VALIANT: Phase 3 Trial of Pegcetacoplan for Patients With Native or Post-Transplant Recurrent C3G or Primary IC-MPGN

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Disclosures

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- **NI** served on an advisory board for Alexion.
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- **DPG, SHH, CL, MINdH,** and **DW** has nothing to disclose
- **DZ** has received consulting fees from Apellis
- **LL and ZW** are employees of Apellis and hold stock or stock options.
- **LLL and JS** are employees of Sobi and hold stock options or shares.
- **FF** has received consulting fees from Apellis, Sobi Novartis, Roche, Alexion.

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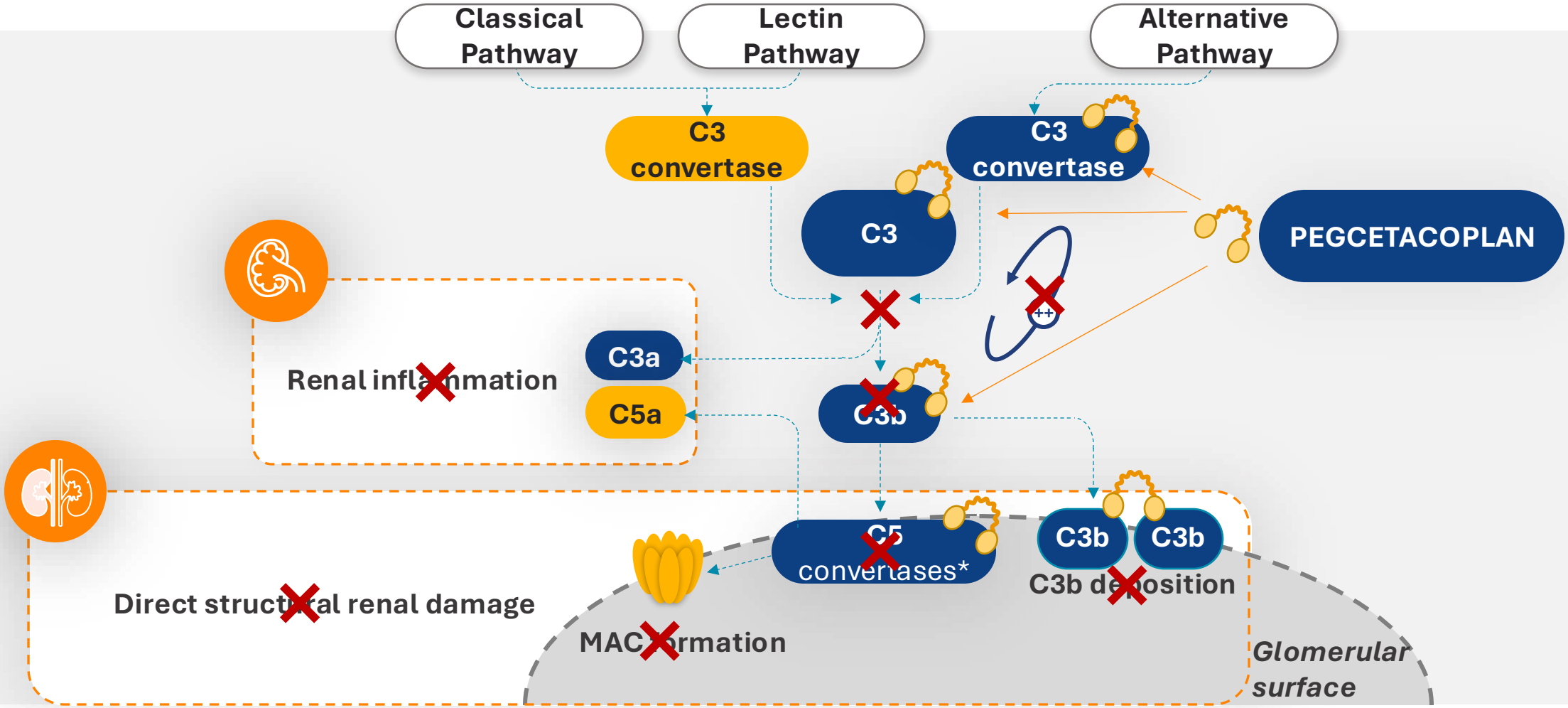
Pegcetacoplan, a Targeted C3 and C3b Inhibitor, Acts Centrally to Block Downstream Complement Activation in C3G and Primary IC-MPGN[1–7]



*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;60:1016342. **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.

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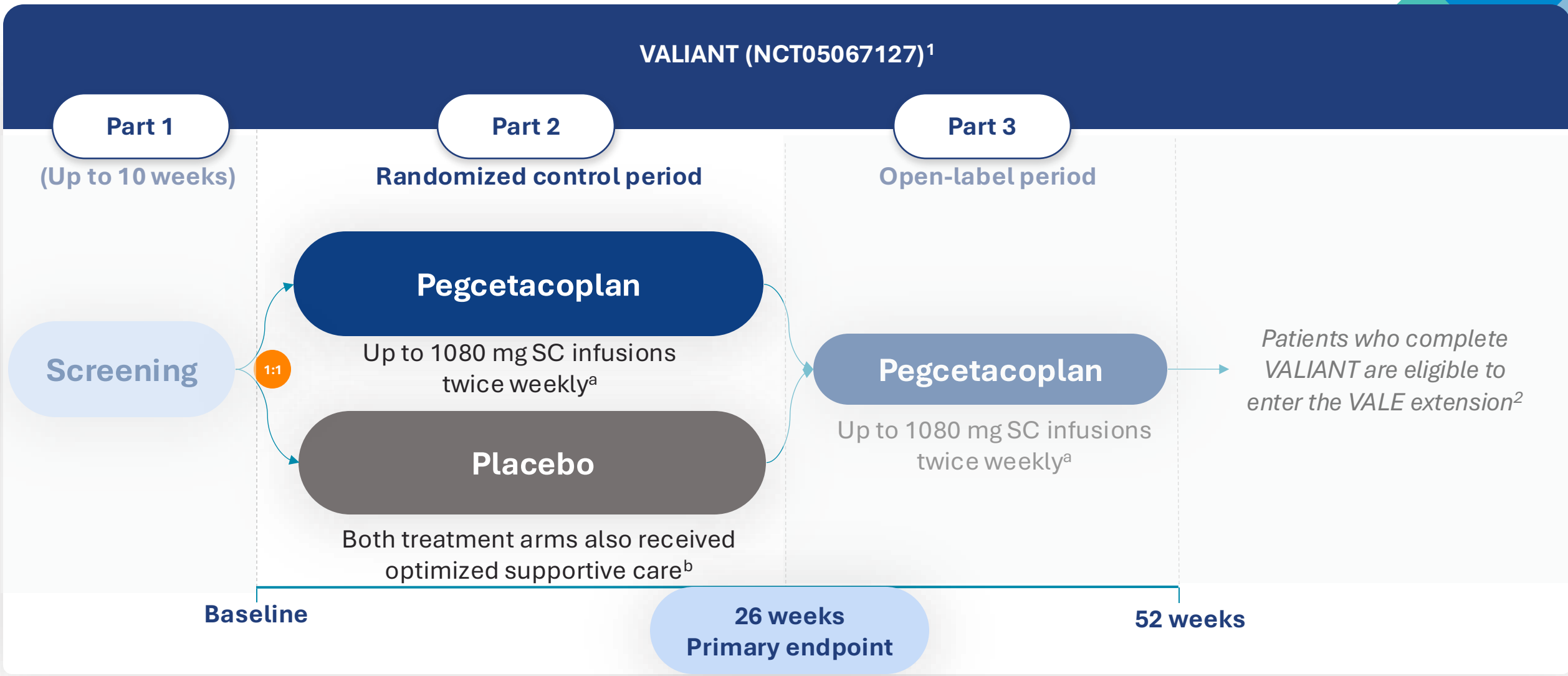
VALIANT: Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial



ACEi, 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/day or equivalent) were permitted.

1. Dixon BP, et al. ASN Kidney Week 2023, Nov 2–5, 2023. **2**. ClinicalTrials.gov. VALIANT. clinicaltrials.gov/study/NCT05067127. Accessed Sep 18, 2024.

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VALIANT: Eligibility Criteria

Key eligibility criteria

Inclusion

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

Exclusion

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

Other eligibility criteria

Inclusion

- Evidence of active disease
- ≥1 g/day of proteinuria on screening urine collection and uPCR ≥1 g/g in 2 or more first-morning spot urine samples
- eGFR ≥30 mL/min/1.73 m^{2a}
- 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

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; C3, complement protein 3; C3G, C3 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; yrs, years. [a]Calculated using the CKD-Epi equation for adults or the Bedside Schwartz equation for adolescents.

VALIANT Included a Broad Patient Population: ≥12 years, Pre- and Post-Transplant, C3G and Primary IC-MPGN

Characteristic[a]	Pegcetacoplan (N=63)	Placebo (N=61)
Age, mean (SD)	28.2 (17.1) yrs	23.6 (14.3) yrs
Adolescents (12–17 yrs) / adults (≥18 yrs), n (%)	28 (**44.4%**) / 35 (55.6%)	27 (**44.3%**) / 34 (55.7%)
Age of adolescents / adults, mean (SD)	14.6 (1.7) yrs / 39.1 (15.9) yrs	14.8 (1.7) yrs / 30.6 (15.9) yrs
Sex, female, n (%)	37 (58.7%)	33 (54.1%)
Race, white, n (%)	45 (71.4%)	46 (75.4%)
Baseline 24 hr uPCR, mean (SD)	3.95 (2.89) g/g	3.29 (2.36) g/g
Baseline triplicate first morning spot uPCR, mean (SD)	3.12 (2.41) g/g	2.54 (2.01) g/g
Baseline eGFR, mean (SD)	78.5 (34.1) mL/min/1.73 m^2	87.2 (37.2) mL/min/1.73 m^2
Underlying disease based on screening biopsy, n (%)		
C3G	**51 (81.0%)**	**45 (73.8%)**
C3GN	45 (71.4%)	41 (67.2%)
DDD	4 (6.3%)	4 (6.6%)
Undetermined	2 (3.2%)	0
Primary IC-MPGN	**12 (19.0%)**	**16 (26.2%)**
Time since diagnosis, mean (SD)	3.6 (3.5) yrs	3.8 (3.6) yrs
Post-transplant recurrent disease, n (%)	**5 (7.9%)**	**4 (6.6%)**

C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; hr, hour; IC-MPGN, immune complex membranoproliferative glomerulonephritis; SD, standard deviation; uPCR, urine protein-to-creatinine ratio; yrs, years. [a]Intent-to-treat population (all randomized patients).

VALIANT: Primary and Key Secondary Endpoints

Primary

- **Log-transformed ratio of uPCR at week 26** compared to baseline

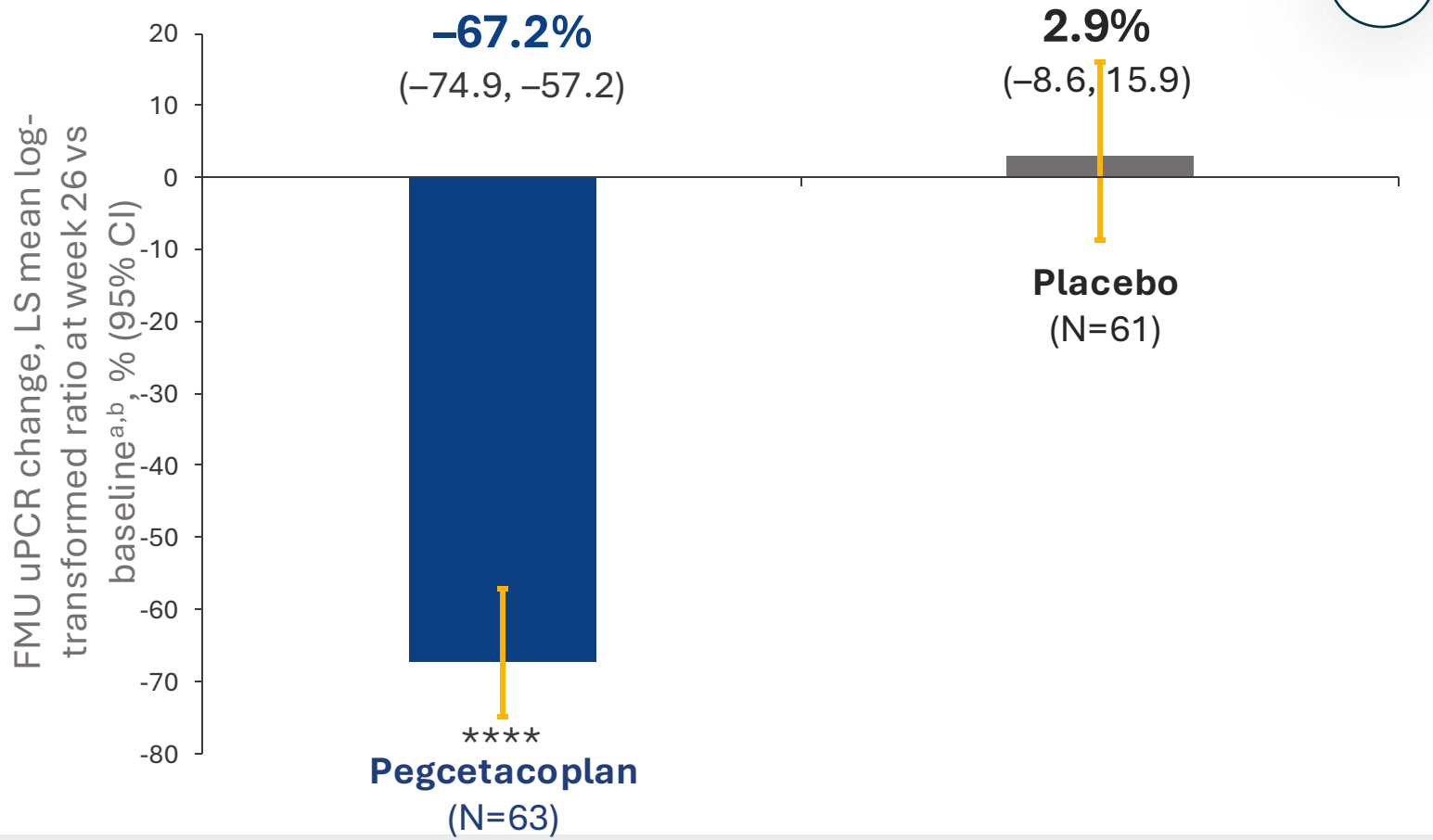
Key Secondary

- Proportion of participants **achieving a composite renal endpoint** (ie, 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) 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
- Proportion of participants with evaluable renal biopsies showing **decreased C3c staining on renal biopsy** from baseline to week 26
- **Change in eGFR** from baseline to week 26

C3c, complement protein 3c; eGFR, estimated glomerular filtration rate; uPCR, urine protein-to-creatinine ratio.

Highly Statistically and Clinically Significant Proteinuria Reduction of 68.1% With Pegcetacoplan vs Placebo

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



Primary endpoint

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

68.1%

(57.3, 76.2)

***P*<.0001**

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

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

**** *P*≤.0001. Intent-to-treat population (all randomized patients). [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.

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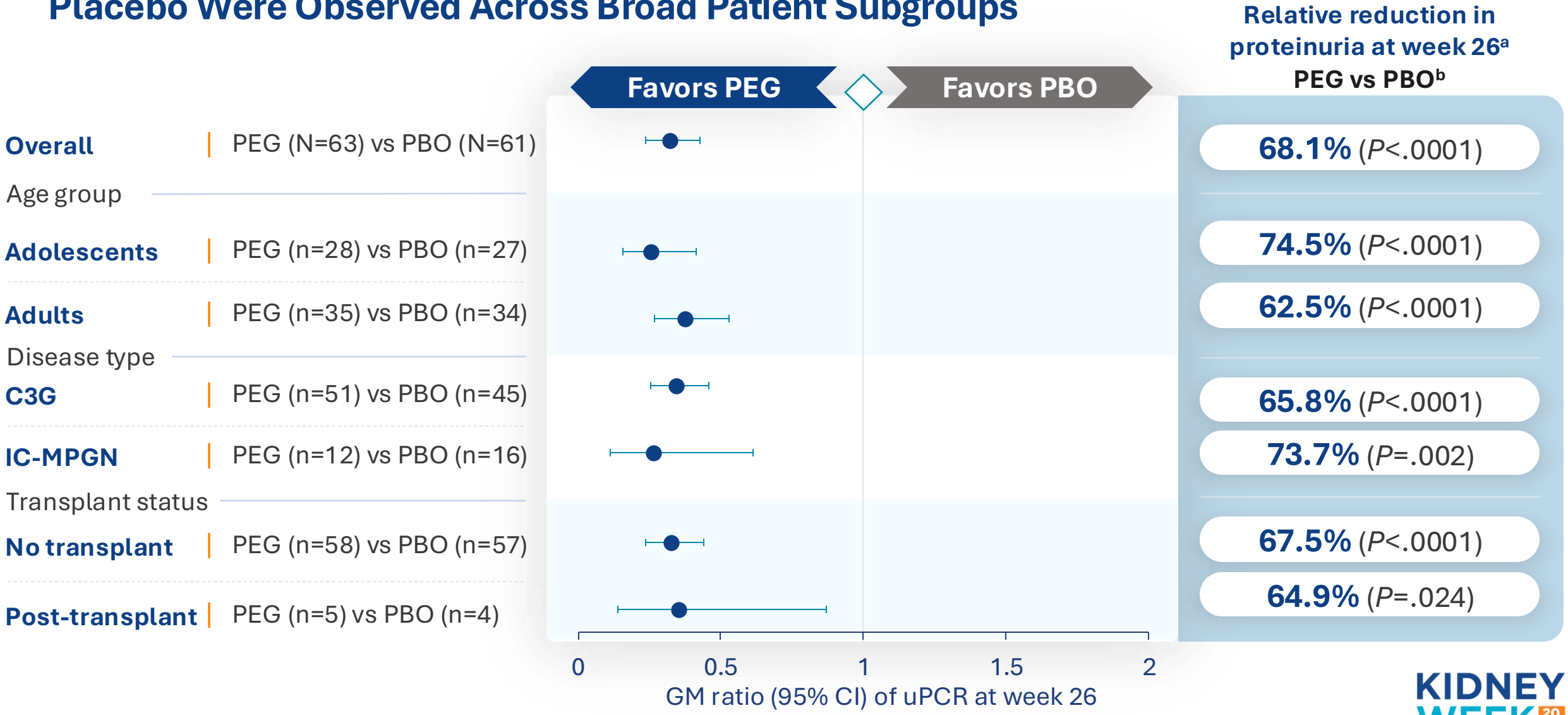
Consistent, Clinically Meaningful Proteinuria Reductions With Pegcetacoplan vs Placebo Were Observed Across Broad Patient Subgroups



C3G, C3 glomerulopathy; CI, confidence interval; GM, geometric mean; IC-MPGN, immune complex membranoproliferative glomerulonephritis; PBO, placebo; PEG, pegcetacoplan; uPCR, urine protein-to-creatinine ratio. Intent-to-treat population (all randomized patients). [a]Using an equal-weighted average over weeks 24, 25, and 26 compared to baseline. [b]Percentages calculated by converting the ratio of geometric means to percentages.

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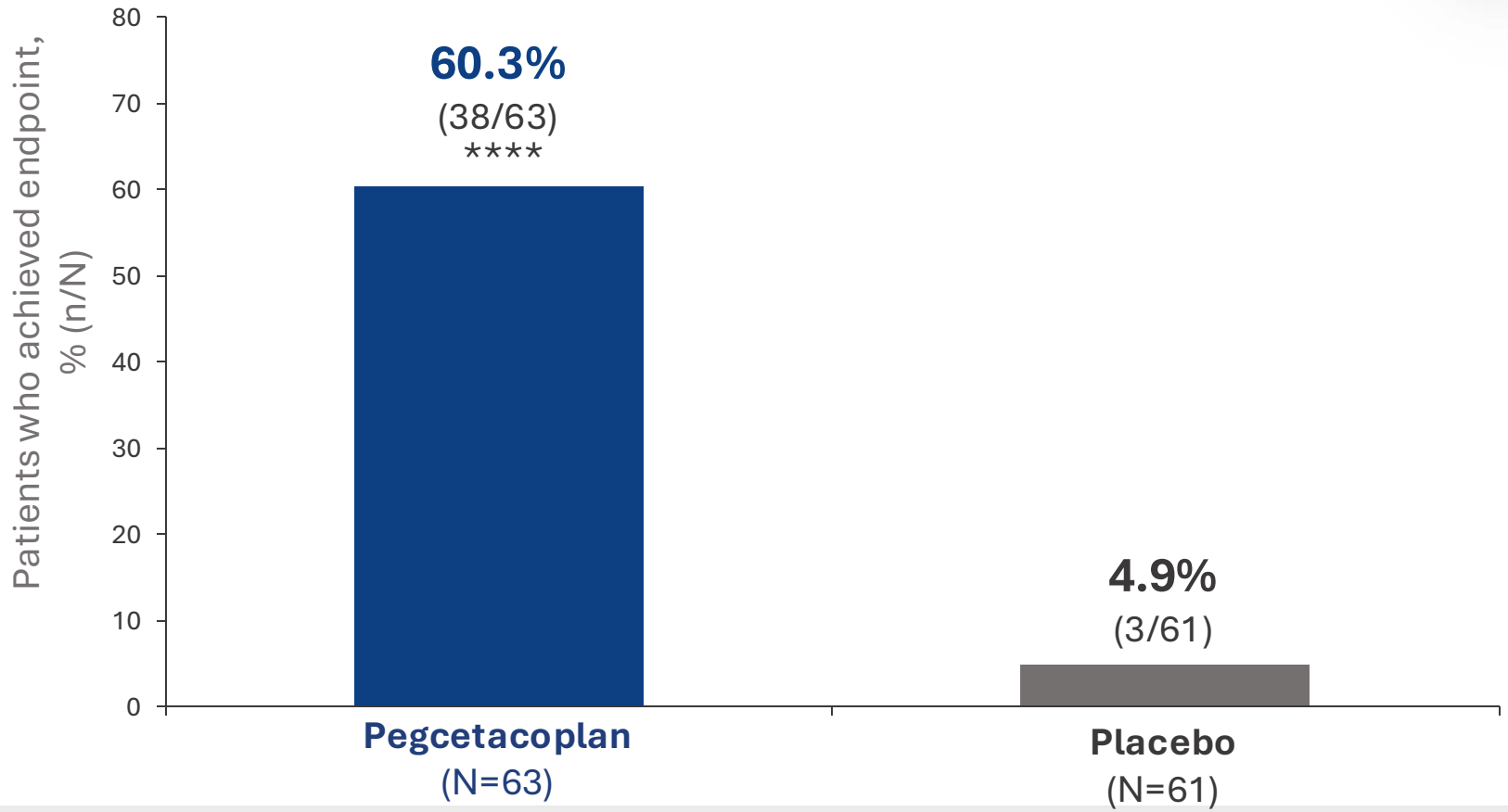
Significantly More Patients Achieved ≥50% Proteinuria Reduction With Pegcetacoplan vs Placebo

≥50% proteinuria reduction



Key secondary endpoint

Odds ratio
Pegcetacoplan vs placebo arms

31x

higher odds of achieving ≥50% proteinuria reduction

***P*<.0001**

****$P \leq .0001$. Intent-to-treat population (all randomized patients). 2-sided *P* values.

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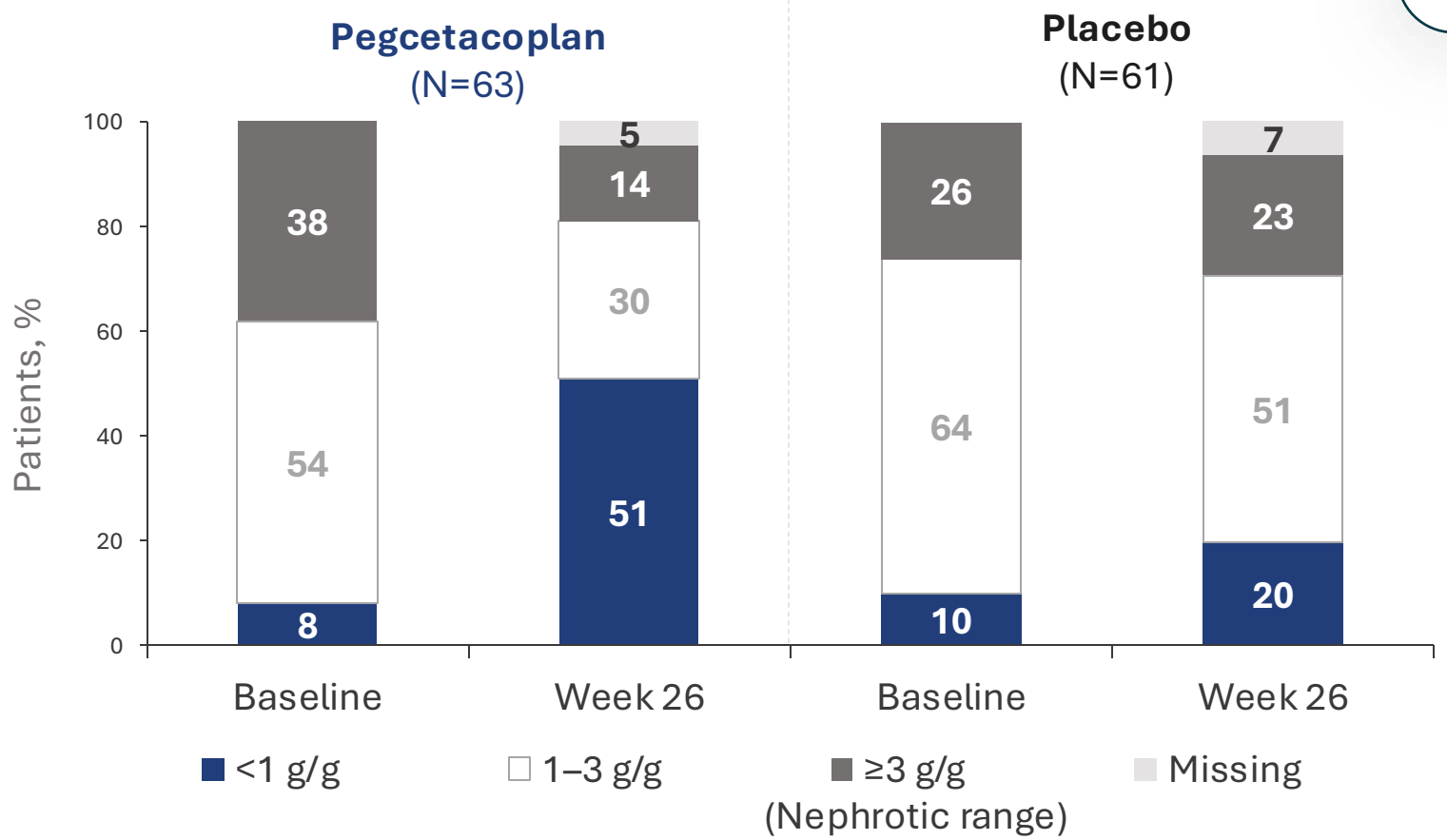
Substantial Improvement in the Percentage of Patients With Proteinuria <1 g/g and Decrease in Percentage in Nephrotic Range (≥3 g/g) Following Pegcetacoplan Treatment

Proteinuria shift analysis (week 26 vs baseline)[a]



***Post hoc* analysis**

Proportion of pegcetacoplan-treated patients with

<1 g/g proteinuria

after 26 weeks

50.8%

FMU, first morning urine; uPCR, urine protein-to-creatinine ratio.

[a]Based on FMU uPCR.

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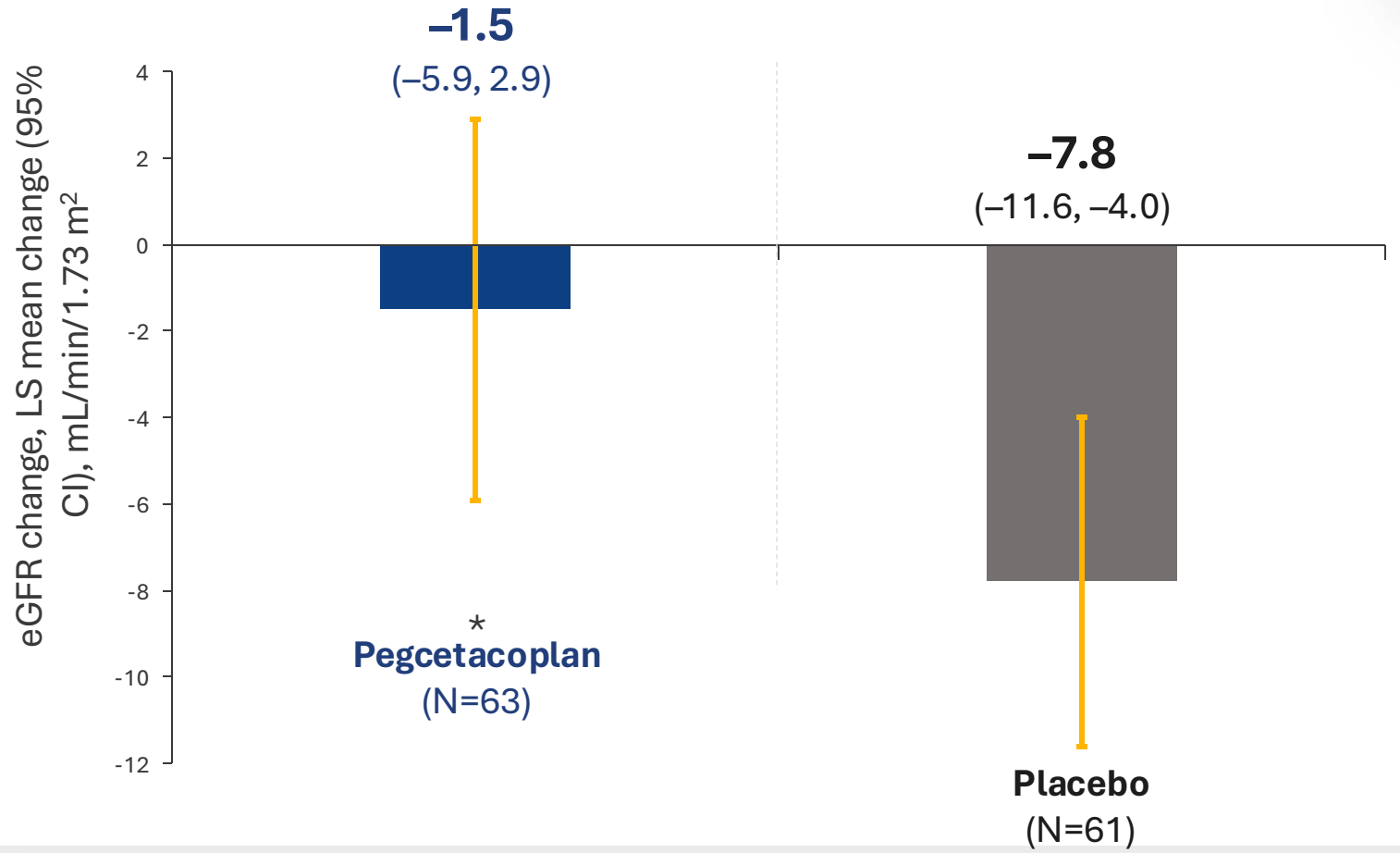
Pegcetacoplan Significantly Stabilized eGFR Compared With Placebo

Change in eGFR (week 26 vs baseline)



Key secondary endpoint

Difference in pegcetacoplan vs placebo arms

+6.3 *mL/min/1.73 m²*

***P*=.03**

nominal[a]

C3G, C3 glomerulopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares.

**P*≤.05. Intent-to-treat population (all randomized patients). [a]Statistical testing stopped after first endpoint to not reach significance between treatment arms (ie, change in activity score of C3G histologic index score at week 26 vs baseline).

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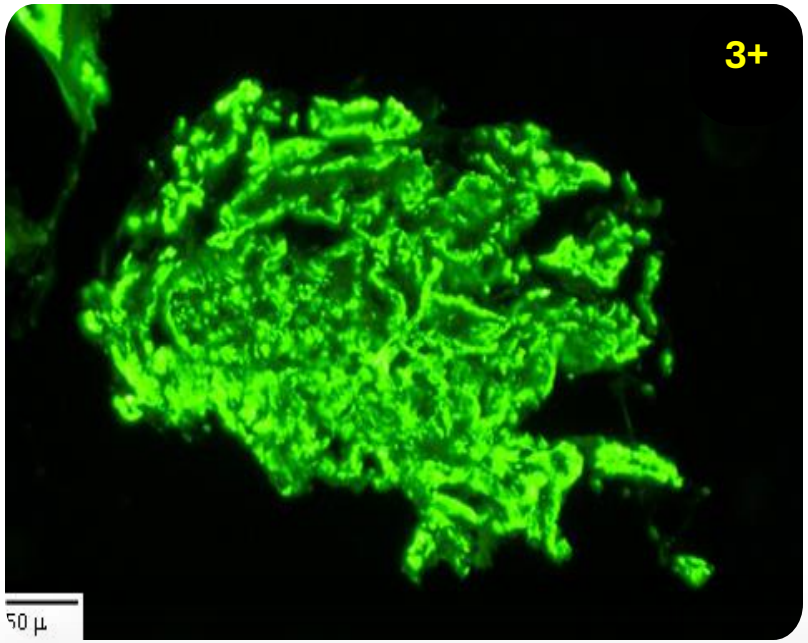
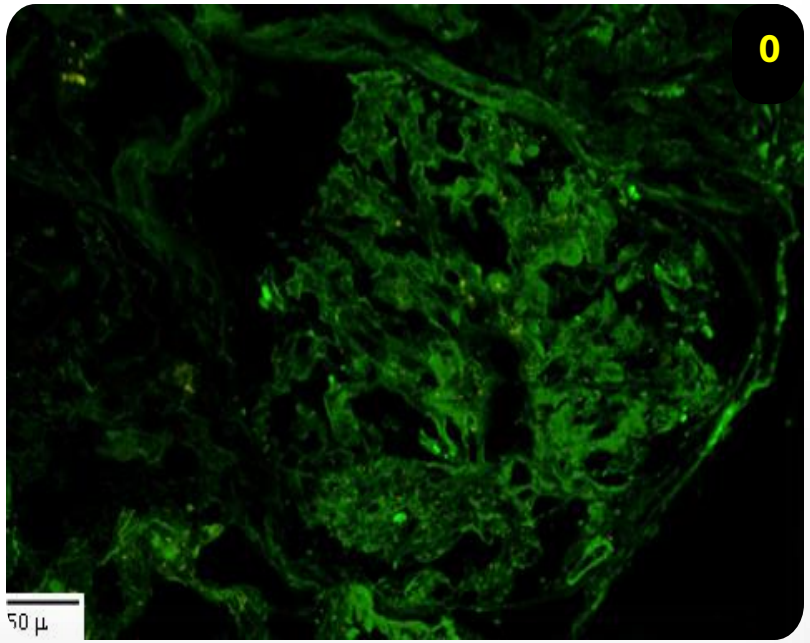
Pegcetacoplan Treatment Resulted in Clinically Significant Clearance of C3c From Renal Biopsies

Renal biopsies from a pegcetacoplan-treated C3G native kidney patient

Baseline



Week 26



71.4% (25/35) of pegcetacoplan treated patients **achieved 0 intensity staining**

Key secondary endpoint

Proportion with reduced C3c renal biopsy staining[a]

Pegcetacoplan	**74.3% (26/35)**
Placebo	11.8% (4/34)

27x higher odds of achieving 2 ≥OOM reduction

(6.5, 115.9); nominal[b]

P<.0001

C3c, complement protein 3c; C3G, C3 glomerulopathy; OOM, orders of magnitude

Intent-to-treat population (all randomized patients). [a]Difference defined as ≥2 OOM at week 26 vs baseline; in all adults. Baseline renal biopsies were not required for adolescent participants. [b]Statistical testing stopped after first endpoint to not reach significance between treatment arms (ie, change in activity score of C3G histologic index score at week 26 vs baseline).

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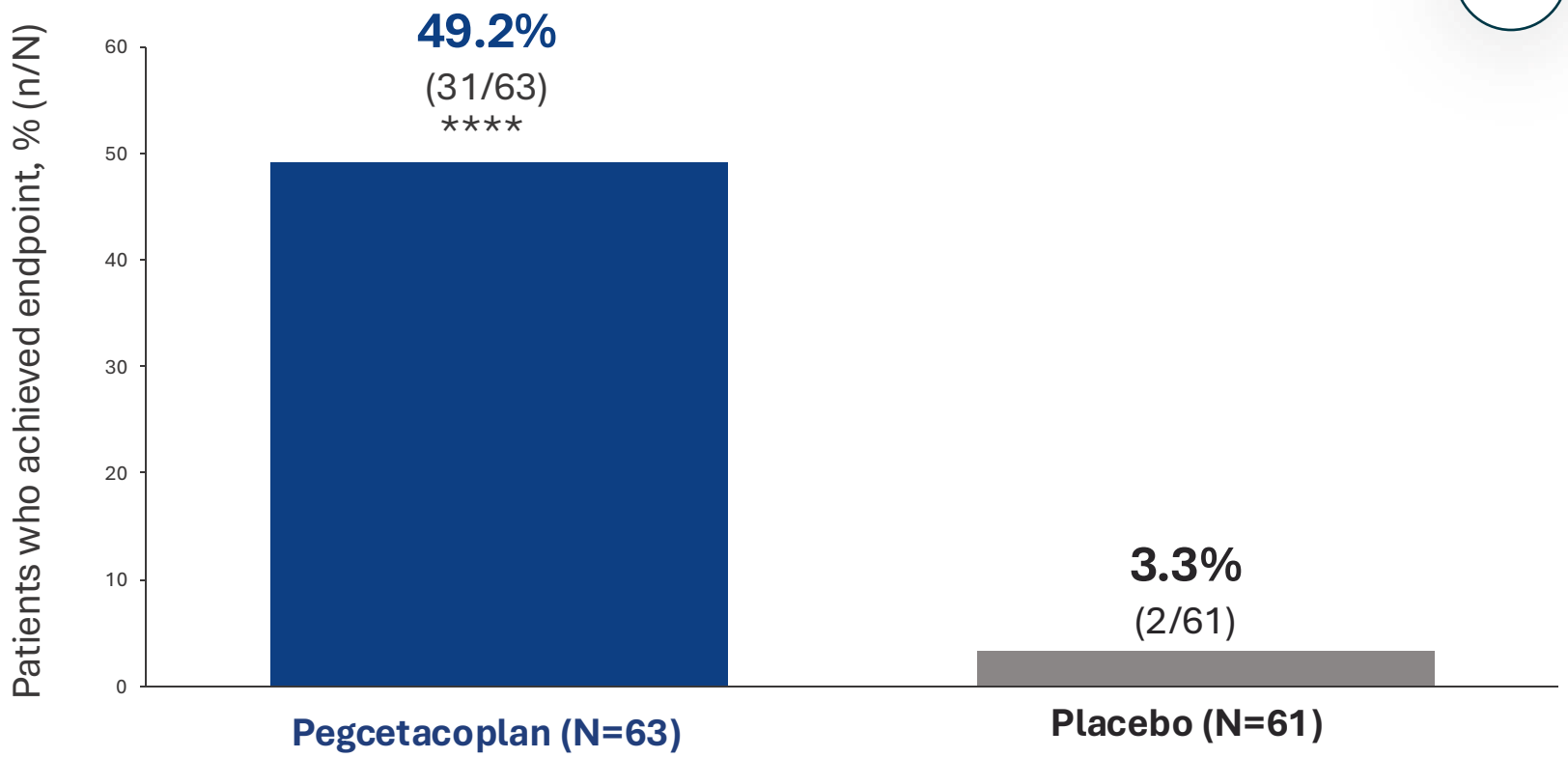
Pegcetacoplan Resulted in Significantly More Patients Achieving the Positive Composite Renal Endpoint

Proportion of 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

27x

higher odds of achieving composite renal endpoint vs placebo

***P*<.0001**

eGFR, estimated glomerular filtration rate; uPCR, urine protein-to-creatinine ratio.
****$P \leq .0001$. Intent-to-treat population (all randomized patients). 2-sided *P* values.

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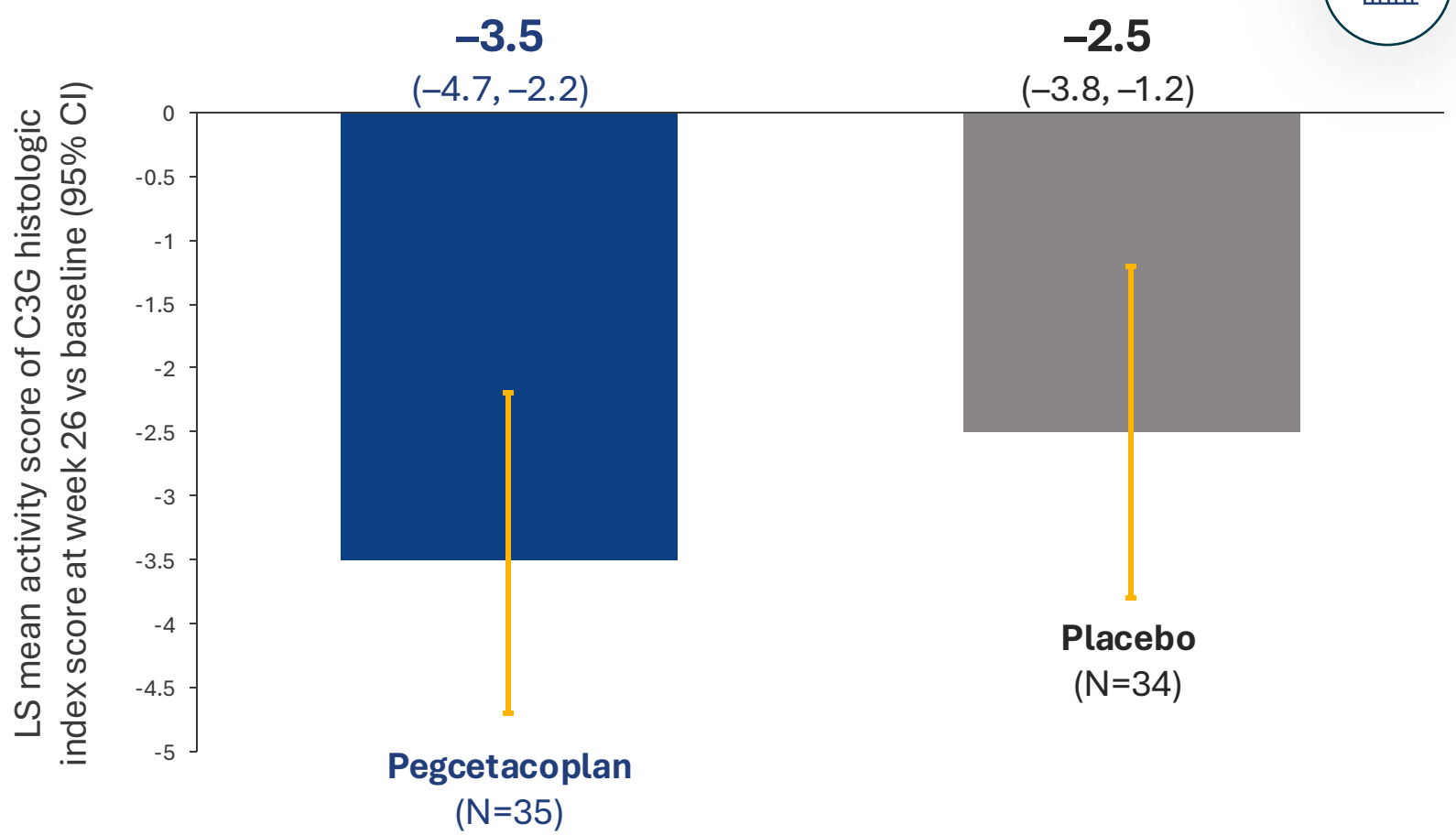
Reduction in Activity Score of C3G Histologic Index Score With Pegcetacoplan

Change in activity score of C3G histologic index score (week 26 vs baseline)[a]



Key secondary endpoint

Adjusted LS mean (95% CI) difference in pegcetacoplan vs placebo arms

–1.0 (–2.8, 0.8)

***P*=.28**

CI, confidence interval; C3G, glomerulopathy; LS, least squares; ns, not statistically significant.
ns P>.05. Intent-to-treat population (all randomized patients).
[a]In adult patients.

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TEAE frequency and severity were similar between treatment arms

Patients, n (%)	Pegcetacoplan (N=63)	Placebo (N=61)
TEAEs	53 (84.1)	57 (93.4)
• Treatment-related TEAEs	25 (39.7)	26 (42.6)
Severe TEAEs	3 (4.8)	4 (6.6)
Serious TEAEs	6 (9.5)	6 (9.8)
• Serious infections		
• COVID-19 pneumonia	1 (1.6)	0
• Influenza	1 (1.6)	0
• Pneumonia	1 (1.6)	0
• Viral infection	0	1 (1.6)
TEAEs leading to treatment discontinuation	1 (1.6)	1 (1.6)
Deaths (COVID-19 pneumonia, unrelated to pegcetacoplan)	1 (1.6)	0

0 encapsulated *N. meningitidis* cases
among the 4 reported serious infections (3 pegcetacoplan; 1 placebo)

Consistent with
>2000 patient-years
of pegcetacoplan exposure[a]

AE, adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.
Safety population (all randomized and treated patients). 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.
[a]Includes exposure in clinical trials and post marketing across multiple indications.

Summary: Pegcetacoplan Safe and Effective in the Phase 3 VALIANT Trial

- ✓ **Proteinuria reduction of 68.1%** pegcetacoplan vs placebo
  - ✓ Highly statistically significant and clinically meaningful
  - ✓ Consistent across subgroups based on disease type, age, and transplant status
  - ✓ Among pegcetacoplan-treated patients, **50.8% achieved <1 g/g proteinuria** at week 26
- ✓ **Statistically significant stabilization of eGFR, +6.3 mL/min/1.73 m^2** pegcetacoplan vs placebo
- ✓ **Zero intensity staining of C3c** achieved in **>70%** of pegcetacoplan-treated patients
- ✓ Pegcetacoplan has been **well tolerated** with **no encapsulated meningitis** reported, consistent with previous trials and more than **2000 patient-years of pegcetacoplan exposure**

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