Pegcetacoplan halts disease progression and reduces proteinuria in adolescent patients with C3G and primary IC-MPGN: Phase 3 VALIANT study results

Dr Dean Wallace

Royal Manchester Children's Hospital, Manchester, UK

Christoph Licht,[1] Gema Ariceta,[2] Yael Borovitz,[3] Bradley P Dixon,[4] Naoya Fujita,[5] Larry A Greenbaum,[6] Antonio Mastrangelo,[7] Nabil Melhem,[8] Nicole van de Kar,[9] Marina Vivarelli,[10] Dean Wallace,[11] Virginia Taliadouros,[12] Johan Szamosi,[12] Katie Gordon,[13] Zhongshen Wang,[13] Carla M Nester[14]

[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Hospital Vall d'Hebron, Barcelona, Spain; [3]Pediatric Nephrology Institute, Schneider Children's Medical Center, Petah Tikva, Israel; [4]University of Colorado School of Medicine, Aurora, CO, USA; [5]Aichi Children's Health and Medical Center, Aichi, Japan; [6]Emory School of Medicine, Atlanta, GA, USA; [7]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [8]Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK; [9]Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, Netherlands; [10]Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [11]Royal Manchester Children's Hospital, Manchester, UK; [12]Swedish Orphan Biovitrum AB, Stockholm, Sweden; [13]Apellis Pharmaceuticals, Inc., Waltham, MA, USA; [14]University of Iowa, Stead Family Children's Hospital, Iowa City, IA, USA

sobi

Apellis

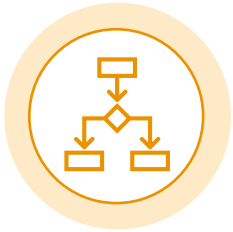
Disclosures

- **CL** received consulting fees and honoraria from Alexion, Apellis, Sobi, Novartis, and Pfizer
- **GA** received honoraria for lectures, educational events, or advisory boards for AstraZeneca (Alexion), Recordati Rare Diseases, Advicenne, Chiesi, Kyowa Kirin, Alnylam, and Dicerna; and served as site investigator for Apellis
- **YB** received honoraria for lectures, educational events, or advisory boards from Novartis and Neopharm Scientific
- **BPD** received consulting fees and honoraria from Alexion, AstraZeneca Rare Disease, Apellis, Novartis, and Arrowhead
- **NF** has nothing to disclose
- **LAG** received research support from Alexion and Apellis; and has served as a consultant for Novartis, Alexion, and Roche
- **AM** received consultant and speaker fees from Sobi
- **NM** received consultancy fees from Sobi, Serb, and Recordati
- **NvdK** received consultancy fees from Sobi, Roche, Novartis, Alexion, and Samsung
- **MV** received consultancy fees from Novartis, Sobi, Travere, Roche, Apellis, Alexion, BioCryst, Purespring, Bayer, and WebMD; participates in clinical trials sponsored by Alexion, Bayer, Novartis, Roche, Chinook, Apellis, and Travere; and serves on speaker bureaus for Novartis, Roche, Vifor, Travere, Sobi, and GlaxoSmithKline
- **DW** received fees for the production of educational materials, and event sponsorship support from Sobi
- **VT** is an employee of Sobi and may hold stocks or stock options
- **JS** is an employee of Sobi and may hold stocks or stock options
- **KG** is an employee of Apellis and may hold stocks or stock options
- **ZW** is an employee of Apellis and may hold stocks or stock options
- **CMN** is the Associate Director for Molecular Otolaryngology and Renal Research Laboratory; receives NIH grant support (2R01DK110023-07); serves on advisory boards for Novartis, Apellis, BioCryst, and Alexion; participates as a site investigator for Novartis, Apellis, BioCryst, and Retrophin; is a member of the data safety monitoring board for Kira; serves as Chair of a data safety monitoring board for FIT4KID; and receives author royalties for UpToDate

Patients with complement-mediated kidney diseases have an unmet clinical need for disease-modifying treatment

C3G and **primary (idiopathic) IC-MPGN are driven by C3 dysregulation**, resulting in the **deposition of C3**; this leads to inflammation, **progressive kidney damage** and, ultimately, **kidney failure**[1–4]

Up to **70% of patients with C3G and primary IC-MPGN develop kidney failure within 10 years.**[3–7] **Patients with UPCR ≥3 g/g (nephrotic range proteinuria)** are at **risk of rapid progression to kidney failure**, highlighting an urgent unmet need[6]



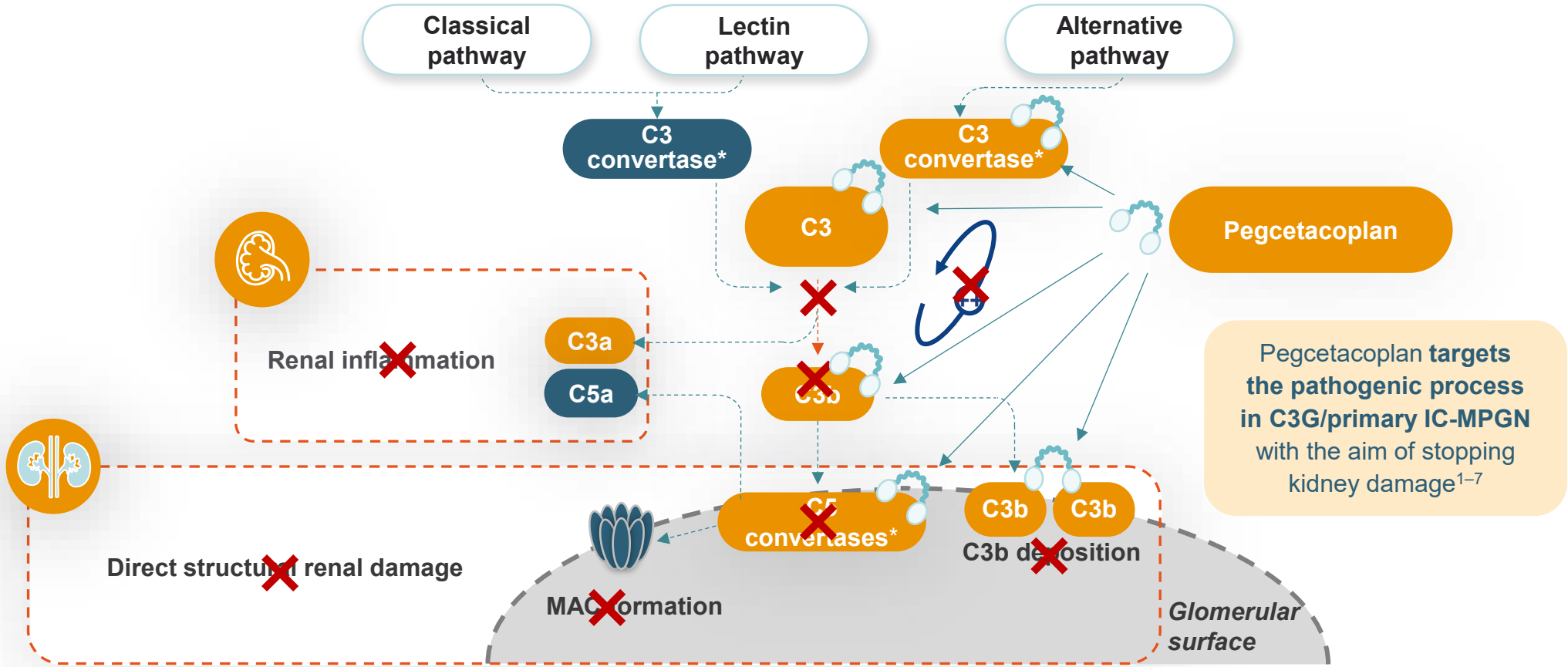
The **Phase 3 VALIANT trial** (NCT05067127) showed that **26 weeks of pegcetacoplan treatment** resulted in **reduced proteinuria and stable eGFR in adolescents (12–17 years)** and was **well tolerated**[8]

Here, we report the findings of a post-hoc analysis of pegcetacoplan's disease-modifying effect in adolescent patients, including those with baseline UPCR ≥3 g/g

C3, complement 3 protein; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney failure; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; UPCR, urine protein-to-creatinine ratio.

1. Bomback AS, et al. *Kidney Int Rep* 2025;10:87–98; **2.** Mastrangelo A, et al. *Front Pediatr* 2020;8:205; **3.** Kirpalani A, et al. *Kidney Int Rep* 2020;5:2313–24; **4.** Caravaca-Fontán F, et al. *Nephron* 2020;144:272–80; **5.** Smith RJH, et al. *Nat Rev Nephrol* 2019;15:129–43; **6.** Nester C, et al. *Clin J Am Soc Nephrol* 2024;19:1201–8; **7.** Wilson GJ, et al. *BMC Nephrol* 2019;20:417; **8.** Mastrangelo A, et al. Oral presentation at ERA 2025. 4–7 June 2025 (Abstract 3413).

Pegcetacoplan blocks C3 dysregulation and downstream complement activation

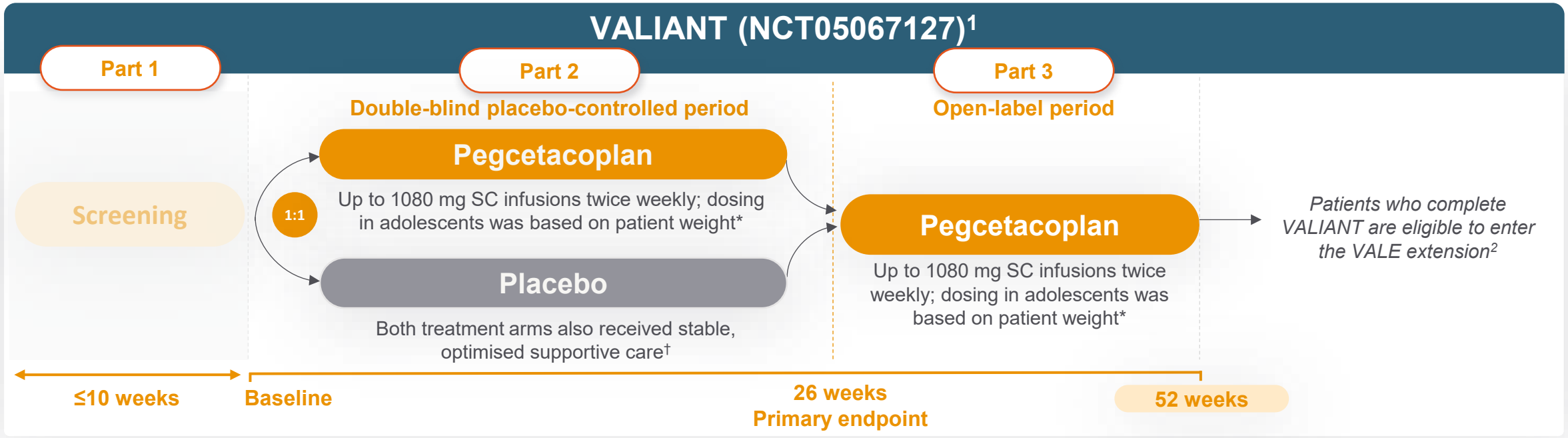


Pegcetacoplan **targets the pathogenic process in C3G/primary IC-MPGN** with the aim of stopping kidney damage[1–7]

*C3 convertases: C4b2a via the classical and lectin pathways, C3bBb via the alternative pathway; C5 convertases: C4b2aC3b and C3bBbC3b.
C3/5, complement 3/5 protein; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MAC, membrane attack complex.

1. Smith RJH, et al. *Nat Rev Nephrol* 2019;15:129–43; **2.** Zipfel PF, et al. *Front Immunol* 2019;10:2166; **3.** Meuleman MS, et al. *Semin Immunol* 2022;60:101634; **4.** Dixon BP, et al. *Kidney Int Rep* 2023;8:2284–93; **5.** EMPAVELI (pegcetacoplan). Apellis Pharmaceuticals, Inc. 2024; **6.** ASPAVELI (pegcetacoplan). Swedish Orphan Biovitrum AB; 2024; **7.** Lamers C, et al. *Nat Commun* 2022;13:5519.

VALIANT: Double-blind, randomised, placebo-controlled Phase 3 study



Key inclusion criteria

- Adolescents (12–17 years) or adults (≥18 years)
- Diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant)
- UPCR ≥1 g/day and eGFR ≥30 ml/min/1.73 m^2
- MMF and corticosteroids (prednisone ≤20 mg/day or equivalent) permitted

Key exclusion criteria

- >50% global glomerulosclerosis or interstitial fibrosis on renal biopsy

Endpoints at Week 26 (vs baseline) for this analysis

- **Primary endpoint:** Log-transformed ratio of UPCR
- Proportion of patients with a reduction of ≥50% in UPCR
- Change in serum albumin levels
- Change in eGFR
- Change in serum C3 levels
- Change in sC5b-9 levels

*All adolescents and adults weighing ≥50 kg self-administered 1080 mg/20 ml. Adolescent patients weighing 30–34 kg received 540 mg/10 ml for the first two doses, and 648 mg/12 ml thereafter. Adolescent patients weighing 35–49 kg received 648 mg/12 ml for the first dose, and 810 mg/15 ml thereafter. †Stable, optimised antiproteinuric regimens: angiotensin-converting enzyme Inhibitors, angiotensin receptor blockers, sodium-glucose cotransporter-2 inhibitors, mycophenolate mofetil, and corticosteroids (prednisone ≤20 mg/day or equivalent) were permitted.

C3/5, complement 3/5 protein; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MMF, mycophenolate mofetil; SC, subcutaneous; UPCR, urine protein-to-creatinine ratio.

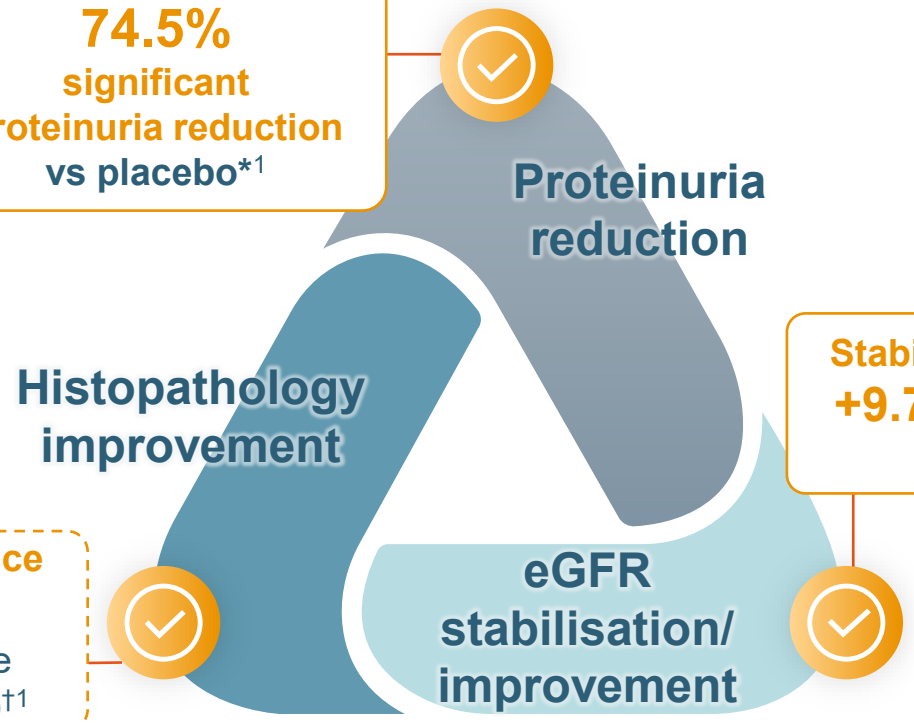
1. Dixon BP, et al. ASN Kidney Week 2023. 2–5 November 2023 (Abstract INFO12-SA); **2.** https://clinicaltrials.gov/study/NCT05809531. Accessed 9 October 2025.

VALIANT: 26-week data demonstrated efficacy of pegcetacoplan in adolescent patients with C3G and primary IC-MPGN

Kidney Health Initiative consensus[2]

Favourable treatment effect on **histopathology, proteinuria, and eGFR**

74.5%
significant proteinuria reduction vs placebo*[1]



Stabilisation of eGFR +9.7 ml/min/1.73 m² vs placebo[1]

Glomerular C3 clearance in 71.4% of adult patients with available biopsies (zero staining)†[1]

*p<0.0001 (nominal). †For ethical reasons, study biopsies were optional in adolescent patients.

C3, complement 3 protein; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis.

1. Mastrangelo A, et al. Oral presentation at ERA 2025. 4–7 June 2025 (Abstract 3413); **2.** Nester C, et al. *Clin J Am Soc Nephrol* 2024;19:1201–8.

VALIANT: Broad adolescent patient population including those with baseline UPCR ≥3 g/g

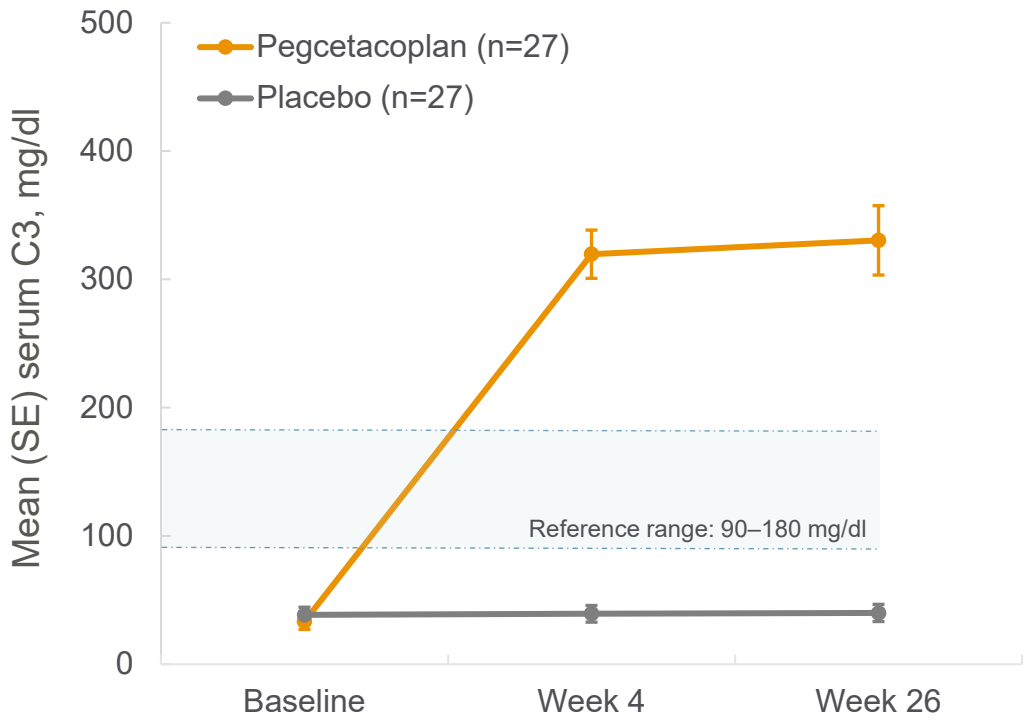
	All adolescents (n=55)		Adolescents with baseline UPCR ≥3 g/g (n=18)	
Baseline characteristic	**PEG (n=28)**	**PBO (n=27)**	**PEG (n=11)**	**PBO (n=7)**
Age, mean (SD), years	14.6 (1.7)	14.8 (1.8)	14.5 (2.1)	14.0 (2.1)
Sex, female, n (%)	18 (64.3)	14 (51.9)	9 (81.8)	4 (57.1)
Triplicate FMS UPCR, mean (SD), g/g	3.5 (3.1)	2.6 (2.3)	6.5 (3.1)	5.8 (2.6)
eGFR,* mean (SD), ml/min/1.73 m^2	92.8 (32.4)	94.0 (34.3)	72.0 (33.5)	69.57 (24.9)
Underlying disease based on screening biopsy, n (%)				
C3G	21 (75.0)	17 (63.0)	6 (54.5)	4 (57.1)
Primary IC-MPGN	7 (25.0)	10 (37.0)	5 (45.5)	3 (42.9)
Hypoalbuminaemia, n (%)	–	–	8 (72.7)	7 (100)
Time since diagnosis, mean (SD), years	3.3 (2.5)	3.4 (3.5)	3.1 (3.1)	2.6 (2.0)

*Calculated using the Bedside Schwartz equation.

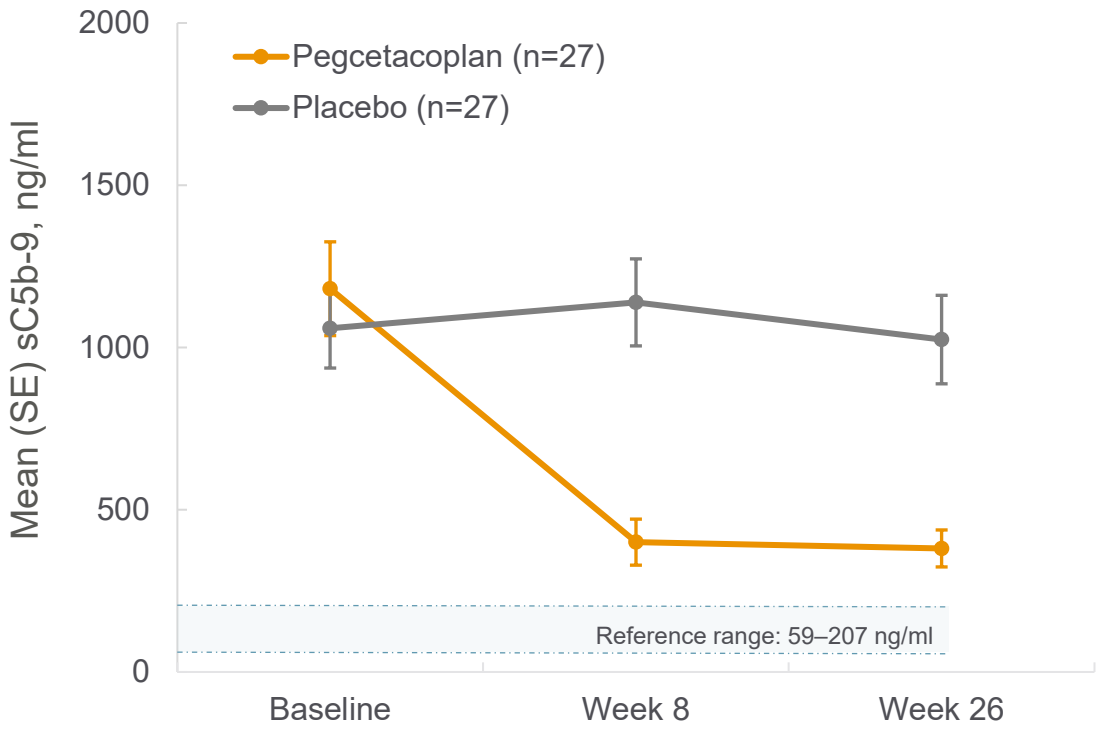
C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; FMS, first morning spot;
IC-MPGN, immune-complex membranoproliferative glomerulonephritis; PBO, placebo; PEG, pegcetacoplan; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

VALIANT: Pegcetacoplan treatment led to a rapid, sustained response in serum C3 and soluble C5b-9 in adolescents

Serum C3



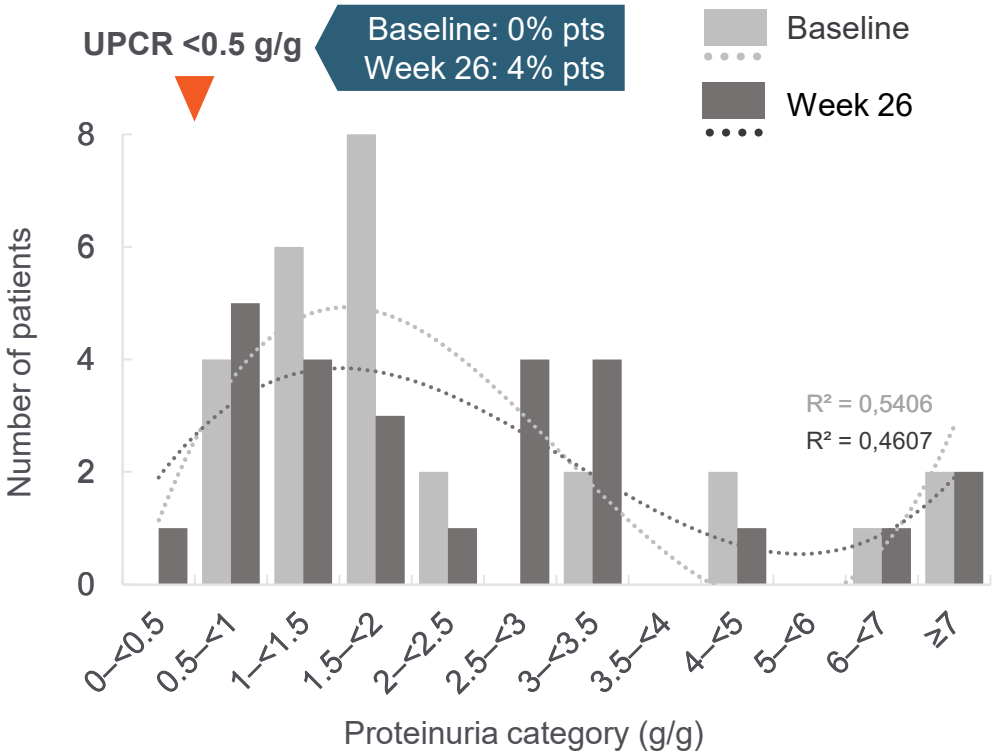
sC5b-9



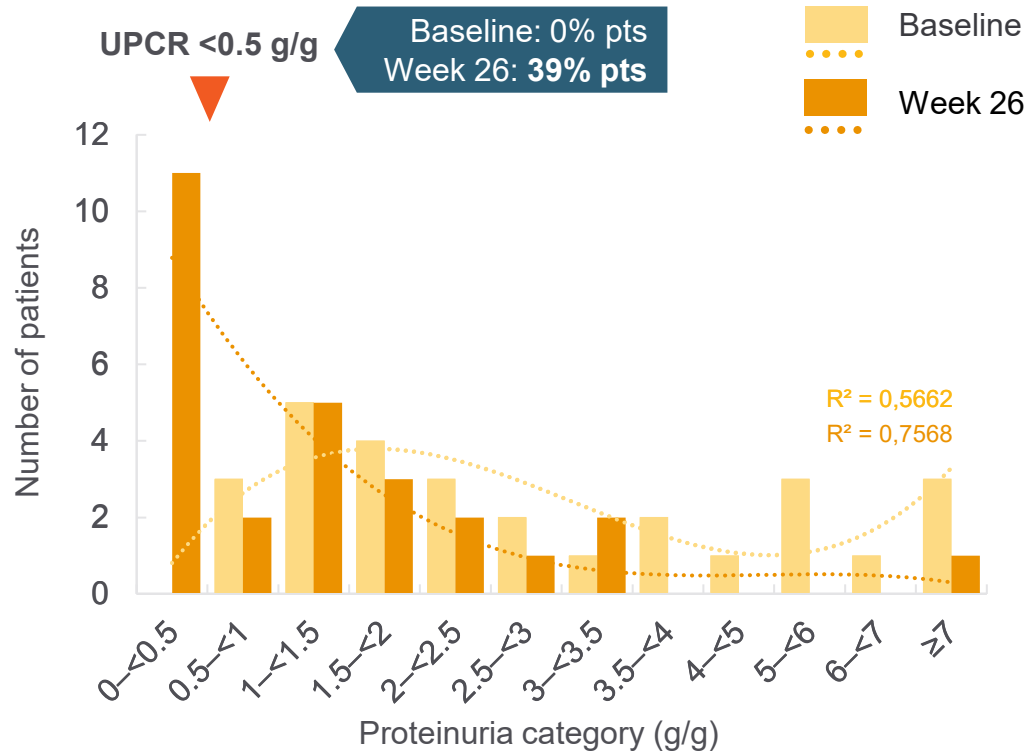
C3, complement 3 protein; sC5b-9, soluble complement 5b-9 protein; SE, standard error.

VALIANT: Adolescent patient distribution across proteinuria ranges shifted towards lower values in the pegcetacoplan arm

Placebo (n=27)*



Pegcetacoplan (n=28)*



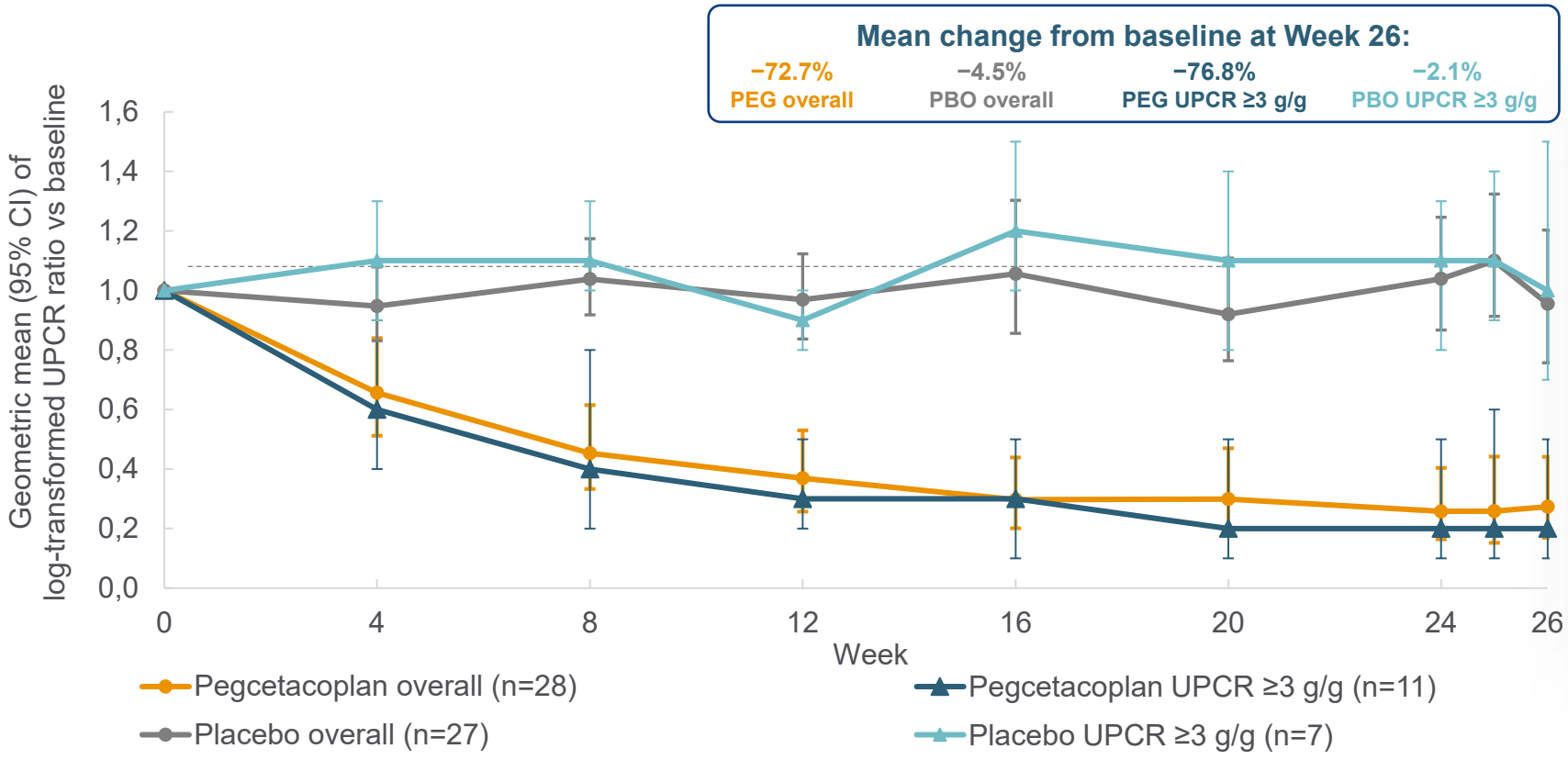
In retrospective studies, **achieving UPCR <1 g/g** was strongly associated with **reduced risk of kidney failure**[1,2]

*Lines of best fit using a polynomial function with 3 parameters.
Pts, patients; UPCR, urine protein-to-creatinine ratio.

1. Masoud S, et al. *Kidney Int.* 2025;108:455–69; **2.** Ghaddar M, et al. *Clin J Am Soc Nephrol.* 2025;20:1119–31.

VALIANT: Pegcetacoplan led to robust proteinuria reductions in adolescents, including in those with baseline UPCR ≥3 g/g

Change in proteinuria at Week 26 in patients with UPCR ≥3 g/g at baseline



Normalisation* of serum albumin

Pegcetacoplan: 75% (6/8) of patients with hypoalbuminaemia at baseline normalised by Week 26

Placebo: 0% (0/7) patients with hypoalbuminaemia at baseline normalised by Week 26

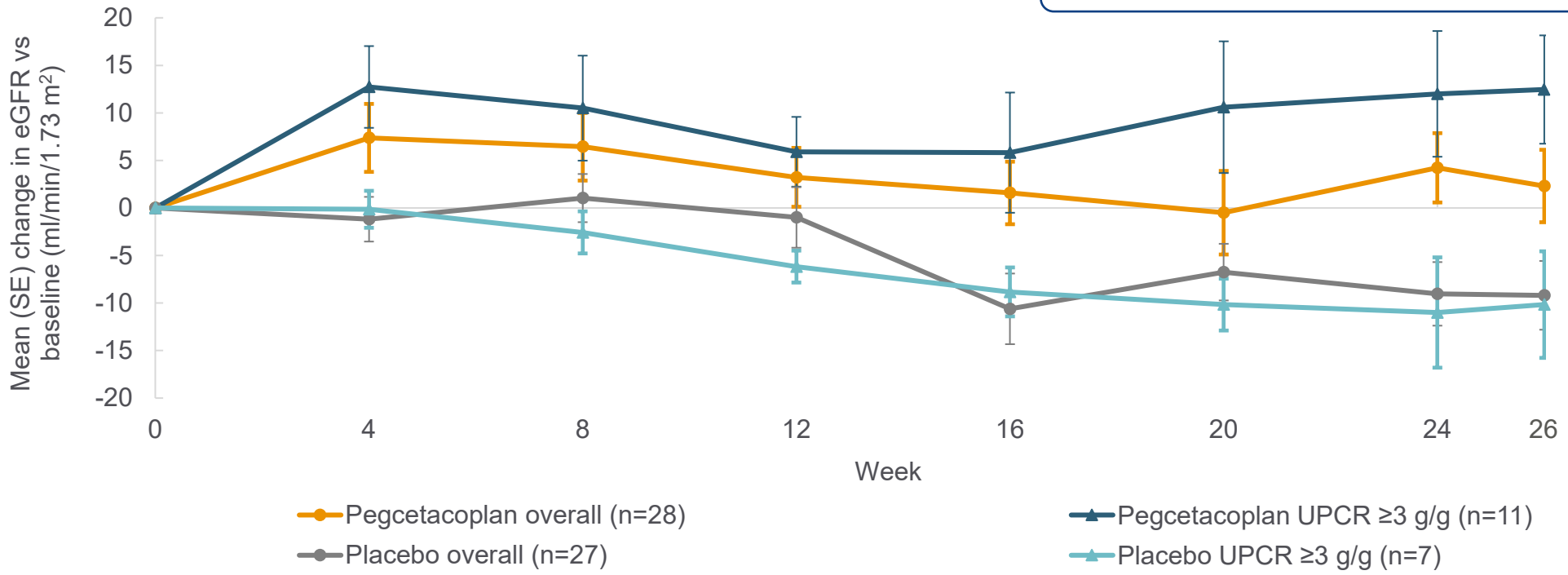
*Normalisation of serum albumin defined as above the lower level of normal.
CI, confidence interval; PBO, placebo; PEG, pegcetacoplan; UPCR, urine protein-to-creatinine ratio.

VALIANT: eGFR improved in adolescent patients receiving pegcetacoplan, including in those with baseline UPCR ≥3 g/g

Change in eGFR at Week 26

Mean change from baseline at Week 26 (ml/min/1.73 m²):

+2.3	−9.2	+12.5	−10.2
PEG overall	PBO overall	PEG UPCR ≥3 g/g	PBO UPCR ≥3 g/g



eGFR, estimated glomerular filtration rate; PBO, placebo; PEG, pegcetacoplan; SE, standard error; UPCR, urine protein-to-creatinine ratio.

VALIANT: Over 26 weeks, TEAEs in adolescents were consistent with the known safety profile for pegcetacoplan

	Adolescents (n=55)		Adolescents with baseline UPCR ≥3 g/g (n=18)	
Characteristic	**PEG (n=28)**	**PBO (n=27)**	**PEG (n=11)**	**PBO (n=7)**
Any TEAE	23 (82.1)	26 (96.3)	11 (100)	7 (100)
Maximum severity				
Mild	12 (42.9)	11 (40.7)	5 (45.5)	2 (28.6)
Moderate	9 (32.1)	14 (51.9)	5 (45.5)	4 (57.1)
Severe	2 (7.1)	1 (3.7)	1 (9.1)	1 (14.3)
Treatment-related TEAE	13 (46.4)	11 (40.7)	6 (54.5)	3 (42.9)
Infusion-related TEAE	9 (32.1)	7 (25.9)	4 (36.4)	1 (14.3)
Serious TEAE*	3 (10.7)	3 (11.1)	2 (18.2)	1 (14.3)
TEAE leading to treatment withdrawal	1 (3.6)†	2 (7.4)	0 (0.0)	1 (14.3)
TEAE leading to dose interruption	2 (7.1)	6 (22.2)	0 (0.0)	0 (0.0)
TEAE leading to study discontinuation	0 (0.0)	1 (3.7)‡	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rejection episodes	0 (0.0)	NA	0 (0.0)	0 (0.0)
Graft loss	0 (0.0)	NA	0 (0.0)	0 (0.0)

- **No meningococcal infections**
- **No deaths**

*In the pegcetacoplan arm, 1 serious TEAE (pyrexia) was considered related to treatment. †Infusion-site reaction. ‡pregnancy.
A TEAE is 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.
NA, not applicable; PBO, placebo; PEG, pegcetacoplan; TEAE, treatment-emergent adverse event; UPCR, urine protein-to-creatinine ratio.

VALIANT: Pegcetacoplan addresses the unmet need in adolescent patients with C3G or primary IC-MPGN

In the overall group, patient distribution across proteinuria ranges shifted towards lower values in the pegcetacoplan arm:

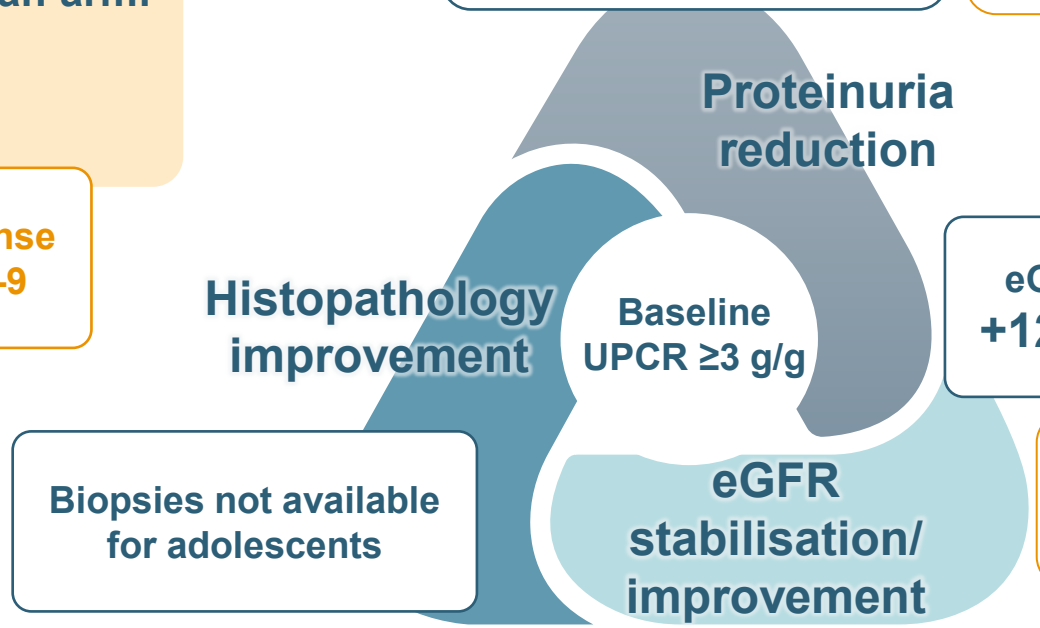
46% <1.0 g/g

39% <0.5 g/g

Rapid, sustained response in **serum C3** and **sC5b-9**

76.8%
proteinuria reduction

75.0% adolescents **normalised serum albumin** vs 0% in placebo



eGFR improvement
+12.5 ml/min/1.73 m²

Adolescents in the **placebo arm** experienced an **eGFR decline of –10.2 ml/min/1.73 m²**

Biopsies not available for adolescents

Pegcetacoplan was well tolerated in the adolescent population, with no new safety signals

C3, complement 3 protein; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; sC5b-9, soluble complement 5b-9 protein; UPCR, urine protein-to-creatinine ratio.

Acknowledgements

The authors thank the patients, investigators, and all other collaborators

This study was funded by Sobi (Swedish Orphan Biovitrum AB) and Apellis Pharmaceuticals, Inc.

Writing assistance was provided by The Salve Healthcare Communications (Cheltenham, UK), and was funded by Sobi (Swedish Orphan Biovitrum AB) and Apellis Pharmaceuticals, Inc.