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Pegcetacoplan for adolescents with C3G or primary IC-MPGN: VALIANT phase 3 double-blind placebo-controlled trial subgroup analysis

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Disclosures

- **MV** received consultancy fees from Novartis, Travere, Roche, Apellis, Alexion, BioCryst, Purespring, Bayer, and WebMD; received research funding from Alexion, ChemoCentryx, Bayer, Novartis, Roche, Chinook, Apellis, and Travere for participation in clinical studies; and served on speakers bureaus for Novartis, Roche, Vifor, Travere, and GSK
- **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
- **BPD** received consulting fees and honoraria from Alexion AstraZeneca Rare Disease, Apellis, Novartis, and Arrowhead
- **LaG** receives research support from Alexion and Apellis; and has served as a consultant for Novartis, Alexion, and Roche
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- **AM** received consultant and speaker fees from Sobi
- **NvdeK** received consultancy fees from Sobi, Roche, Novartis, Alexion, and Samsung
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- **LL** is an employe of Apellis and may hold stock or stock options
- **LLL** and **JS** are employees of Sobi and may hold stock or stock options

C3G and primary IC-MPGN are rare, chronic, and heterogeneous complement-mediated diseases with a high unmet need in children

Disease is driven by complement 3 overactivation, resulting in the accumulation of **C3 deposits in the glomeruli** (in addition to **immunoglobulins in IC-MPGN**), leading to inflammation and progressive **kidney damage that can result in permanent loss** of kidney function[1,2]

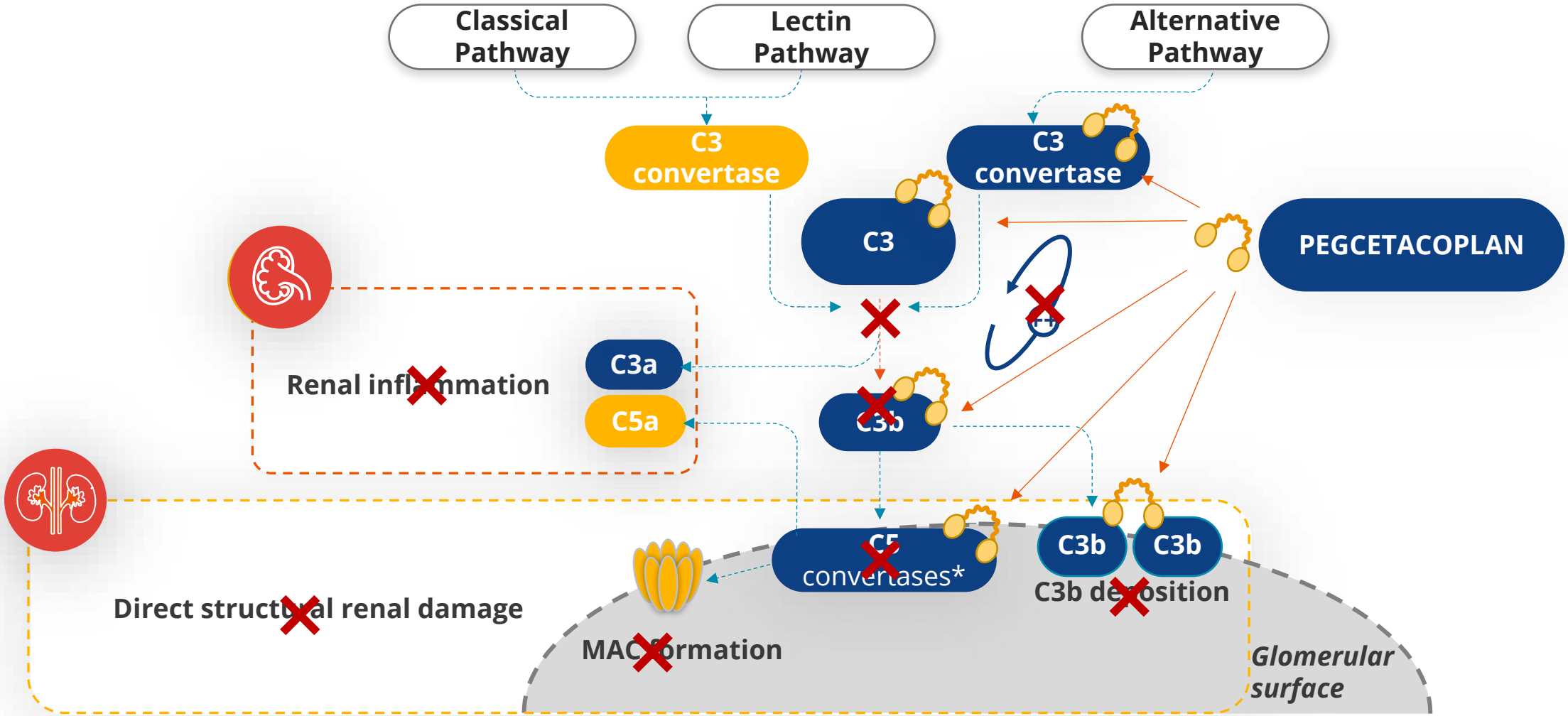
Children may present with **varying degrees of proteinuria** (mild to nephrotic), hematuria (microscopic to macroscopic), and low serum C3 levels. Disease **presentation and progression are heterogeneous**, **requiring a kidney biopsy** for definitive diagnosis[3-5]

Approximately **20% of children develop kidney failure within 10-15 years of diagnosis** despite treatment,[3-5] requiring dialysis or kidney transplantation. There is a **high likelihood of recurrence after transplantation**

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

1. Bomback AS, et al. *Kidney Int Rep.* 2024. doi:10.1016/j/ekir.2024.09.017. **2.** Mastrangelo A, et al. *Front Pediatr.* 2020;8:205. **3.** Kirpalani A, et al. *Kidney Int Rep.* 2020;5:2313–2324. **4.** Spartà G, et al. *Clin Kidney J.* 2018;11:479–490. **5.** Wong EKS, et al. *Clin J Am Soc Nephrol.* 2021;16:1639–1651.

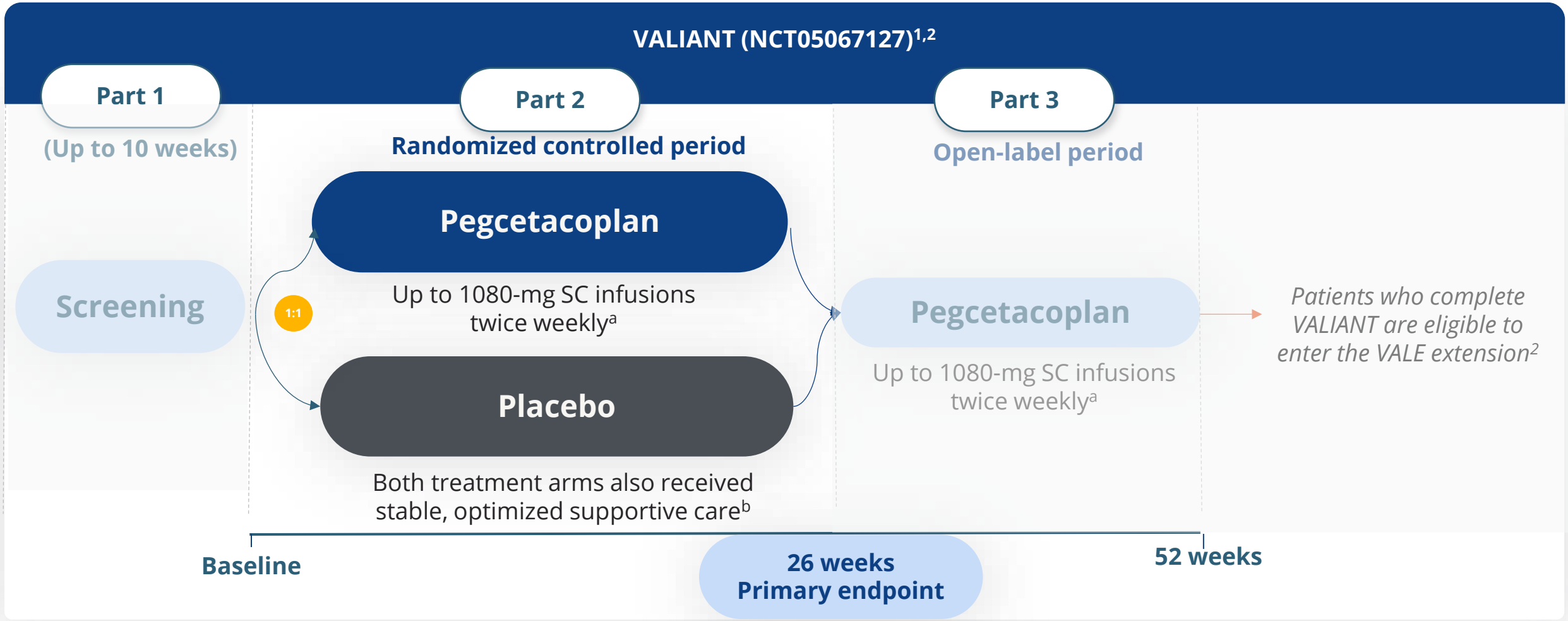
Pegcetacoplan, a C3 and C3b inhibitor, blocks C3 dysregulation and downstream complement activation in C3G and primary IC-MPGN[1–7]



*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



ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MMF, mycophenolate mofetil; SC, subcutaneous; SGLT2is, sodium-glucose cotransporter-2 inhibitors.

[a]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. [b]Stable, optimized antiproteinuric regimens: ACEis, ARBs, SGLT2is, MMF, and corticosteroids (prednisone ≤20 mg/d or equivalent) were permitted.

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 Sept. 18, 2024.

VALIANT: Eligibility criteria

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[a]
- 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; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; 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.

[a]Calculated using the CKD-Epi equation for adults or the Bedside Schwartz equation for adolescents.

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
- For participants with evaluable renal biopsies, **change in the activity score of the C3G histologic index score** from baseline to week 26 *(not mandatory for adolescents)*
- Proportion of participants with evaluable renal biopsies showing **decreased C3c staining on renal biopsy** from baseline to week 26[a]
- **Change in eGFR** from baseline to week 26

eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio. [a]For participants with evaluable renal biopsies. Biopsy was not mandatory for adolescents

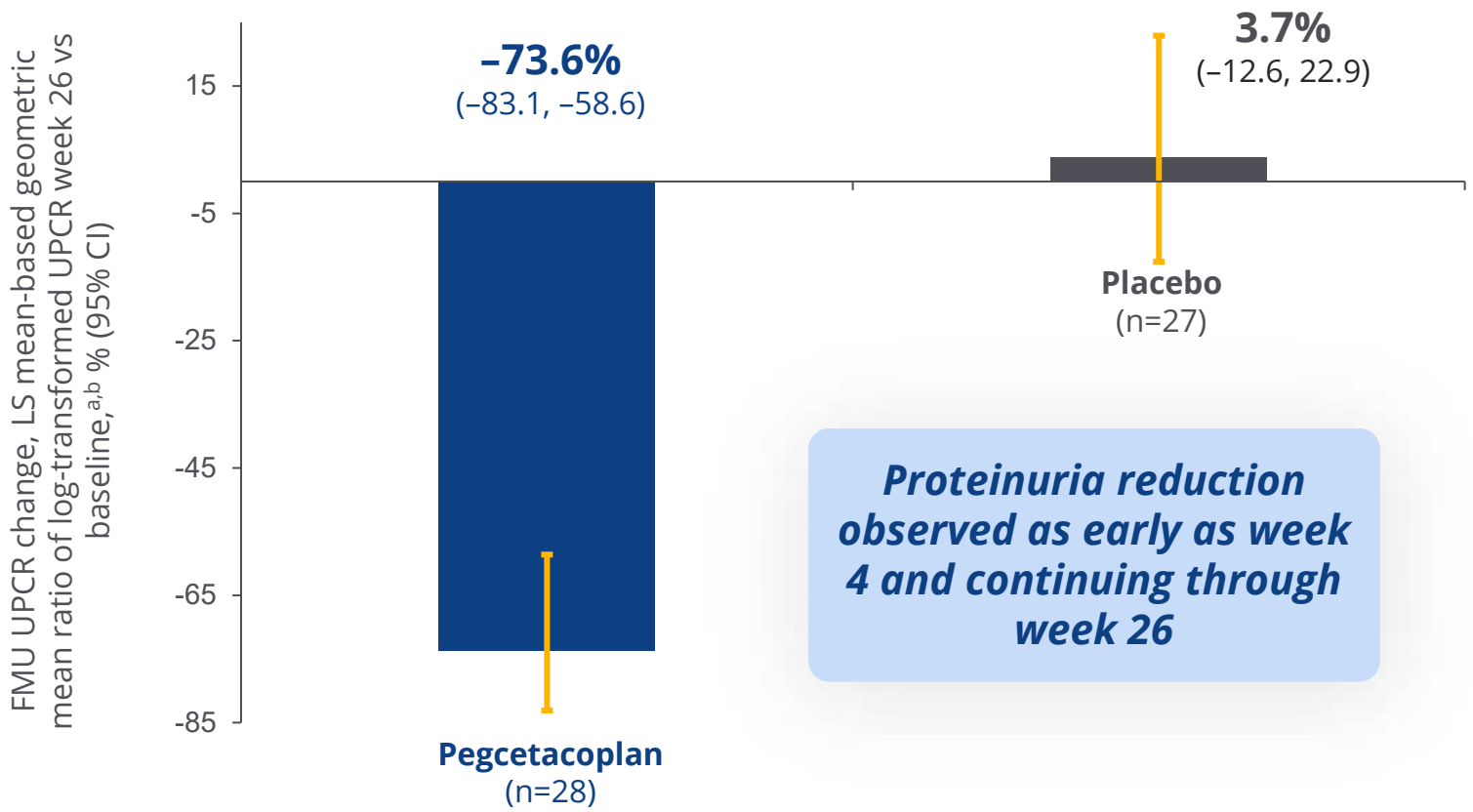
VALIANT Included a broad patient population with a large proportion of adolescents

Characteristic	Adolescents		Overall population	
	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 (1.7)	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)	4.0 (3.4)	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 m^2	92.0 (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; UPCR, urine protein-to-creatinine ratio.

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

Change in proteinuria (week 26 vs baseline)[a,b]



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

Primary endpoint

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

74.5%

(58.5, 84.3)

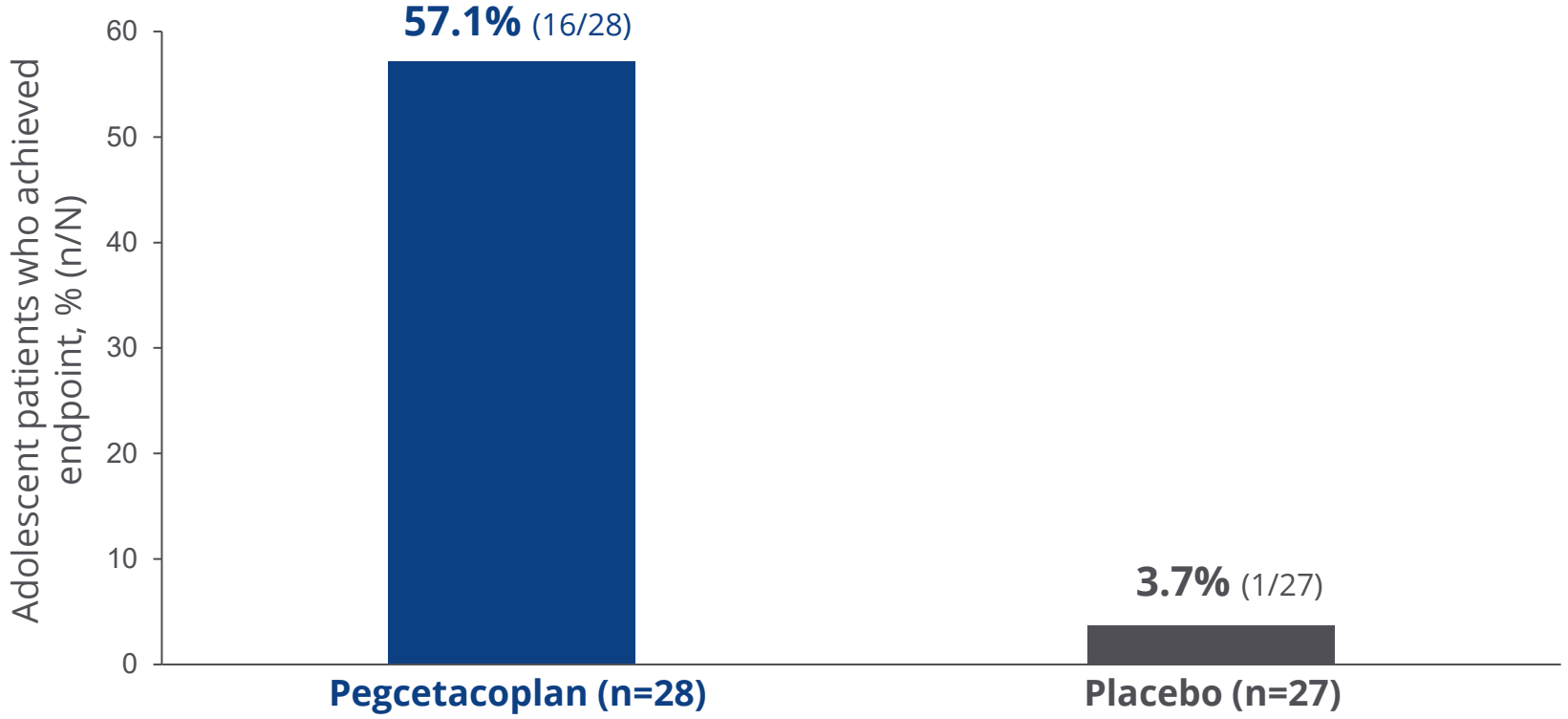
***P*<.0001**

nominal[c]

C3G, complement 3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis;, UPCR urine protein-to-creatinine ratio. [a]Using an equal-weighted average from FMU over weeks 24, 25, and 26. [b]Percentages calculated by converting the ratio of geometric means to percentages [c]Comparison was not corrected for multiplicity.

Pegcetacoplan resulted in significantly more adolescents achieving the composite renal endpoint

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: pegcetacoplan vs placebo arms

37x

higher odds of achieving composite renal endpoint

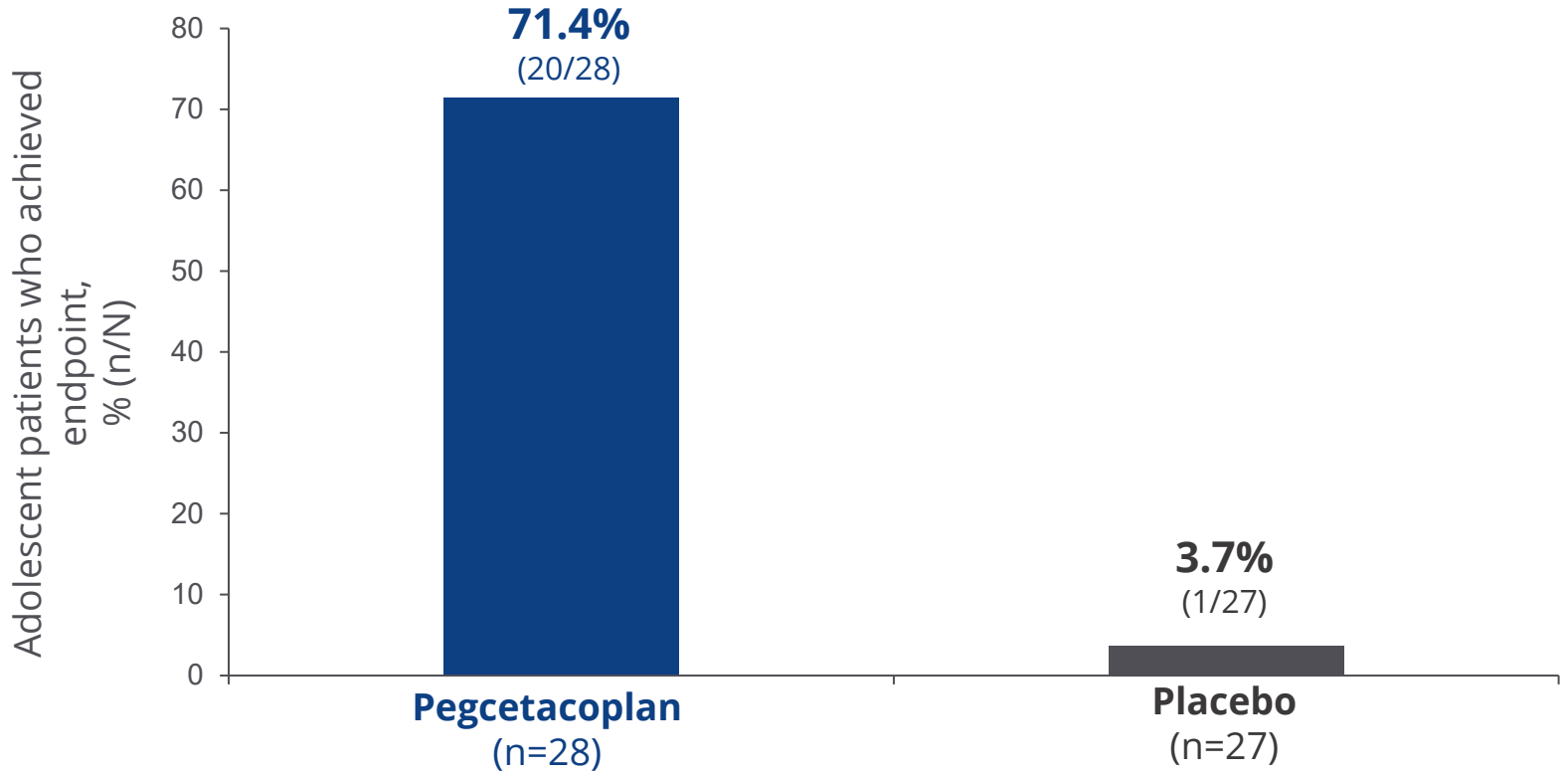
***P*<.0016**

nominal[a]

eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio. Intent-to-treat population (all randomized patients). 2-sided *P*-values. [a]Comparison was not corrected for multiplicity.

71% of adolescents who received pegcetacoplan achieved ≥50% proteinuria reduction, significantly more than placebo

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



Key secondary endpoint

Odds ratio:
pegcetacoplan vs placebo arms

62x

higher odds of achieving ≥50% proteinuria reduction

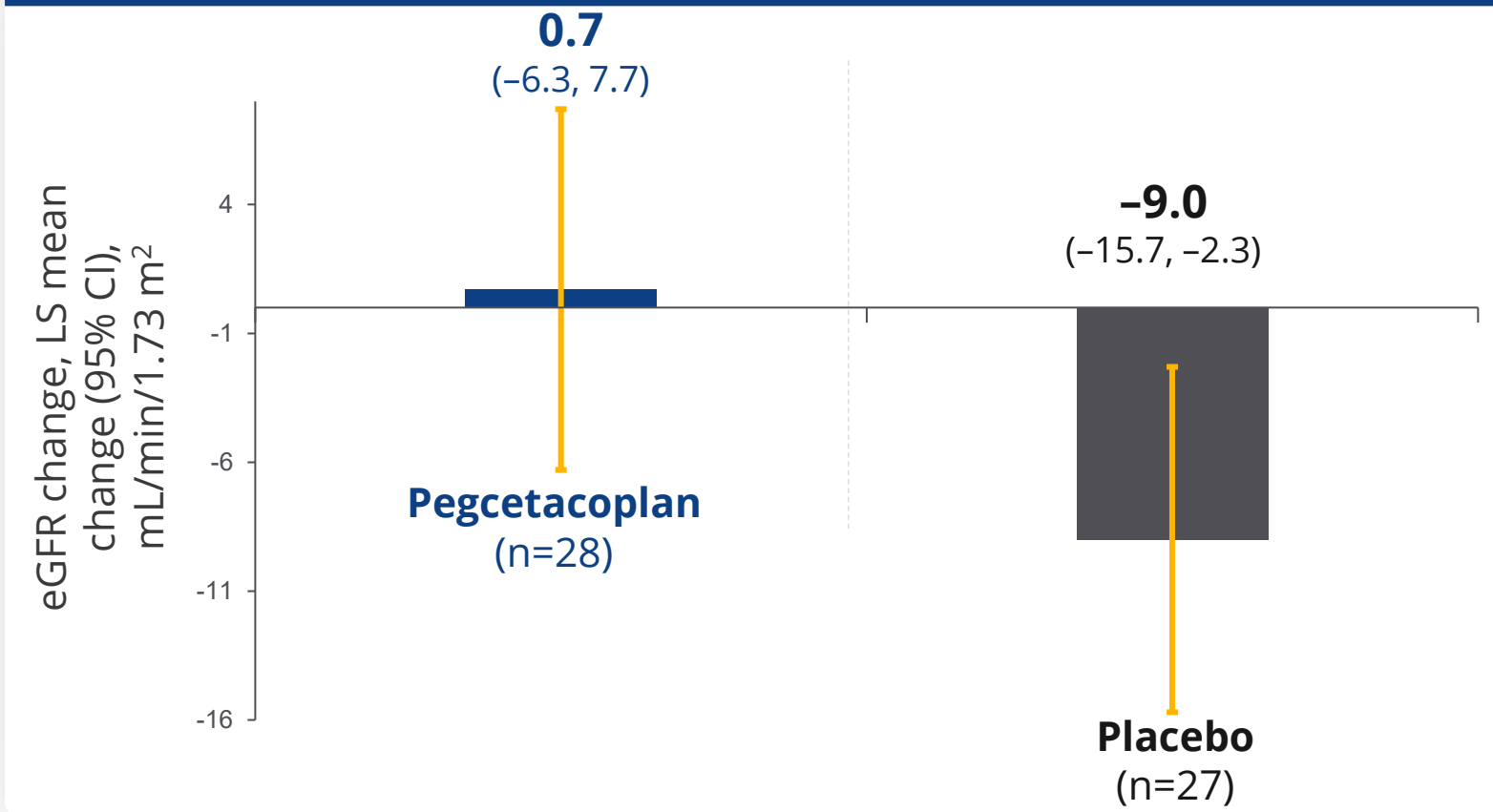
***P*<.0002**

nominal[a]

[a]Comparison was not corrected for multiplicity.

Pegcetacoplan stabilized eGFR compared with placebo among adolescents

Change in eGFR (week 26 vs baseline)



Key secondary endpoint

Difference in pegcetacoplan vs placebo arms

+9.7 *mL/min/1.73 m²*

P=.05

nominal[a]

C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; LS, least squares. [a]Comparison was not corrected for multiplicity.

Pegcetacoplan demonstrated an acceptable safety profile among adolescents

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

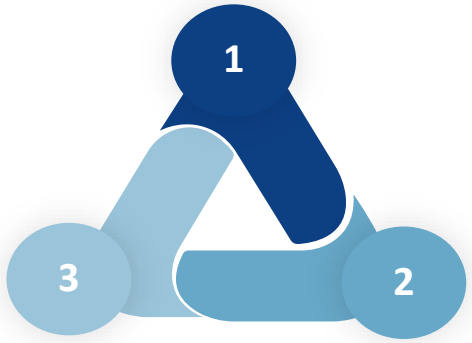
TEAE, treatment-emergent adverse event.

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.

Pegcetacoplan demonstrates safety and efficacy for adolescent patients in the phase 3 VALIANT trial

74.5% clinically meaningful **proteinuria reduction** vs placebo

71% of adult patients achieved **zero glomerular C3 staining**



eGFR stabilisation **+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 >2200 patient-years of pegcetacoplan exposure

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