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Targeted Treatment with Pegcetacoplan for Adolescents with C3G or Primary (Idiopathic) IC-MPGN in the VALIANT Phase 3 Trial

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Disclosures

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- **AM** received consultant and speaker fees from Sobi
- **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 Glaxo Smith Klyne
- **GA** received honoraria for lectures, educational events, or advisory boards for AstraZeneca (Alexion), Recordati Rare Disease, 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
- **CL** received consulting fees and honoraria from Alexion, Apellis, Sobi, Novartis and Pfizer
- **NvdeK** received consultancy fees from Sobi, Roche, Novartis, Alexion, and Samsung
- **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
- **DW** has received fees for production of educational materials and event sponsorship support from Sobi
- **NM** received consultancy fees fro Sobi, Serb and Recordati
- **LL** was an employee of Apellis and may hold stock or stock options
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C3G and primary IC-MPGN are **rare, chronic, and heterogeneous complement-mediated diseases** with a **high unmet need in children**

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Diseases are driven by C3 dysregulation, resulting in the accumulation of **C3 downstream effectors in the glomeruli** (with addition of **immunoglobulins in IC-MPGN**), leading to inflammation and progressive **kidney damage** and **ultimately kidney failure**[1,2]

Children may present with **varying degrees of proteinuria** (mild to nephrotic), hematuria (microscopic to macroscopic), and low serum C3 levels. Disease **presentation and progression are heterogeneous**, **requiring a kidney biopsy** for definitive diagnosis[3-5]

Approximately **20% of children progress to kidney failure within 10-15 years of diagnosis**.[3-5]

Up to **89% likelihood of recurrence after transplantation**[6,7]

C3, complement 3 protein; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis.

1. Bomback AS, et al. *Kidney Int Rep* 2024;10:17-28 **2.** Mastrangelo A, et al. *Front Pediatr* 2020;8:205
3. Kirpalani A, et al. *Kidney Int Rep* 2020;5:2313–24 **4.** Spartà G, et al. *Clin Kidney J* 2018;11:479–90 **5.** Wong EKS, et al. *Clin J Am Soc Nephrol* 2021;16:1639–51
6. O'Shaughnessy MM, et al. *J Am Soc Nephrol* 2017;28:632–44 **7.** Heiderscheit AK, et al. *Am J Med Genet C Semin Med Genet* 2022;190C:344–57.

Pegcetacoplan, a C3 and C3b inhibitor, **blocks C3 dysregulation and downstream complement activation** in C3G and primary IC-MPGN[1–7]

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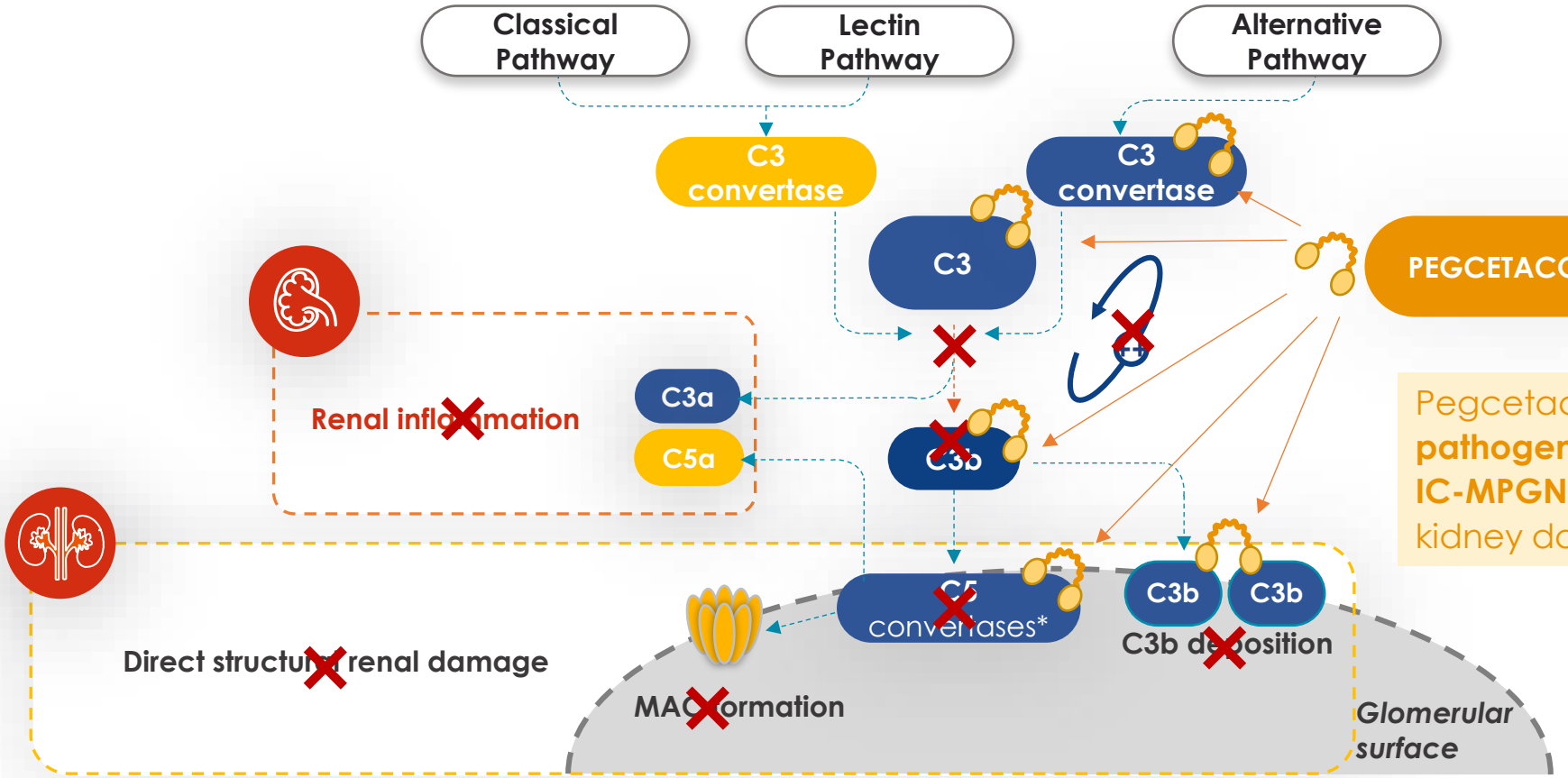

Pegcetacoplan **targets the pathogenic process in C3G/primary IC-MPGN** with the aim of stopping kidney damage

*C5 convertases: C4b2aC3b and C3bBbC3b.
C3/5, complement 3/5; 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) US PI 2024 **6.** ASPAVELI Summary of Product Characteristics 2024
7. Lamers C, et al. *Nat Commun* 2022;13:5519.

VALIANT: Double-blind, randomized, placebo-controlled phase 3 study

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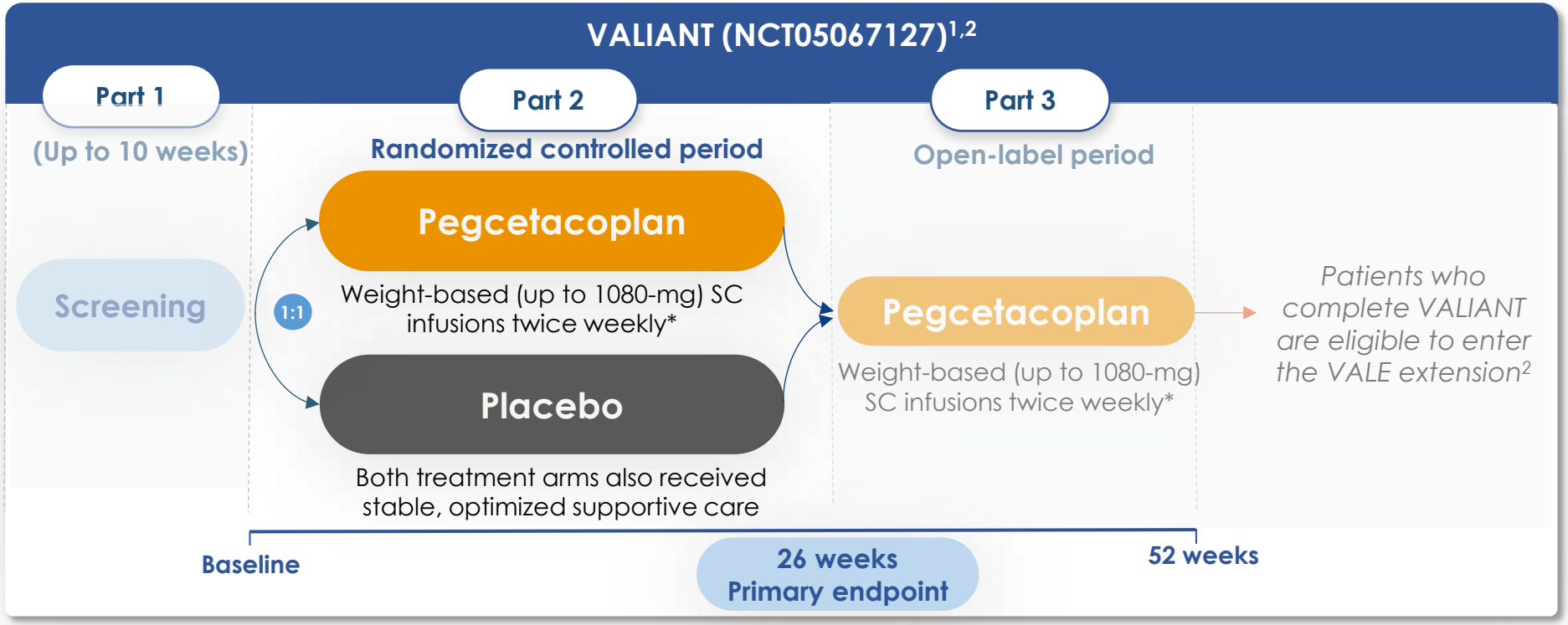

Objective of the post-hoc analysis:
Evaluate safety and efficacy of pegcetacoplan for **adolescents** at Week 26

* All adults and adolescents weighing ≥50 kg self administered 1080 mg/20 mL. Adolescent patients weighing 30–34 kg received 540 mg/10 mL for the first 2 doses, then 648 mg/12 mL. Adolescent patients weighing 35–49 kg received 648 mg/12 mL for the first dose, then 810 mg/15 mL. SC, subcutaneous.

1. Dixon BP, et al. ASN Kidney Week 2023. Nov. 2–5, 2023. Abstract INFO12-SA **2.** ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed April 16, 2025.

VALIANT: **Eligibility criteria**[1]

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Key eligibility criteria

Inclusion

- **Adolescents** (12–17 y) **or adults** (≥18 y)
- **Diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant)**
- **MMF and corticosteroids (prednisone ≤20 mg/d or equivalent) permitted**

Exclusion

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

Other eligibility criteria

Inclusion

- Evidence of active disease
- ≥1 g/d of proteinuria on screening urine collection and UPCR ≥1 g/g in ≥2 first-morning spot urine samples
- eGFR ≥30 mL/min/1.73 m^2
- Mandatory vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (types A, C, W, Y, and B), and *Haemophilus influenzae* (type B)
- Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is

Exclusion

- Evidence of transplant rejection
- Diagnosis of secondary C3G or IC-MPGN
- Severe infection within 14 days prior to first dose
- Recurrent or chronic severe infections or history of meningococcal disease
- Previous exposure to pegcetacoplan or another complement inhibitor
- Evidence of improving renal disease

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; MMF, mycophenolate mofetil; SGLT2is, sodium-glucose cotransporter-2 inhibitors; UPCR, urine protein-to-creatinine ratio; y, years. **1.** ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed April 16, 2025.

VALIANT: **Primary and key secondary endpoints**

Primary

- **Log-transformed ratio of UPCR at week 26** compared with baseline

Key Secondary

- Proportion of participants **achieving a composite renal endpoint** (a stable or improved eGFR compared with the baseline visit [≤15% reduction in eGFR] and a ≥50% reduction in UPCR compared with the baseline visit) at week 26
- Proportion of participants with **a reduction of ≥50% in UPCR** from baseline to week 26
- **Change in the activity score of the C3G histologic index score** from baseline to week 26*
- Proportion of participants with evaluable renal biopsies showing **decreased C3 staining on renal biopsy** from baseline to week 26*
- **Change in eGFR** from baseline to week 26

* For participants with evaluable renal biopsies. Biopsy was not mandatory for adolescents.
C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.
1. ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed April 16, 2025.

VALIANT overall study results (26 weeks): **Pegcetacoplan's efficacy** in C3G and primary IC-MPGN[1]

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Kidney Health Initiative (KHI) consensus[2]:
Favorable treatment effect on **histopathology, proteinuria and eGFR**

68%
significant proteinuria reduction
vs placebo*

Proteinuria reduction

Stabilization of eGFR
+6.3 mL/min/1.73 m²
vs placebo

eGFR stabilization/ improvement

Histopathology improvement

Glomerular C3 clearance in 71% of patients
(zero staining)

* Consistent across subgroups (age, disease type, transplant status).
C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis.
1. Nester CM et al. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92) **2.** Nester C, et al. *Clin J Am Soc Nephrol* 2024;19:1201–8.

VALIANT **included a broad patient population** with a **large proportion (44%) of adolescents**

Characteristic	Adolescents (n=55)		Overall population (N=124)	
	Pegcetacoplan	Placebo	Pegcetacoplan	Placebo
Patients, n (%)	28 (44.4)	27 (44.3)	63 (100.0)	61 (100.0)
Age, mean (SD), y	14.6 (1.7)	14.8 (1.8)	28.2 (17.1)	23.6 (14.3)
Sex, female, n (%)	18 (64.3)	14 (51.9)	37 (58.7)	33 (54.1)
Race, white, n (%)	20 (71.4)	19 (70.4)	45 (71.4)	46 (75.4)
Baseline 24-h UPCR, mean (SD), g/g	4.6 (3.8)	3.5 (2.8)	4.0 (2.9)	3.3 (2.4)
Baseline triplicate first morning spot UPCR, mean (SD), g/g	3.5 (3.1)	2.6 (2.3)	3.1 (2.4)	2.5 (2.0)
Baseline eGFR, mean (SD), mL/min/1.73 m²	92.8 (32.4)	94.0 (34.3)	78.5 (34.1)	87.3 (37.2)
Underlying disease based on screening biopsy, n (%)				
C3G	21 (75.0)	17 (63.0)	51 (81.0)	45 (73.8)
C3GN	19 (67.9)	15 (55.6)	45 (71.4)	41 (67.2)
DDD	2 (7.1)	2 (7.4)	4 (6.3)	4 (6.6)
Undetermined	0	0	2 (3.2)	0
Primary IC-MPGN	7 (25.0)	10 (37.0)	12 (19.0)	16 (26.2)
Time since diagnosis, mean (SD), y	3.3 (2.5)	3.4 (3.5)	3.6 (3.5)	3.8 (3.6)
Post-transplant recurrent disease, n (%)	1 (3.6)	0	5 (7.9)	4 (6.6)

C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

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Primary Endpoint:
Clinically significant proteinuria reduction of 74.5% among adolescents with pegcetacoplan vs placebo

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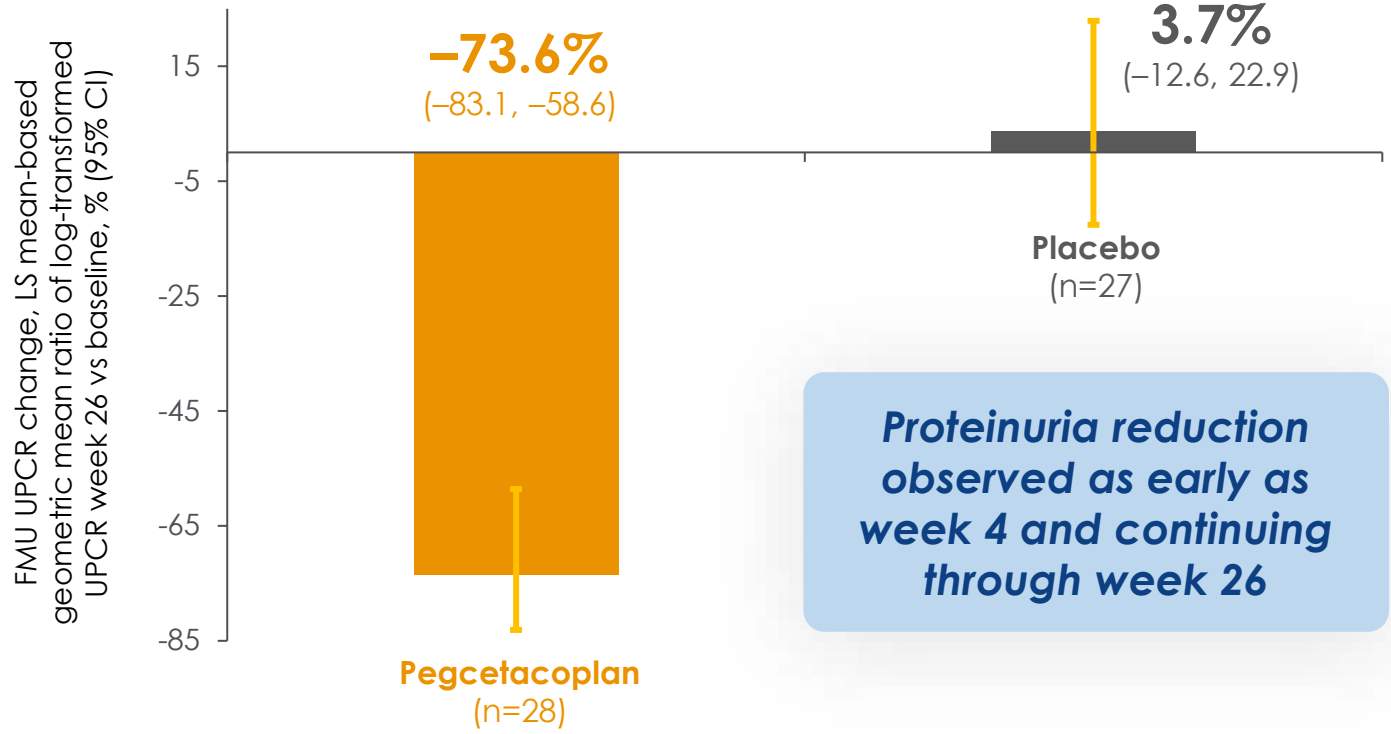
Change in proteinuria (Week 26 vs baseline)



Proteinuria reduction observed as early as week 4 and continuing through week 26

Primary endpoint

Relative reduction (95% CI) in pegcetacoplan vs placebo arms

74.5%

(58.5, 84.3)

***p*<0.0001**

nominal

Relative reduction achieved by **adolescents similar to that among overall population** (**68.1%** [95% CI 57.3, 76.2], *p*<0.0001)

CI, confidence interval; FMU, first morning urine; LS, least squares; UPCR urine protein-to-creatinine ratio.

Rapid and continuous reduction of proteinuria with pegcetacoplan

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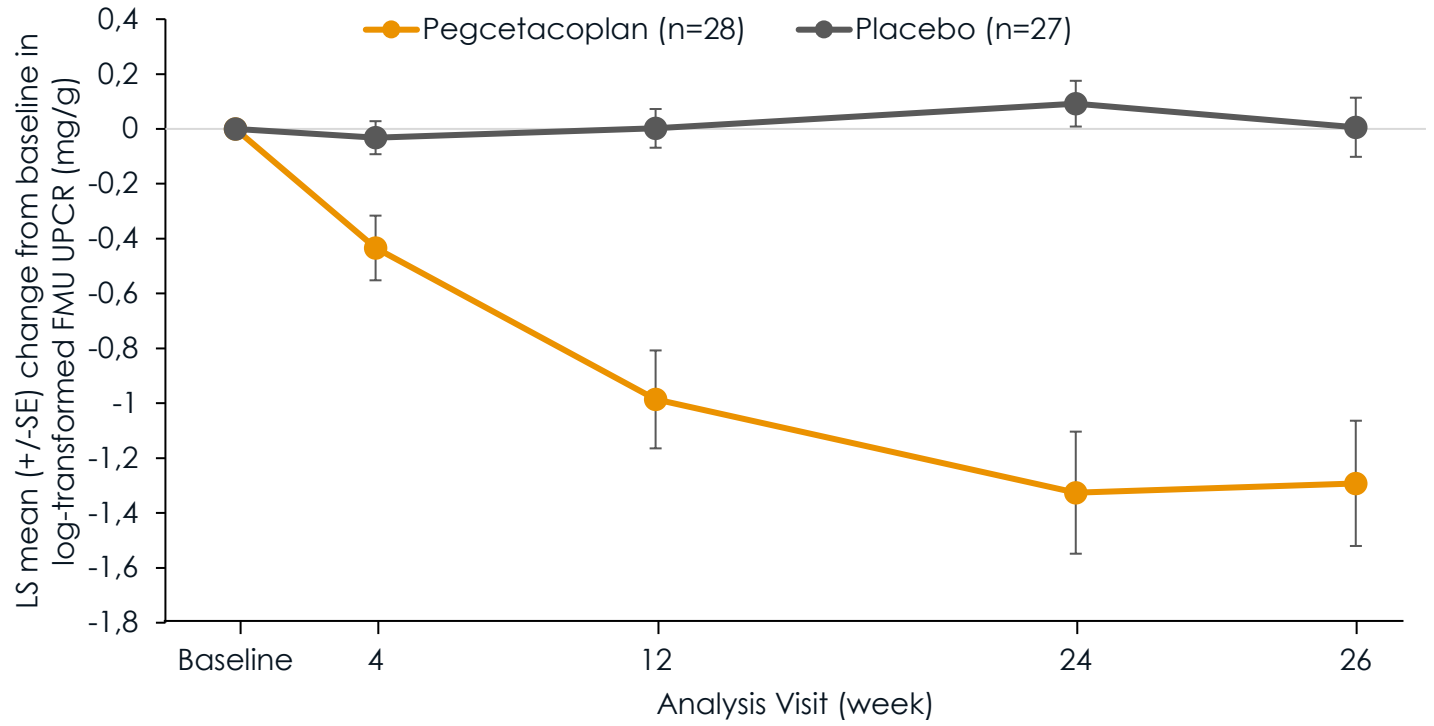
Mean (SE) change from baseline in proteinuria



Similar to overall population, ***proteinuria reduction*** *observed* ***as early as week 4 and continuing through week 26***

FMU, first morning urine; ITT, intent-to-treat; LS, least squares; SE, standard error; UPCR, urine protein-creatinine-ratio.

71% of adolescents who received pegcetacoplan **achieved ≥50% proteinuria reduction**

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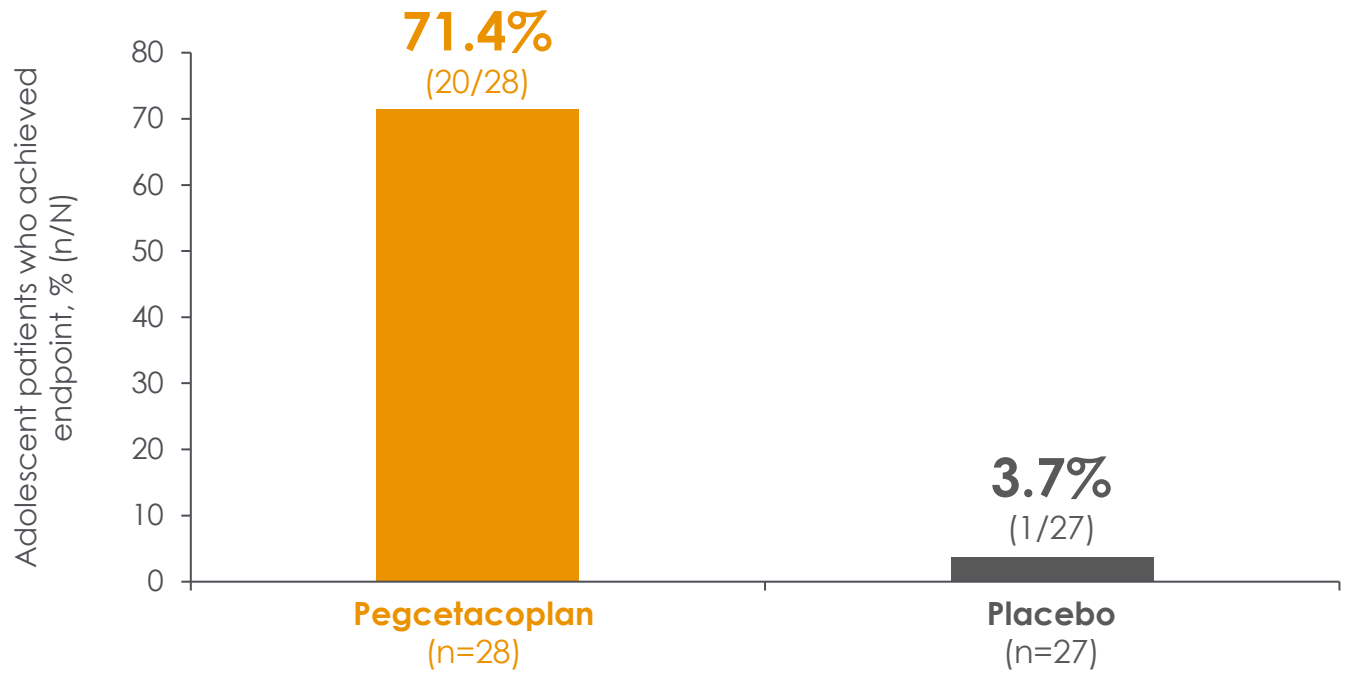
Proportion of adolescent patients who achieved ≥50% proteinuria reduction (Week 26 vs baseline)



Key secondary endpoint

Odds ratio (95% CI): pegcetacoplan vs placebo arms

62x

higher odds of achieving ≥50% proteinuria reduction

p<0.0002

nominal

Overall population:
31x higher odds of reaching this endpoint with pegcetacoplan (*p*<0.0001)

Registry data show that a **≥50% reduction in proteinuria** at 6 or 12 months correlated with a **significantly lower risk of kidney failure** in C3G and primary IC-MPGN patients[1,2]

CI, confidence interval; C3G, C3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis.

1. Masoud S, et al. medRxiv 2024;DOI:10.1101/2024.02.03.24301605v2 **2.** Caravaca-Fontán F et al. *Nephrol Dial Transplant* 2022;37:1270–80.

Pegcetacoplan stabilized eGFR compared with placebo among adolescents

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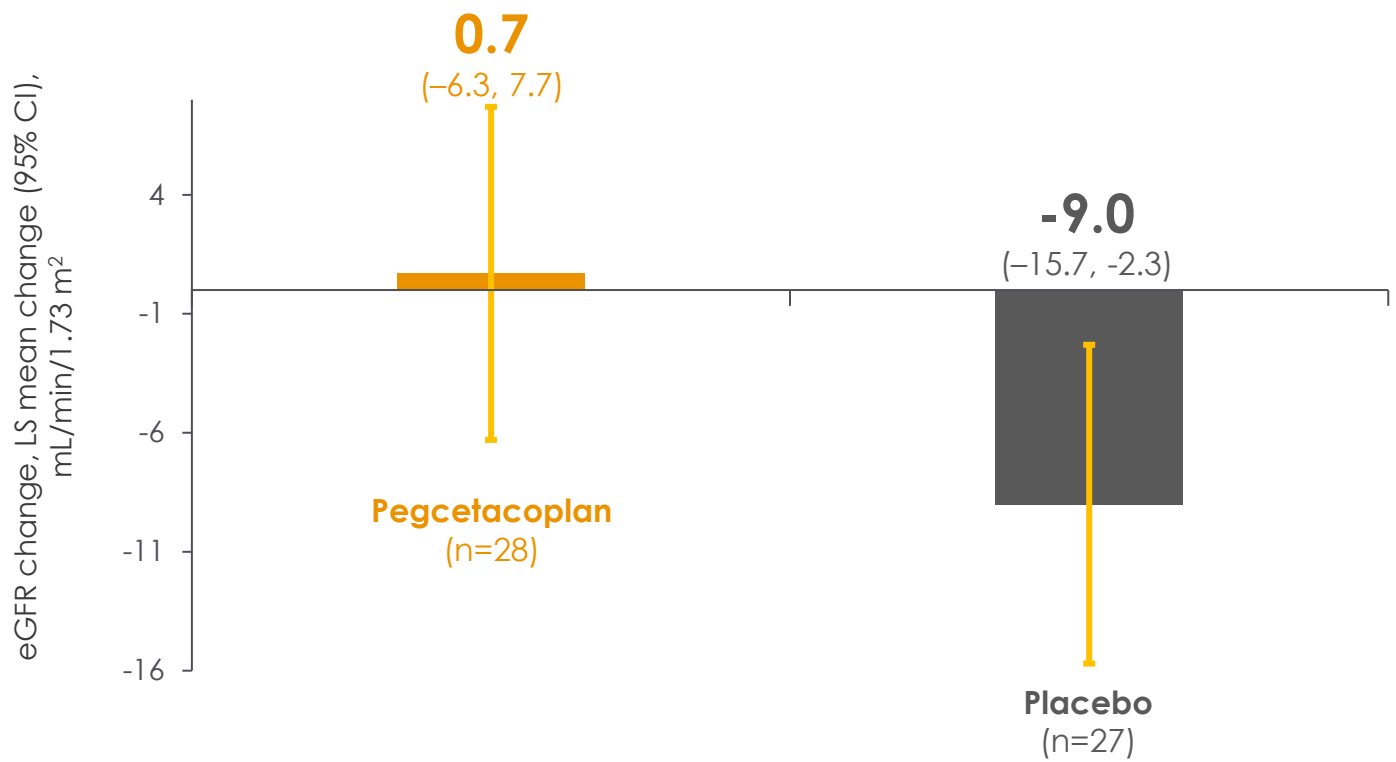
Change in eGFR (Week 26 vs baseline)



Key secondary endpoint

Difference (95% CI) in pegcetacoplan vs placebo arms

+9.7 mL/min/1.73 m²

(0.0, 19.4)

***p*<0.0506**

nominal

Change in the **overall population** was **+6.3** mL/min/1.73 m² (nominal *p*=0.03), in favor of pegcetacoplan

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares.

Pegcetacoplan resulted in **substantially more adolescents achieving the composite renal endpoint**

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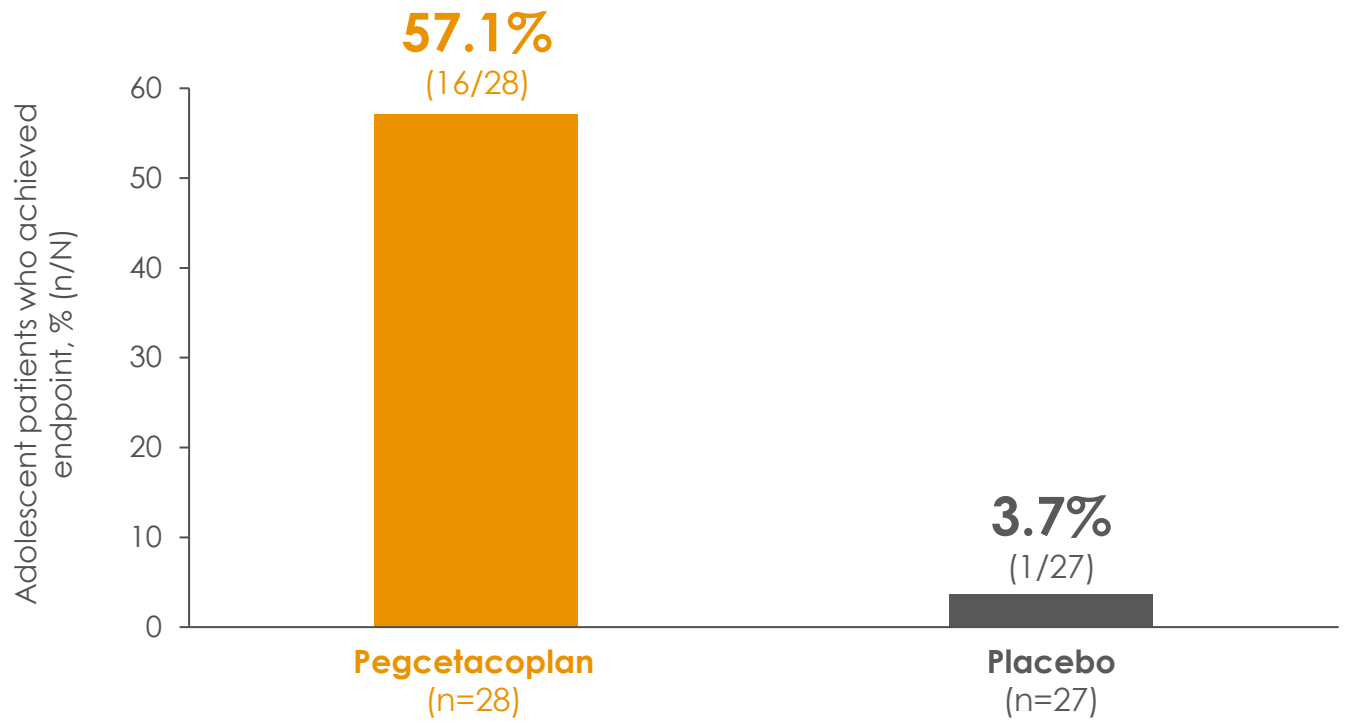
Proportion of adolescent patients who achieved a composite renal endpoint (≥50% reduction in UPCR and ≤15% reduction in eGFR) (Week 26 vs baseline)



Key secondary endpoint

Odds ratio (95% CI): pegcetacoplan vs placebo arms

37x

higher odds of achieving composite renal endpoint

p<0.0016

nominal

Overall population:
27x higher odds of achieving composite endpoint with pegcetacoplan (*p*<0.0001)

CI, confidence interval; eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

Pegcetacoplan demonstrated an acceptable safety profile among adolescents

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TEAE frequency and severity were similar between treatment groups for the adolescent population

- 23 adolescents (82.1%) in the pegcetacoplan arm and 26 (96.3%) in the placebo arm experienced TEAEs
- Serious TEAEs occurred in 3 adolescents in each treatment group (pegcetacoplan, 10.7%; placebo, 11.1%)
- In the pegcetacoplan arm, 1 serious TEAE (pyrexia) was considered related to treatment

No TEAEs led to study discontinuation
No TEAEs led to death
No graft loss or rejection in post-transplant patient
No serious infections caused by encapsulated bacteria

TEAEs defined as any new AE that began, or any preexisting condition that worsened in severity, after the first dose of study drug and ≤56 days beyond the last dose of study drug.
AE, adverse event; TEAE, treatment-emergent adverse event.

Pegcetacoplan demonstrated favorable safety and efficacy for adolescent patients in the VALIANT trial

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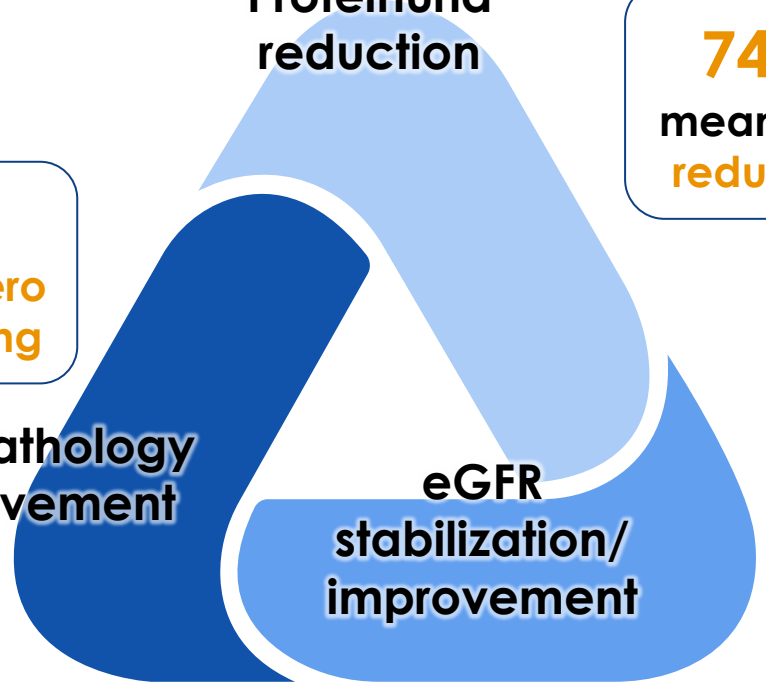

74.5% clinically meaningful proteinuria reduction vs placebo

71% of adult patients achieved zero glomerular C3 staining

eGFR stabilization
+9.7 mL/min/1.73 m²
vs placebo

Proteinuria reduction and eGFR stabilization results among adolescents were consistent with those of the full VALIANT population

Pegcetacoplan has been well tolerated, consistent with previous trials and >2,000 patient-years of pegcetacoplan exposure

eGFR, estimated glomerular filtration rate.

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

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