	0
TEAE leading to dose interruption	1 (20.0)	1 (25.0)
TEAE leading to study discontinuation	0	0
TEAE leading to death	0	0
Rejection episodes	0	0
Graft loss	0	0

Abbreviation: n = number of participants; TEAE = treatment-emergent adverse event.
Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event is counted only once in the total unique events count, but all occurrences were counted in the total events count.
Note: A treatment-related AE was defined as a TEAE with a relationship to study drug of definitely related, or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug.
Rejection episodes and graft loss was summarized for posttransplant participant only. Percentage was based on posttransplant participant.

Most common reported TEAE

The most frequently reported (≥40%) TEAEs by SOC included infections and infestations (pegcetacoplan: 35 [55.6%]; placebo: 27 [44.3%]), and general disorders and administration site conditions (pegcetacoplan: 29 [46.0%]; placebo: 29 [47.5%]). The most commonly reported TEAEs (≥10%) in either group were pyrexia, nasopharyngitis, headache and vomiting.The following TEAEs were reported by ≥5% of participants in the pegcetacoplan group than placebo: pyrexia, nasopharyngitis, influenza, nausea, cough, contusion, acute kidney injury, fatigue. All of these events were observed in the PNH indication or similar class products.

Study APL2-C3G-310, OLP

TEAEs by age group

Adolescents: The number of participants who had any TEAE was: 15 (57.7%) in the pegcetacoplan-to-pegcetacoplan and 16 (64.0%) in the placebo-to-pegcetacoplan group, most were mild or moderate. Adults: The number of participants who had any TEAE was 22 (66.7%) in the pegcetacoplan-to-pegcetacoplan and 17 (53.1%) in the placebo-to-pegcetacoplan group; most were mild or moderate. See Table 21 below for the overview of reported TEAEs *per* age group.

Table 21. Overall Summary of TEAEs by Age Group During the OLP (Safety Set)

Adolescents (12 to 17 years) Events	Pegcetacoplan-to-pegcetacoplan (N = 26) n (%)	Placebo-to-pegcetacoplan (N = 25) n (%)	Total (N = 51) n (%)
Any TEAE	15 (57.7)	16 (64.0)	31 (60.8)
Treatment-related TEAE	5 (19.2)	7 (28.0)	12 (23.5)
Infusion related TEAEs	3 (11.5)	6 (24.0)	9 (17.6)
Serious TEAE	1 (3.8)	2 (8.0)	3 (5.9)
Maximum severity of TEAEs			
Mild	8 (30.8)	10 (40.0)	18 (35.3)
Moderate	6 (23.1)	4 (16.0)	10 (19.6)
Severe	1 (3.8)	2 (8.0)	3 (5.9)
Infusion site reaction	2 (7.7)	5 (20.0)	7 (13.7)
TEAE leading to treatment withdrawn	0	0	0
TEAE leading to dose interruption	2 (7.7)	3 (12.0)	5 (9.8)
TEAE leading to study discontinuation	0	0	0
TEAE leading to death	0	0	0
Rejection episodes	0	0	0
Graft loss	0	0	0

Adults ≥18 years Events	Pegcetacoplan-to-pegcetacoplan (N = 33) n (%)	Placebo-to-pegcetacoplan (N = 32) n (%)	Total (N = 65) n (%)
Any TEAE	22 (66.7)	17 (53.1)	39 (60.0)
Treatment-related TEAE	3 (9.1)	9 (28.1)	12 (18.5)
Infusion related TEAEs	2 (6.1)	4 (12.5)	6 (9.2)
Serious TEAE	3 (9.1)	1 (3.1)	4 (6.2)
Maximum severity of TEAEs			
Mild	13 (39.4)	9 (28.1)	22 (33.8)
Moderate	8 (24.2)	6 (18.8)	14 (21.5)
Severe	1 (3.0)	2 (6.3)	3 (4.6)
Infusion site reaction	3 (9.1)	6 (18.8)	9 (13.8)
TEAE leading to treatment withdrawn	0	1 (3.1)	1 (1.5)
TEAE leading to dose interruption	4 (12.1)	3 (9.4)	7 (10.8)
TEAE leading to study discontinuation	0	1 (3.1)	1 (1.5)
TEAE leading to death	0	0	0
Rejection episodes	0	0	0
Graft loss	0	0	0

Abbreviations: n = number of participants; TEAE = treatment-emergent adverse event.

Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. A treatment-related AE was defined as a TEAE with a relationship to study drug of definitely related, or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug. Rejection episodes and graft loss were summarized for posttransplant participant only. Percentage was based on posttransplant participant.

TEAEs by transplant history

Nontransplant: The number of participants who had any TEAE was: 35 (64.8%) in the pegcetacoplan-to-pegcetacoplan and 31 (58.5%) in the placebo-to-pegcetacoplan group; most were mild or moderate. Posttransplant: The number of participants who had any TEAE was 2 (40.0%) in the pegcetacoplan-to-pegcetacoplan and 2 (50.0%) in the placebo-to-pegcetacoplan group; most were mild or moderate. See Table 22 below for the overview of reported TEAEs *per tr*ansplant history.

Table 22. Overall Summary of TEAEs by Transplant History During the OLP (Safety Set)

Nontransplant Events	Pegcetacoplan-to-pegcetacoplan (N = 54) n (%)	Placebo-to-pegcetacoplan (N = 53) n (%)	Total (N = 107) n (%)
Any TEAE	35 (64.8)	31 (58.5)	66 (61.7)
Treatment-related TEAE	7 (13.0)	15 (28.3)	22 (20.6)
Infusion related TEAEs	5 (9.3)	10 (18.9)	15 (14.0)
Serious TEAE	4 (7.4)	2 (3.8)	6 (5.6)

Nontransplant Events	Pegcetacoplan-to-pegcetacoplan (N = 54) n (%)	Placebo-to-pegcetacoplan (N = 53) n (%)	Total (N = 107) n (%)
Maximum severity of TEAEs			
Mild	20 (37.0)	18 (34.0)	38 (35.5)
Moderate	13 (24.1)	10 (18.9)	23 (21.5)
Severe	2 (3.7)	3 (5.7)	5 (4.7)
Infusion site reaction	5 (9.3)	10 (18.9)	15 (14.0)
TEAE leading to treatment withdrawn	0	0	0
TEAE leading to dose interruption	6 (11.1)	6 (11.3)	12 (11.2)
TEAE leading to study discontinuation	0	0	0
TEAE leading to death	0	0	0
Rejection episodes	0	0	0
Graft loss	0	0	0

Posttransplant Events	Pegcetacoplan-to-pegcetacoplan (N = 5) n (%)	Placebo-to-pegcetacoplan (N = 4) n (%)	Total (N = 9) n (%)
Any TEAE	2 (40.0)	2 (50.0)	4 (44.4)
Treatment-related TEAE	1 (20.0)	1 (25.0)	2 (22.2)
Infusion related TEAEs	0	0	0
Serious TEAE	0	1 (25.0)	1 (11.1)
Maximum severity of TEAEs			
Mild	1 (20.0)	1 (25.0)	2 (22.2)
Moderate	1 (20.0)	0	1 (11.1)
Severe	0	1 (25.0)	1 (11.1)
Infusion site reaction	0	1 (25.0)	1 (11.1)
TEAE leading to treatment withdrawn	0	1 (25.0)	1 (11.1)
TEAE leading to dose interruption	0	0	0
TEAE leading to study discontinuation	0	1 (25.0)	1 (11.1)
TEAE leading to death	0	0	0
Rejection episodes	0	0	0
Graft loss	0	0	0

Abbreviation: n = number of participants; TEAE = treatment-emergent adverse event.
Notes: A TEAE was defined as any new adverse event that began, or any pre-existing condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count and the event was counted only once in the total unique events count, but all occurrences were counted in the total events count. A treatment-related AE was defined as a TEAE with a relationship to study drug of definitely related, or possibly related. Any AEs with missing or unknown relationship was considered as related to study drug. Rejection episodes and graft loss were summarized for posttransplant participant only. Percentage was based on posttransplant participant.

Most common reported TEAE

The most frequently reported TEAEs during by SOC included infections and infestations (28 [24.1%]), general disorders and administration site conditions (21 [18.1%]), and gastrointestinal disorders (18 [15.5%]). The most frequently reported TEAEs (>5%) in both groups included diarrhoea and vomiting. Generally, TEAEs did not increase over time after adjusting for exposure.

Serious adverse event/deaths/other significant event

Deaths

Study APL2-C3G-310: One death occurred in the RCP: a participant in the pegcetacoplan group, with a history of chronic obstructive pulmonary disease (COPD) and diabetes mellitus, was diagnosed with COVID-19 pneumonia and respiratory failure and died 9 days later of respiratory failure due to COVID-19 pneumonia. COPD and use of immunosuppressants was assessed as the likely cofounders leading towards the development of COVID-19 pneumonia and the subsequent respiratory failure. There were no deaths reported during the OLP.

Studies APL2-C3G-314, APL2-C3G-204, APL2-201: No deaths were reported.

Serious Adverse Events (SAEs)

Study APL2-C3G-310 RCP: Please see Table 23 below.

Table 23. Serious TEAEs by SOC and PT during the RCP (safety set)

System Organ Class Preferred Term	Statistics	Pegcetacoplan N = 63 n (%)	Placebo N = 61 n (%)
Any serious TEAEs	n (%) m	6 (9.5) 9	6 (9.8) 10
Infections and infestations	n (%)	3 (4.8)	1 (1.6)
COVID-19 pneumonia	n (%)	1 (1.6)	0
Influenza	n (%)	1 (1.6)	0
Pneumonia	n (%)	1 (1.6)	0
Viral infection	n (%)	0	1 (1.6)
Renal and urinary disorders	n (%)	2 (3.2)	4 (6.6)
Acute kidney injury	n (%)	1 (1.6)	2 (3.3)
Nephrotic syndrome	n (%)	1 (1.6)	0
Proteinuria	n (%)	0	1 (1.6)
Tubulointerstitial nephritis	n (%)	0	1 (1.6)
General disorders and administration site conditions	n (%)	1 (1.6)	0
Pyrexia	n (%)	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	n (%)	1 (1.6)	0
Respiratory failure	n (%)	1 (1.6)	0
Vascular disorders	n (%)	1 (1.6)	0
Hypertension	n (%)	1 (1.6)	0
Gastrointestinal disorders	n (%)	0	1 (1.6)
Vomiting	n (%)	0	1 (1.6)
Investigations	n (%)	0	1 (1.6)
Blood creatinine increased	n (%)	0	1 (1.6)
Pregnancy, puerperium and perinatal conditions	n (%)	0	1 (1.6)
Abortion spontaneous	n (%)	0	1 (1.6)
Pregnancy	n (%)	0	1 (1.6)

Abbreviations: n = number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event.
Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to System Organ Class and Preferred Term using MedDRA Version 26.0

TEAEs by age group

Adolescents: Six participants had a serious TEAE during: 3 (10.7%) participants with 4 events in the pegcetacoplan and 3 (11.1%) with 6 events in the placebo group. With the exception of AKI, which was reported by 2 participants (7.4%) in the placebo group. No serious TEAEs were reported by more than 1 participant in either group. Adults: Six participants had a serious TEAE during the RCP: 3 (8.6%) participants with 5 events in the pegcetacoplan and 3 (8.8%) with 4 events in the placebo group. No serious TEAEs occurred in more than 1 participant in either group.

SAEs by transplant history

Nontransplant: Ten participants had a serious TEAE during the RCP: 6 (10.3%) participants with 9 events in the pegcetacoplan and 4 (7.0%) with 8 events in the placebo group. With the exception of AKI, which was reported by 2 participants (3.5%) in the placebo group, no serious TEAEs were reported by more than 1 participant in either group. Posttransplant: Two participants (50.0%) in the placebo group had 2 serious TEAEs during the RCP. No serious TEAEs were reported by more than 1 participant in either group.

Study APL2-C3G-310, OLP: Please see Table 24 below.

Table 24. Serious TEAEs by SOC and PT during the OLP (safety set)

System Organ Class Preferred Term	Pegcetacoplan to pegcetacoplan (N = 59) n (%) m	Placebo to pegcetacoplan (N = 57) n (%) m	Total (N = 116) n (%) m
Any serious TEAE	4 (6.8) 8	3 (5.3) 6	7 (6.0) 14
Infections and infestations	2 (3.4)	1 (1.8)	3 (2.6)
Herpes zoster meningoencephalitis	0	1 (1.8)	1 (0.9)
Pneumonia streptococcal	1 (1.7)	0	1 (0.9)
Viral infection	1 (1.7)	0	1 (0.9)
General disorders and administration site conditions	0	1 (1.8)	1 (0.9)
Pyrexia	0	1 (1.8)	1 (0.9)
Injury, poisoning and procedural complications	1 (1.7)	1 (1.8)	2 (1.7)
Post procedural haematoma	1 (1.7)	0	1 (0.9)
Shunt malfunction	0	1 (1.8)	1 (0.9)
Metabolism and nutrition disorders	1 (1.7)	1 (1.8)	2 (1.7)
Dehydration	1 (1.7)	1 (1.8)	2 (1.7)
Hypoalbuminaemia	0	1 (1.8)	1 (0.9)
Renal and urinary disorders	2 (3.4)	0	2 (1.7)
Acute kidney injury	2 (3.4)	0	2 (1.7)
Nephrotic syndrome	1 (1.7)	0	1 (0.9)
Vascular disorders	1 (1.7)	0	1 (0.9)
Hypertensive urgency	1 (1.7)	0	1 (0.9)
Gastrointestinal disorders	0	1 (1.8)	1 (0.9)
Vomiting	0	1 (1.8)	1 (0.9)

Abbreviation: m = number of events; n = number of participants; TEAE= treatment-emergent adverse event.
Notes: A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to System Organ Class and Preferred Term using MedDRA Version 26.0.

SAEs by age group

Adolescents: One participant (3.8%) in the pegcetacoplan-to-pegcetacoplan group reported 3 serious TEAEs (dehydration, viral infection, and AKI) and 2 participants (8.0%) in the placebo-to-pegcetacoplan group reported 5 serious TEAEs (pyrexia, dehydration, hypoalbuminemia, vomiting, and shunt malfunction). Adults: Three participants (9.1%) in the pegcetacoplan-to-pegcetacoplan group reported 5 serious TEAEs (pneumonia streptococcal, post procedural hematoma, AKI, nephrotic syndrome, and hypertensive urgency) and 1 participant (3.1%) in the placebo-to-pegcetacoplan group reported 1 serious TEAE (herpes zoster meningoencephalitis).

SAEs by transplant history

Nontransplant: Four participants (7.4%) in the pegcetacoplan-to-pegcetacoplan group reported 8 serious TEAEs (pneumonia streptococcal, viral infection, post procedural haematoma, dehydration, AKI, nephrotic syndrome, hypertensive urgency) and 2 participants (3.8%) in the placebo-to-pegcetacoplan group reported 5 serious TEAEs (pyrexia, shunt malfunction, dehydration, hypoalbuminemia, vomiting). Posttransplant: One participant (25.0%) had 1 serious TEAE (herpes zoster meningoencephalitis); there were none in the in the placebo-to-pegcetacoplan group.

Study APL2-C3G-314: As of the data cutoff date, only 1 (1.9%) of the 53 participants had experienced SAE in this study; this participant reported SAEs of end stage renal disease and renal impairment, both assessed as not related to pegcetacoplan.

Study APL2-C3G-204: No SAEs were reported in group 2. In group 1, 5 participants (50.0%) had SAEs during the controlled portion, with the most common SOC being renal and urinary disorders

(2 participants [20.0%]). AKI was reported twice in the same participant, and genital herpes simplex and nephropathy toxic were also reported in the same participant. Remaining SAEs were considered not related to the IP by both investigator and sponsor. All SAEs resulted in hospitalisation or prolongation of existing hospitalisation, but none resulted in death, life-threatening outcome, persistent or significant disability or permanent damage. They were considered to be related to the IP due to presence of confounding factors.

Study APL2-201: Nine SAEs were reported in 4 subjects in the PMN cohort. No SAEs were reported in the IgAN, LN, or C3G cohorts and none were considered related to study drug.

Immunogenicity

Study APL2-C3G-310, RCP: During RCP, of the 62 participants exposed to pegcetacoplan who had a baseline result, 47 (75.8%) participants were classified as ADA negative for anti–pegcetacoplan peptide antibodies. Fourteen (22.6%) participants developed a positive treatment-emergent response (ADA positive); and 2 (3.2%) participants developed anti-pegcetacoplan peptide neutralising antibodies. In the placebo group, no participant had anti–pegcetacoplan peptide antibodies. Of 14 ADA positive participants in the pegcetacoplan group, 12 participants (85.7%) reported TEAEs, which included mainly pyrexia and nausea.

Laboratory findings

Laboratory analyses were prespecified and evaluated for studies APL2 C3G 310, APL2 C3G 204, and APL2 201 and *post hoc* haematology labs were evaluated in study APL2 C3G 314. These evaluations did not reveal clinically relevant trends or unexpected safety issue, were consistent with those expected in patients with C3G or primary IC-MPGN. Changes in the parameters were consistent with the efficacy findings that pegcetacoplan improves kidney function.

Safety in special populations

Age group: Adolescents weighing at least 30kg and adults (participants aged ≥18 years) were enrolled in studies APL2 C3G 310 and APL2 C3G 314. As of the data cut-off, the AE profiles were similar between adults and adolescents and between the pegcetacoplan and placebo treated adolescents. The percentages of participants with any AE were lower in pegcetacoplan groups compared to the placebo groups among the adults (85.7% and 91.2%, respectively) and among the adolescents (82.1% vs 96.3%, respectively).

The percentage of adolescents with any AE was lower in the pegcetacoplan than in the placebo treated adolescents: 82.1% (23 of 28 adolescents) and 96.3% (26 of 27 adolescents), respectively. AEs of pyrexia were similar between pegcetacoplan and placebo treated adolescents: 25.0% (7 of 28 adolescents) and 22.2% (6 of 27 adolescents), respectively. When comparing pegcetacoplan treated adolescents to pegcetacoplan treated adults, the percentages of participants with any AE were similar between the adolescents and adults during RCP (82.1% and 85.7%), during OLP (60.8% and 60.0%), and when combining all participants since first dose of pegcetacoplan in Studies APL2 C3G 310 and APL2 C3G 314 (78.0% and 78.6%, each respectively).

The AEs that occurred in adolescents in study APL2 201 are similar to what was observed in Studies APL2 C3G 310 and APL C3G 314.

Serious adverse events: Among the adolescents, the same number of participants in the pegcetacoplan and placebo group had any SAE and number of occurrences of SAEs was similar between the pegcetacoplan treated adolescents and placebo treated adolescents. The only SAEs

occurring in >1 pegcetacoplan treated adolescents were pyrexia and dehydration, and each occurred in 2 of 50 adolescents (4.0%). No SAEs occurred in the adolescents in study APL2 201.

Transplant status: All participants with post-transplant disease recurrence had an AE during RCP, but none of those AEs among the pegcetacoplan treated participants were serious or severe or led to treatment withdrawal. The safety observed in participants with post-transplant disease recurrence is similar to that of the overall systemic pegcetacoplan safety profile.

Safety related to drug-drug interactions and other interactions

Pegcetacoplan has a low potential to inhibit the metabolism of drugs that are substrates of the cytochrome P450 (CYP) isoforms evaluated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). It also has low potential to induce the metabolism of drugs that are substrates of CYP isoforms evaluated (CYP1A2, CYP2B6, and CYP3A4). Pegcetacoplan is neither a substrate nor inhibitor of human drug transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P gp, and breast cancer resistance protein.

Discontinuation due to adverse events

No trends were observed in the AEs leading to treatment withdrawal across studies APL2 C3G 310, APL2 C3G 314, APL2 C3G 204, and APL2 201 (Table 25). Of the 8 AEs that led to treatment withdrawal while on pegcetacoplan, 3 were SAEs, and 4 were assessed by the investigator as possibly related to pegcetacoplan.

Table 25. AEs leading to treatment withdrawal while on pegcetacoplan in APL2-C3G-310, APL2-C3G-314, APL2-C3G-204, and APL2-201

Study	SOC	PT	Seriousness	Relatedness
APL2-C3G-310	General disorders and administration site conditions	Infusion site reaction	Nonserious	Possibly related
	Respiratory, thoracic and mediastinal disorders	Respiratory failure	Serious	Not related
	Infections and infestations	Herpes zoster meningoencephalitis	Serious	Possibly related
APL2-C3G-314	Renal and urinary disorders	Nephrotic syndrome	Nonserious	Not related
	Renal and urinary disorders	End stage renal disease	Serious	Not related
APL2-C3G-204	Investigations	Weight decreased	Nonserious	Possibly related
	Investigations	Weight decreased	Nonserious	Possibly related
APL2-201	Renal and urinary disorders	Chronic kidney disease	Nonserious	Not related

Abbreviations: AE = adverse event; PT = Preferred Term; SOC = System Organ Class.

The percentage of participants withdrawing from treatment due to an AE was low and similar between treatment groups in Study APL2 C3G 310 during RCP: 2 of 63 participants (3.2%) and 2 of 61 participants (3.3%) in the pegcetacoplan and placebo groups, respectively.

Post marketing experience

Pegcetacoplan is approved in the EU, USA, Great Britain, Australia, Saudi Arabia, Canada, Switzerland, Japan, Argentina, Russia, Kuwait, Brazil, and other countries. The estimated cumulative postmarketing exposure is 747 patients and 930.69 patient years (13 May 2024), with

a cumulative total number of postmarketing cases since the international birth date being 295 spontaneous and 58 solicited cases. There have been 834 ADRs in the 295 spontaneous cases, and 223 spontaneous ADRs were serious. There have been 80 serious ADRs in the 58 solicited cases.

Serious spontaneous ADRs (among 223 events) were most frequent in the blood and lymphatic system disorders (94 events) where the most frequent serious spontaneous ADRs by PT were haemolysis (36 events), breakthrough haemolysis (35 events), and thrombocytopenia (8 events). In infections and infestations PT (26 events), the most frequent serious spontaneous ADRs by PT were COVID 19 and pneumonia (3 events each). There have been 112 postmarketing cases involving hypersensitivity; 462 nonserious and 84 serious. The most frequent serious events were anaphylactic reaction/shock; 3 with sufficient information to conclude that these can be considered at least possibly related to pegcetacoplan treatment. The MAH continues to provide safety information in regular PSURs.

2.5.1. Discussion on clinical safety

Safety data for the new indication were derived from the pivotal study APL2 C3G 310 and in 3 supportive studies APL2 C3G 314, APL2 C3G 204, and APL2 201. However, in the overall pegcetacoplan development programme, 605 participants were exposed to pegcetacoplan (1048.42 patient years). In the postmarketing setting, the exposure was 1164 participants (1486.58 patient years), which allows for comparison of the global safety profile with the one reported in the different studies.

Study APL2 C3G 310: Globally, 153 participants were exposed to systemic pegcetacoplan. The number of patients exposed to at least one dose of pegcetacoplan during the 52 weeks of trial was 120. During the RCP and OLP, the mean durations of treatment were similar between treatment groups and during the OLP and the treatment groups from the exposed 124 patients were overall well balanced, but fewer patients with post-transplant recurrence were included (N=9). Compared to C3G, fewer patients with IC-MPGN were also enrolled. In the pooled data configuration of the pivotal study, fewer IC-MPGN patients (N=20) than C3G (N=92) were included.

Pooling updated data from studies APL2-C3G-310, APL2-C3G-314 and APL2-C3G-204 increased the number of post-transplant patients to 22. The incidence of AEs was higher in the post-transplant group than in the non-transplant group (88.9% *vs* 77.5%) during 310/314 studies and 84.6% during 204 study (part A). The most common AEs in post-transplant patients were infections. AKI was reported more frequently in post-transplant participants than in non-transplant participants (22.2% *vs* 4.5%) during the 310/314 studies and even higher in 30.8% of patients in the 204 study. SAEs (11.1% vs 9.9%) and severe AEs (11.1% *vs* 7.2%) occurred more frequently in the post-transplant group than in the non-transplant group during 310/314 studies and in 30.8% (4/13, severe) and 46.2% (6/13, serious) in the 204 study. Based on the available data, the safety profile of post-transplant participants appears to be comparable to that of non-transplant with somewhat higher frequency of severe SAEs, as naturally expected in this population. There was only one post-transplant adolescent in the pivotal study and based on the above conclusion, no differences in safety profile are expected in this sub-group.

Furthermore, when stratifying by transplant status, the differences in terms of serum C3 were mostly not statistically significant nor meaningful, as serum C3 can vary much between patients. Baseline biopsy characteristics were balanced between groups with the exception of glomerular crescents. A special focus on the safety of the 8 patients with crescents was important to appreciate the relatedness of some AEs to the treatment or the ability of the treatment to restore/conserve renal function. It was clarified that 4 out of the 8 participants underwent follow-

up biopsies and no crescents were found, suggesting low clinical significance of that baseline crescents in C3G and IC-MPGN population.

The number of participants who had TEAEs in the RCP was high but similar between the two treatment groups (pyrexia, injection site pain, and injection site swelling). Twelve out of 14 ADA positive participants in the pegcetacoplan group reported TEAEs. The MAH clarified that most ADA responses were transient, resolved spontaneously, and were not associated with any consistent pattern of clinical worsening or loss of efficacy. Neutralizing antibodies did not lead to reduced exposure/diminished pharmacodynamic effects. The results suggest that ADA do not represent a high clinical risk for patients. The SmPC sufficiently informs the prescriber about these findings.

The infusion related TEAEs were similar between the groups during the RCP. Upon further review of common TEAEs of injection site pain, which were mild and non-serious and required no action with study drug, this was deemed coincidental. Most injection site pain events in the placebo group occurred early in treatment and mainly in younger participants, though age distribution was similar across groups. During the OLP, infusion-related TEAEs decreased in participants continuing pegcetacoplan, however, they were higher in the placebo-to-pegcetacoplan group. The MAH conducted a temporal analysis and found that no participants had anti-pegcetacoplan antibodies before switching, and 5 developed them only at Week 52, long after infusion-related TEAEs occurred. Infusion reactions such as mild pruritus or swelling appeared in participants both with and without anti-PEG antibodies, showing no consistent temporal link. All events were non-serious, resolved without treatment modification, and showed no evidence of immunological causality.

In C3G and IC-MPGN clinical studies, 10 serious events of acute kidney injury were reported in 8 patients (5.7%) treated with, of which 5 events were observed in 4 post-transplant patients. Of these serious events, only 1 led to drug withdrawal and 1 to dose interruption. All events recovered and resolved, except the single event that led to drug withdrawal.

Most SAEs reported in APL2-C3G-310 study were expected ADRs of pegcetacoplan. AEs leading to treatment withdrawal were infrequent. Laboratory evaluations did not reveal clinically relevant trends suggesting any unexpected safety issue. No new or confounding safety risks were identified related to comorbidities, concomitant medication use, or mineral supplement interactions.

Supportive studies: To evaluate the long-term safety of pegcetacoplan in the post-transplant population with recurrent disease, pooled data from studies APL2-C3G-310, APL2-C3G-314, and APL2-C3G-204 were analysed by transplant status using exposure-adjusted incidence rates. Infections had exposure adjusted incidence rate (EAIR) of 114.9/100 patient-years in the post-transplant group compared to 80.9 in non-transplant group. Renal disorders had a EAIR of 49.0 vs. 16.0 per 100 patient-years in the non-transplant and it was 25.2 vs 6.3 for AKI. The MAH considered the observed renal toxicity not due to pegcetacoplan but to the underlying disease and heavy immunosuppressive treatment and high baseline risks. Most AKI events resolved without discontinuation of pegcetacoplan treatment. The MAH stated that all patients had preexisting renal disorders but does not clarify whether reported AKIs were new events or recurrent condition. Time-to-event analyses for infections and AKI in patients with post-transplant recurrent disease, stratified by transplant status, using data from Study APL2-C3G-310 and long-term incidence analyses across APL2-C3G-310, 314, and 204 support that pegcetacoplan does not substantially increase infection or AKI risk over time in post-transplant patients. However, the small patient numbers, lack of formal statistical metrics, and limited adjustment for confounders mean the conclusions should be interpreted with caution. SmPC has been updated with the relevant information about AKI.

The planned long-term safety and efficacy study in the extended indication (part of RMP), will collect patient data related to serious infections, serious hypersensitivity reactions, immunogenicity, malignancies and haematologic abnormalities, potential long-term effects of PEG accumulation, and long-term safety (>1 year). Serious adverse reactions are listed in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

Based on the data provided, pegcetacoplan demonstrated manageable safety and tolerability, consistent with its established safety profile. There is no new safety concern arising from the new population studied. The most common serious adverse reactions are listed in section 4.8 of the SmPC. In order to evaluate long term safety and efficacy in the extended indication, the MAH committed to conduct an open-label, non-randomised, multicentre extension study to evaluate the long-term safety and efficacy of pegcetacoplan in participants with C3G or IC-MPGN and more specifically collect information on serious infections, serious hypersensitivity reactions, immunogenicity, malignancies and hematologic abnormalities, potential long term effects of PEG accumulation, and long-term safety (>1 year). This is reflected in the RMP as a category 3 study. Besides this, a phase 4 multi-country study will monitor the real-world effectiveness, safety, patient-reported outcomes, and biomarkers. The MAH will report relevant safety results from all studies and from post-marketing experience in the PSURs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. IVH after drug discontinuation 4. Immunogenicity 5. Malignancies and hematologic abnormalities 6. Potential long-term effects of PEG accumulation

Abbreviations: IVH; Intravascular hemolysis; PEG, Polyethylene glycol.

The MAH initially submitted an updated RMP version 3.2 with this application, which was a subject to modifications during the assessment. The main RMP changes were the following: Update of proposed indication in the relevant sections of the RMP; update with new clinical data from C3G and IC-MPGN studies; update of exposure data concerning clinical studies and post-marketing exposure. The MAH also proposed to conduct a trial to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with C3G or primary IC-MPGN and monitor serious infections, serious hypersensitivity reactions, immunogenicity, malignancies and hematologic abnormalities, potential long-term effects of PEG accumulation, and long-term safety (>1 year). The CHMP received the following PRAC advice on the submitted RMP: The PRAC considered that the updated risk management plan version 5.0 is acceptable.

Pharmacovigilance plan

Table 26. Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
PASS Sobi.PEGCET-301	To evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan	• Serious infections • Serious hypersensitivity reactions • IVH after drug discontinuation (PNH indication only) • Immunogenicity • Malignancies and hematologic abnormalities • Potential long-term of effects of PEG accumulation • Use in patients with BMF (PNH indication only) • Long-term safety (>1 year)	Submission of final protocol: Submission of protocol amendment: Start of data collection: End of data collection: Progress report: Final study report:	Within 6 months of synopsis approval (submitted 13 June 2022) Q4 2024 June 2023 Q3 2029 Within the PSUR Q1 2030
Study APL2-307 **Ongoing**	To evaluate the long-term safety and efficacy of pegcetacoplan in subjects with PNH	• Serious infections • Serious hypersensitivity reactions • IVH after drug discontinuation (PNH indication only) • Immunogenicity • Malignancies and hematologic abnormalities • Potential long-term effects of PEG accumulation • Long-term safety (>1 year)	Final report:	Q2 2026
Study APL2-C3G-314 **Ongoing**	To evaluate the long-term safety and efficacy of pegcetacoplan in subjects with C3G or primary IC-MPGN	• Serious infections • Serious hypersensitivity reactions • Immunogenicity • Malignancies and hematologic abnormalities • Potential long-term effects of PEG accumulation • Long-term safety (>1 year)	Final report	Q4 2027

Abbreviations: BMF, Bone marrow failure; C3G, Complement 3 glomerulopathy; IC-MPGN, Immune-complex membranoproliferative glomerulonephritis; IVH, Intravascular hemolysis; N/A, Not applicable; PASS, Postauthorization safety study; PEG, Polyethylene glycol; PNH, Paroxysmal nocturnal hemoglobinuria; PSUR, Periodic Safety Update Report: Q, Quarter.

Risk minimisation measures

Table 27. Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risks		
Serious infections	Routine risk minimization measures: • SmPC Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet • Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient card • Patient/carer guide • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines) • System for controlled distribution	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension study APL2-307 2. PASS Sobi.PEGCET-301 3. Collection of safety data from long-term extension Study APL2-C3G-314
Serious hypersensitivity reactions	Routine risk minimization measures: • SmPC Section 4.3 and Section 4.4. • Package Leaflet Section 2. Additional risk minimization measures: • Guide for healthcare professionals Patient/carer guide	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301 3. Collection of safety data from long-term extension Study APL2-C3G-314
IVH after drug discontinuation (PNH indication only)	Routine risk minimization measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient/carer guide	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301
Immunogenicity	Routine risk minimization measures: • SmPC Section 4.8 Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301 3. Collection of safety data from long-term extension Study APL2-C3G-314
Malignancies and hematologic abnormalities	Routine risk minimization measures: • None. Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Study Sobi.PEGCET-301
Potential long-term effects of PEG accumulation	Routine risk minimization measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimization measures: • Guide for healthcare professionals	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Study Sobi.PEGCET-301 3. Collection of safety data from long-term extension Study APL2-C3G-314
Missing information		
Use in patients with BMF (PNH indication only)	Routine risk minimization measures: • None Additional risk minimization measures:	Additional pharmacovigilance activities: 1. PASS Study Sobi.PEGCET-301

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• None	
Use in pregnant women	Routine risk minimization measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 Additional risk minimization measures: • None	
Long-term safety (>1 year)	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, and Section 5.2 • Package Leaflet Section 4 Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS (Study Sobi.PEGCET-301) 3. Collection of safety data from long-term extension Study APL2-C3G-314

Abbreviations: BMF, Bone marrow failure; IVH, Intravascular hemolysis; PASS, Post authorization safety study; PEG, Polyethylene glycol; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

2.7. Update of the product information

In this new indication addition, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is also updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP. Please refer to the full PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH has been found acceptable for the following reasons: it is not considered that the updates, made as a consequence of the new therapeutic indication submission, are significant such that a further user-consultation on the readability of the package leaflet would be required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The C3G the IC-MPGN are rare kidney diseases characterised by chronic glomerular inflammation driven by abnormal activation of the complement system. While they share overlapping histologic features, such as mesangial proliferation and capillary wall thickening, they differ in the underlying mechanism of complement involvement. C3G is primarily caused by dysregulation of the alternative complement pathway, often due to genetic mutations or acquired factors such as autoantibodies (e.g., C3 nephritic factor), leading to dominant deposition of complement C3 fragments in the glomeruli with minimal or no immunoglobulin deposition. The IC-MPGN is typically driven by immune complex formation that activates the classical and/or lectin pathways, resulting in deposition of both immunoglobulins and complement components.

3.1.2. Available therapies and unmet medical need

At the time of the submission, there was no authorised product in the targeted indication. The standard of care for C3G and IC-MPGN is supportive and non-specific, aiming to delay progression to end-stage renal disease, such as the use of RAS blockers, ACEi(s) or ARBs, expecting to reduce proteinuria and preserve kidney function. SGLT2 inhibitors are used for their renoprotective effects, though evidence in C3G/IC-MPGN is indirect. Immunosuppressive therapy (corticosteroids, mycophenolate mofetil, cyclophosphamide) can also be used, particularly in IC-MPGN with clear immune complex involvement. Anti-complement therapies eculizumab and ravulizumab are used off-label. The patient care includes management of complications as blood pressure control, treatment of dyslipidaemia, and avoidance of nephrotoxic agents. During this assessment of this procedure, Fabhalta (iptacopan) was approved in the EU for the treatment of adult patients with C3G in combination with a RAS inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.

3.1.3. Main clinical studies

Main efficacy evidence is based on a single pivotal phase 3 study APL2-C3G-310, a randomised, placebo-controlled, double-blinded, multicentre trial conducted in adults and adolescents (≥12 years, ≥30 kg) with C3G or IC-MPGN. The treatment period consists of a randomised controlled period of 26 weeks, and an open-label period of 26 weeks, during which patients from the two initial groups received pegcetacoplan. Overall, 124 subjects were included (63 in the pegcetacoplan and 61 in the placebo arm). Among them, the large majority had native kidney and 9 were posttransplant. Supportive data were derived from:

- 13 patients with post-transplant recurrence of C3G or IC-MPGN enrolled in the open-label, randomised, controlled phase 2 study APL2-C3G-204;

- 8 patients with C3G enrolled in open-label, single-arm phase 2 study APL2-201;

- open-label, non-randomised, multicentre extension study APL2-C3G-314 evaluating the long-term safety and efficacy of pegcetacoplan patients who had completed participation in the phase 3 study APL2-C3G-310 (53 patients enrolled at the cut-off date).

3.2. Favourable effects

- Demographic characteristics were balanced across the two arms of the phase 3 study and the primary endpoint was met. The analysis conducted in a superiority setting (ITT population) showed a statistically significant difference in proteinuria from baseline at Week 26, with a difference in LS mean of log-transformed uPCR between pegcetacoplan and placebo was -1.144 (95% CI: -1.437 to -0.851]; p <.0001). The supplemental and sensitivity analysis as well as majority of the subgroup analysis were consistent with the primary findings.
- The overall 52-week data derived from the pivotal trial show good stabilisation of eGFR and there is sufficient literature reporting on increasing body of real-world evidence that proteinuria reduction in patients with C3G or primary IC-MPGN is associated with a reduction in the risk of developing kidney failure.
- The first key secondary composite endpoint defined as the proportion of participants who achieved at week 26 a ≥ 50% reduction in uPCR and a stable or improved eGFR compared to the baseline visit (15% reduction in eGFR) compared to the baseline visit was also met. The difference in proportion between pegcetacoplan and placebo was 45.6% (95% CI: 21.2;70.0,

p <.0001). Consistent results were found for the proteinuria component which is the second key secondary endpoint. A difference in the proportion of participants who achieved a ≥50% reduction in uPCR at Week 26 of 52.7% (95% CI: 29.2;0.762, p < .0001) between pegcetacoplan and placebo was noted. Beyond the fact that no formal testing could be done on the change on eGFR from baseline at Week 26, a difference (95% CI) in LS mean of 6.312 (0.501-12.122) between pegcetacoplan and placebo was observed.

- Pharmacodynamics parameters support the proposed mechanism of action. An increase of C3 serum level in the pegcetacoplan *vs* placebo group was observed. Plateau was reached around months 1 and 2, remaining stable over time. The sC5b-9 plasma levels decrease with a clear separation of the curve across the pegcetacoplan and the placebo groups. Observed was also a difference in proportion of participants who had a reduction in C3c staining on kidney biopsy of at least 2 orders of magnitude of intensity of immunofluorescence from baseline at Week 26 of 64.3% (CI 95%: 41.4;87.2) between pegcetacoplan and placebo groups.

3.3. Uncertainties and limitations about favourable effects

The 26-weeks duration of the randomised controlled period is rather short. While the trial includes a long-term open-label extension, the absence of a control arm beyond 26 weeks somewhat limits data interpretability. The choice of the primary endpoint initially raised concerns, as the reduction in proteinuria is a currently a surrogate marker, not yet fully validated as a predictor of long-term renal outcome, but the MAH supplied sufficient argumentation including further clinical data and literature reference describing the relevance of proteinuria reduction for the improvement of patients with C3G and IC-MPGN.

Nine patients underwent kidney transplant. Among them, 8 received 1 kidney transplant – 4 in each group – and 1 with two kidney transplants, enrolled in the pegcetacoplan group. The limited scope of this subset raised concerns about the generalisability of the findings, particularly regarding the detection of rare adverse events and the potential influence of immunosuppressive treatments. These uncertainties will be addressed in the planned phase 4, multi-country study (target enrolment of 150 patients with at least 2 years of follow-up) as part of the post-authorisation commitments. The MAH will present relevant safety data from all studies and post-marketing experience in the upcoming PSURs.

While the first key secondary endpoint was met (≥ 50% reduction in uPCR and a stable or improved eGFR compared to the baseline visit [15% reduction in eGFR]), there were some concerns about the construction and the validation of this composite outcome. The results seem driven by the proteinuria; this is another limitation of the relevance of the results. Furthermore, the study did not show a statistically significant difference in change C3G Histologic Index Score from baseline at Week 26 (-3.482 *vs*. -2.480). Given the hierarchical strategy to control the alpha risk, no formal testing is done after this failed analysis, and hence, the subsequent results, including change in eGFR, are seen as exploratory only.

Patient related outcomes measures, such as questionnaires, showed modest benefits of pegcetacoplan.

3.4. Unfavourable effects

The SmPC describes that the most common ADRs in patients with C3G or primary IC-MPGN treated with pegcetacoplan were infusion site reactions and upper respiratory tract infections. The most common serious adverse reactions were acute kidney injury and pneumonia, as reported in the 26-week RCP of APL2-C3G-310 trial.

Patients treated with pegcetacoplan also developed anti–pegcetacoplan peptide antibodies compared to patients treated with placebo (22.6% *vs* 0%). As for the cases of injection site pain, which were mild, non-serious and required no action related to study drug, the observed higher frequency in the placebo group was deemed coincidental.

Pooled data from trials APL2-C3G-310, APL2-C3G-314 and APL2-C3G-204 analysed by transplant status revealed that infections rate, renal disorders and AKI were somewhat higher in the post-transplant compared to non-transplant group.

Laboratory evaluations did not reveal clinically relevant trends suggesting an unexpected safety issue.

3.5. Uncertainties and limitations about unfavourable effects

Safety data are mainly derived from pivotal trial APL2-C3G-310 and 3 additional supportive studies. The overall safety database is limited in terms of number of patients in each disease category and duration of exposure, as well as comparative long-term safety data, but as C3G and IC-MPGN are rare diseases, long term data will be collected in post-authorisation with increased number of patients treated, and this is accepted. Pegcetacoplan was considered to demonstrate a manageable safety and tolerability, consistent with its established profile (see section 4.8 of the SmPC).

In patients who did develop anti–pegcetacoplan peptide antibodies compared to patients treated with placebo, no differences in the incidence of AEs were observed between ADA-positive and ADA-negative pegcetacoplan patients (85.7% and 85.1%), with pyrexia and nausea being the most notable difference. Although hypersensitivity reactions occurred more frequently in ADA-positive (4/14, 28.6%) than in ADA-negative patients treated with pegcetacoplan (4/47, 8.5%), the number of these patients is too small to draw any conclusions and hence, no detectable impact of ADAs on the safety of pegcetacoplan treatment is stated in the SmPC.

In the transplanted patients with post-transplant recurrent C3G or primary IC-MPGN (N=22), included in studies APL2-C3G-310, and APL2-C3G-204, the overall safety profile appeared consistent with that of the general population results; regarding the observed renal toxicity in the post-transplant patients, the MAH considered them not related to pegcetacoplan, but to the underlying disease and heavy immunosuppressive treatment. Most AKI events resolved without discontinuation of treatment. Of note, incomplete medical histories made it impossible to determine whether AKI cases were *de novo* or recurrent.

In the adolescents, pyrexia, nasopharyngitis, vomiting, and abdominal pain were reported. There is a slight difference in the incidence of severe AEs, but the number of participants with severe AEs is too small to draw a firm conclusion, although the safety profile of adolescents appears to be comparable to that of the adults. The relevant ARs are reflected in the SmPC.

With the low number of patients and events in the controlled study period, the assessment of the relationship of an AE to active treatment is limited. However, even in this case and due to the rarity of the conditions, the safety profile of pegcetacoplan remains acceptable since the overall number of events was low, as stated in the SmPC. The updated RMP and post-authorisation commitments are acceptable to follow up on proposed safety uncertainties.

3.6. Effects Table

Table 28. Effects table for pegcetacoplan development plan.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Proteinuria	Change in log-transformed ratio of uPCR at week 26 compared to baseline	LS mean (SE)	1.115 (0.1356)	0.029 (0.0606)	Surrogate endpoint	APL2-C3G-310
Renal composite endpoint	≥50% reduction in uPCR and stable or improved eGFR (≤15% reduction in eGFR), at week 26 compared to baseline	Proportion (SE)	0.490 (0.250; 0.735)	0.034 (0.006; 0.158)	Construction of the endpoint not justified No validation provided	APL2-C3G-310
Responder analysis in proteinuria	Participants with ≥50% reduction in uPCR at Week 26	Proportion (SE)	0.568 (0.312; 0.793)	0.041 (0.009; 0.164)	No validation provided	APL2-C3G-310
eGFR	Change from baseline at week 26	LS mean (SE) in mL/min/ 1.73 m^2	-1.497 (-5.892 to 2.899)	-7.808 (-11.570 to -4.047)	No formal testing could be done because the 3rd key secondary was a failed in the hierarchical testing	APL2-C3G-310
Unfavourable Effects						
			Pegcetacoplan-to-pegcetacoplan (N = 61)	Placebo-to-pegcetacoplan (N = 57)		
Category of AE, n (%)						APL2-C3G-310 (26week RCP)
All AEs		n (%)	47 (77.0)	42 (73.7)		APL2-C3G-310 (26week RCP)
Treatment related AEs		n (%)	10(16.4)	19(33.3)		APL2-C3G-310 (26week RCP)
Infusion related AEs		n (%)	6 (9.8)	12 (21.1)		APL2-C3G-310 (26week RCP)
SAEs		n (%)	6 (9.8)	4 (7.0)		APL2-C3G-310 (26week RCP)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AEs leading to death		n (%)	0	0		APL2-C3G-310 (26week RCP)
SAE **SOC, n (%)** PT, n (%)		n (%)				APL2-C3G-310 (26week RCP)
			Pegcetacoplan (N = 63)	**Placebo(N = 61)**		
Infections and infestations			28 (45.9)	16 (28.1)		
Upper respiratory tract infection			4 (6.6)	1 (1.8)		
General disorders and administration site conditions			16 (26.2)	18 (31.6)		
Gastrointestinal disorders			15 (24.6)	14 (24.6)		
Skin and subcutaneous tissue disorders			10 (16.4)	12 (21.1)		
Respiratory, thoracic and mediastinal disorders			9 (14.8)	7 (12.3)		
Metabolism and nutrition disorders			5 (8.2)	7 (12.3)		
Nervous system disorders			10 (16.4)	7 (12.3)		
Renal and urinary disorders			11 (18.0)	5 (8.8)		
Vascular disorders			7 (11.5)	5 (8.8)		

Notes: Abbreviation: m = number of events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants; OLP = open-label period; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event.
Notes: The column "overall" refers to overall since first dose of pegcetacoplan. A TEAE was defined as any new adverse event that began, or any preexisting condition that worsened in severity, after the first dose of study drug and up to 56 days beyond the last dose of study drug. If a participant had multiple occurrences of a TEAE, the participant was counted only once in the participant count (n) and all occurrences were counted in the total events count (m). Adverse events were coded to SOC and PT using MedDRA version 26.0.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The confirmatory efficacy and safety evidence for pegcetacoplan, a complement C3 inhibitor, intended to bind and block C3 and its cleavage product C3b, is derived from a single pivotal randomised, parallel, placebo-controlled, double blind phase 3 study APL2-C3G-310. The primary endpoint and the two first key secondary endpoints (see sec. 2.4.1) were met. The key benefit of

pegcetacoplan is the reduction in proteinuria, with a statistically significant 68.1% (95% CI: 57.3%-76.2%) result compared to placebo at week 26. Although, the 26-weeks duration of the randomised controlled period is somewhat short to provide indubitable support for a long-term efficacy, the 1-year results suggest a maintenance of the effect over the time, which is reassuring, especially in view of the rarity of the conditions. Furthermore, the recent literature references submitted are also reporting on good corelation between proteinuria lowering effect and renal function maintenance/improvement.

A large majority of the patients received concomitant medications as a standard of care for C3G or IC-MPGN during the study, and this is now reflected in the approved indication:

"Aspaveli is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated"

Overall, the safety database in C3G and IC-MPGN programme is considered quite limited in terms of number of patients in each disease category and duration of exposure, as well as comparative long-term safety data. As C3G and IC-MPGN are rare diseases, it is acceptable that safety information is limited. This extended indication includes adolescents and post-transplant patients whose safety profile appears to be comparable to that of the overall population. Based on the data provided so far, pegcetacoplan demonstrated a manageable safety and tolerability, consistent with its established safety profile. There is no new safety concern arising from the new population studied. The most common serious adverse reactions are listed in section 4.8 of the SmPC. The MAH committed to submit ongoing long-term extension studies APL2-C3G-204 and APL2-C3G-314 and the planned phase 4 multi-country study (target 150 patients, ≥2 years follow-up) as post-authorisation measures. The MAH will report relevant safety results from all studies and from post-marketing experience in the PSURs.

3.7.2. Balance of benefits and risks

The single pivotal phase 3 study met the primary and the two first key secondary endpoints. Proteinuria is not a fully validated surrogate marker for predicting long-term renal outcome. However, the totality of the data supports the primary findings and is therefore considered sufficient to demonstrate efficacy of pegcetacoplan in the claimed indication. As per the CHMP's request, the indication reflects the studied population, with respect to the concomitant medication (sec. 2.4.2). Moreover, the long-term data at year 1 indicate maintenance of the effect over time. The post-transplant subgroup is small, with safety findings influenced by background immunosuppression and disease stage but the data in this difficult to treat patient population also indicate convincing efficacy and are corroborated by the data from non-transplanted patients. Pegcetacoplan demonstrated manageable safety and tolerability, consistent with its established safety profile observed in PNH. Further data, in particular on safety will be generated by means of the ongoing long-term extension studies APL2-C3G-204 and APL2-C3G-314 (cat. 3 in the RMP) and a phase 4 multi-country study (target 150 patients, ≥2 years follow-up) is planned to monitor real-world effectiveness, safety, patient-reported outcomes, and biomarkers. The MAH also committed to submit all ongoing and planned study results as post-authorisation commitments and/or in PSURs.

3.8. Conclusions

The overall B/R of Aspaveli is positive for the following indications:

- *Aspaveli is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.*

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Changes to therapeutic indication - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adults and adolescents aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune complex membranoproliferative glomerulopathy (IC-MPGN) for Aspaveli, based on interim results from study APL2-C3G-310; this is a randomised, placebo-controlled, double-blinded, multicentre study to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with C3G or primary IC-MPGN and results from Phase 2 study APL2-C3G-204, an open-label, randomised, controlled study to evaluate the efficacy and safety of pegcetacoplan in posttransplant recurrence of C3G or primary IC-MPGN. As a consequence, sections 4.1, 4.2, 4.8, 4.9, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP is approved. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the RMP.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP. In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures** *(originating from the PNH indication)*

Prior to the launch of Aspaveli in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational and controlled distribution programme is aimed at:

- Ensuring patients receive vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* at least 2 weeks before starting treatment with Aspaveli
- Ensuring that patients who cannot wait 2 weeks before starting treatment with Aspaveli receive broad-spectrum antibiotics until 2 weeks after receiving the vaccines
- Ensuring that Aspaveli is only dispensed after written confirmation that the patient has received vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or is receiving prophylactic antibiotic according to national guidelines
- Ensuring prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*)
- Providing information about the signs and symptoms of serious infections to healthcare providers and patients
- Ensuring that prescribers provide patients with the package leaflet and patient card and explain the main risks of Aspaveli using these materials
- Ensuring that patients who experience symptoms of serious infections seek emergency medical treatment and present their patient card to the emergency care provider
- Educate prescribers and patients about the risk of IVH after discontinuation of the medicinal product and postponement of administration and the need to maintain effective complement inhibitor treatment (PNH indication only).
- Educate prescribers about the risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.

The MAH shall ensure that in each Member State where Aspaveli is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Aspaveli have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The SmPC
- Guide for healthcare professionals
- Patient card

- **Guide for healthcare professionals:**
  - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria.
  - The need for patients to be vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Risk of IVH after discontinuation and postponement of administration of the medicinal product, its criteria, the required post-treatment monitoring, and its proposed management (PNH indication only).
  - Risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.
  - The need to educate patients/carers of the following:
    - the risks of treatment with Aspaveli
    - signs and symptoms of serious infections, hypersensitivity reactions, and what action to take
    - the patient/carer guides and its content
    - the need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with Aspaveli
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the PASS (where available)
  - Instructions on how to handle possible adverse events.
  - Information about the PASS (where available), the importance of contributing to such a study, and how to enter patients.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
- **Patient card:**
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Aspaveli.
  - Signs or symptoms of the serious infections and warning to seek immediate attention from a healthcare professional if above is present.
  - Contact details of the Aspaveli prescriber.

The patient information pack:

- Patient information leaflet
- Patient/carer guide

- **Patient/carer guide:**
  - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria, serious hypersensitivity reactions, and PNH-specific risk of IVH after discontinuation of the medicinal product.
  - A description of the signs and symptoms of serious infections, hypersensitivity reactions, IVH after discontinuation of the medicinal product, and the need to seek emergency care at the nearest hospital.
  - The importance of vaccination prior to treatment with Aspaveli and/or to receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Detailed description of the modalities used for the self-administration of Aspaveli.
  - Recommendation for use of effective contraception in women of childbearing potential.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
  - Instructions on how to view the patient self-treatment video on any internet-connected device.
  - Enrolment in the PASS (where available).

Annual reminder of mandatory revaccinations

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense Aspaveli, a reminder in order that the prescriber/pharmacist checks if a re-vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* is required for his/her patients on treatment with Aspaveli, in accordance with national vaccination guidelines.

System for controlled distribution

The MAH shall ensure that in each Member State where Aspaveli is marketed, a system aimed to control distribution beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed.

- Submission of written confirmation, or equivalent as permitted by national legislation, of the patient's vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or prophylactic antibiotic treatment according to national vaccination guidelines.

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Aspaveli is not similar to Fabhalta within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to scientific discussion 'Aspaveli-H-C-5553-II-EMAVR0000248937'

Attachments

1. SmPC, Annex II, Labelling and Package Leaflet (changes highlighted)

Appendix

1. CHMP AR on similarity dated 11 December 2025