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Challenge Your Thinking

Pegcetacoplan population pharmacokinetics and exposure-response analysis in adolescent and adult patients with C3G or primary IC-MPGN

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CONCLUSIONS

- Population pharmacokinetic (PK) analyses support a twice weekly (BIW) subcutaneous (SC) dosing regimen of 1080 mg in adults and a corresponding weight-adjusted dosing regimen in adolescents with complement 3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN).
- In these analyses, pegcetacoplan had a consistent and reliable PK profile and urine protein-to-creatinine ratio (UPCR) response across various subgroups (age, diagnosis, kidney transplant status, and anti-drug antibodies).
- The exposure achieved with pegcetacoplan 1080 mg SC BIW, or the corresponding weight-adjusted adolescent dose, was near the plateau of the exposure-response (E-R) relationship for UPCR, with 95% of patients attaining ≥75% of the maximal UPCR response.

INTRODUCTION

- C3G and primary IC-MPGN are rare, chronic, progressive kidney diseases, driven by C3 dysregulation.[1–4]
- Pegcetacoplan, a targeted C3 and C3b inhibitor, has demonstrated efficacy and safety in adults and adolescents with C3G or primary IC-MPGN.[1,5]
- Pegcetacoplan is approved for use in adults and adolescents with C3G or primary IC-MPGN ≥12 years old and weighing ≥30 kg.[6]
- Pegcetacoplan is administered via SC infusion at a dose of 1080 mg BIW in adults, with adjustments based on body weight for adolescents.[6]

AIMS

- To evaluate pegcetacoplan serum concentration, UPCR response, and the impact of covariates and anti-drug antibodies in adults (≥18 years old) and adolescents (12 to <18 years old) with C3G or primary IC-MPGN.
- To characterise pegcetacoplan E-R relationships in adults and adolescents with C3G or primary IC-MPGN.
- To predict pegcetacoplan exposure across the paediatric age range (2 to <18 years old) and to verify dosing specifically in adolescents (12 to <18 years old).

METHODS

- Overall, the PK model included data from 14 clinical studies, and the PK/pharmacodynamic (PD) model used data from three nephrology studies.
- An existing population PK model for pegcetacoplan serum concentration in healthy adults, adults with renal impairment, and adults with paroxysmal nocturnal haemoglobinuria was updated with data for adults and adolescents with C3G or primary IC-MPGN.
- A PK/PD model was developed using data for adults and adolescents with C3G or primary IC-MPGN to generate pegcetacoplan exposure and UPCR response data, and to assess the typical E-R relationship.
- The influence of intrinsic factors on pegcetacoplan exposure, including age (adults/adolescents), diagnosis (C3G/primary IC-MPGN), kidney transplant status (native/transplant), estimated glomerular filtration rate (eGFR), and UPCR, as well as anti-drug antibodies (anti-peptide and anti-polyethylene glycol antibodies) and UPCR response, was assessed.
- Simulations for paediatric patients (2 to <18 years old), using weight-stratified dosing regimens for patients <50 kg, were performed to inform dosing through exposure matching to adults.

RESULTS

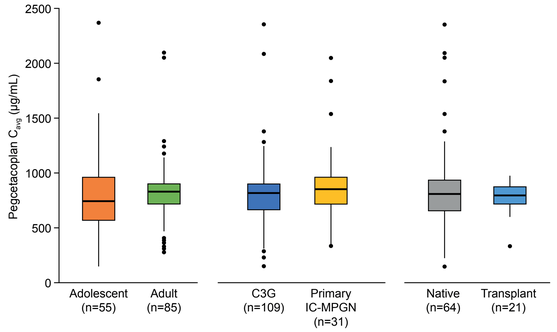
Population PK model

- The PK profile of pegcetacoplan was described by a one-compartment model with a first-order transit absorption compartment (n=1) and first-order elimination.
- Typical PK parameters for patients with C3G or primary IC-MPGN weighing 70 kg with a baseline serum C3 concentration of 0.7 g/L were: clearance, 0.0123 L/h (0.295 L/day); volume, 4.49 L; absorption rate constant, 0.0375 1/h; and bioavailability, 0.767.

Pegcetacoplan exposure and UPCR response

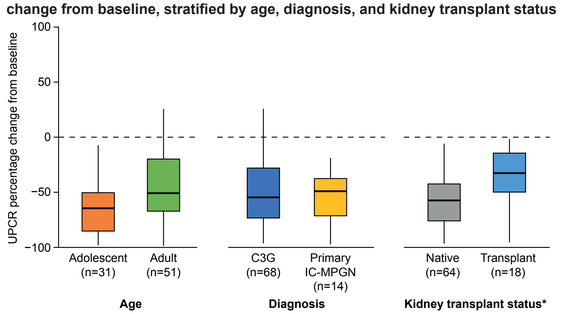
- There was no clinically relevant difference in steady-state pegcetacoplan exposure (**Figure 1**) and UPCR response (**Figure 2**) across age (adults/adolescents), diagnosis (C3G/primary IC-MPGN), and kidney transplant status (native/transplant).

Figure 1. Bayesian-predicted steady-state pegcetacoplan exposure in patients with C3G or primary IC-MPGN, stratified by age, diagnosis, and kidney transplant status



Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively. Median is shown as the horizontal line inside the box. Whiskers represent the minimum and maximum values within 1.5 IQR below Q1 or above Q3.
*Data presented for adult patients only.
C3G, complement 3 glomerulopathy; C_{avg}, average concentration; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IQR, interquartile range.

Figure 2. Bayesian-predicted steady-state pegcetacoplan UPCR percentage change from baseline, stratified by age, diagnosis, and kidney transplant status

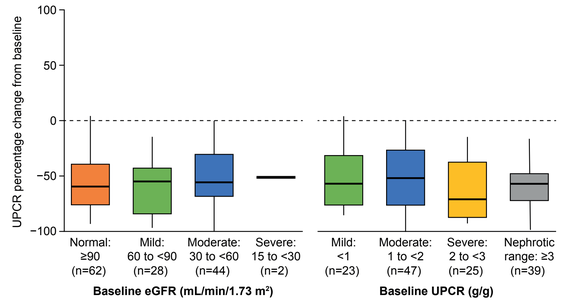


Dashed line: 0% UPCR reduction from baseline. Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively. Median is shown as the horizontal line inside the box. Whiskers represent the minimum and maximum values within 1.5 IQR below Q1 or above Q3. *Data presented for adult patients only.
C3G, complement 3 glomerulopathy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IQR, interquartile range; UPCR, urine protein-to-creatinine ratio.

Impact of eGFR and UPCR on pegcetacoplan exposure and UPCR response

- Analysis of eGFR and UPCR over time showed that renal impairment did not have a clinically meaningful impact on pegcetacoplan exposure.
- Furthermore, baseline eGFR and UPCR did not have a clinically meaningful impact on UPCR response to pegcetacoplan treatment (**Figure 3**).

Figure 3. Bayesian-predicted steady-state UPCR percentage change from baseline, stratified by baseline eGFR and baseline UPCR



Dashed line: 0% UPCR reduction from baseline. Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively. Median is shown as the horizontal line inside the box. Whiskers represent the minimum and maximum values within 1.5 IQR below Q1 or above Q3.
eGFR, estimated glomerular filtration rate; IQR, interquartile range; UPCR, urine protein-to-creatinine ratio.

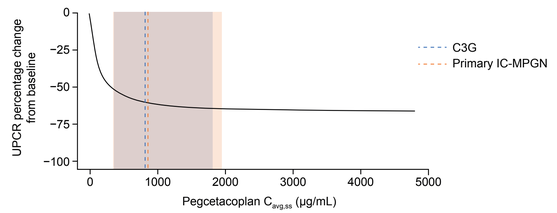
Anti-drug antibodies

- The incidence of anti-peptide and anti-polyethylene glycol antibodies was 28.9% (39/135) and 25.9% (35/135), respectively; however, anti-drug antibodies had no clinically meaningful impact on pegcetacoplan exposure or UPCR response.

E-R analysis

- Estimated median steady-state pegcetacoplan serum concentrations were 812.8 µg/mL in adolescents and adults with C3G and 856.7 µg/mL in those with primary IC-MPGN.
- Based on the E-R relationship, a maximum UPCR percentage reduction from baseline of 68% was identified following pegcetacoplan treatment.
- A dosing regimen of pegcetacoplan 1080 mg SC BIW, or the corresponding weight-adjusted adolescent dosing, resulted in a median serum concentration achieving >80% of the maximum effect (**Figure 4**).
- Serum concentrations near the E-R plateau were reached, with 95% of patients attaining ≥75% of the maximal UPCR response.

Figure 4. E-R for the C3G and primary IC-MPGN patient populations

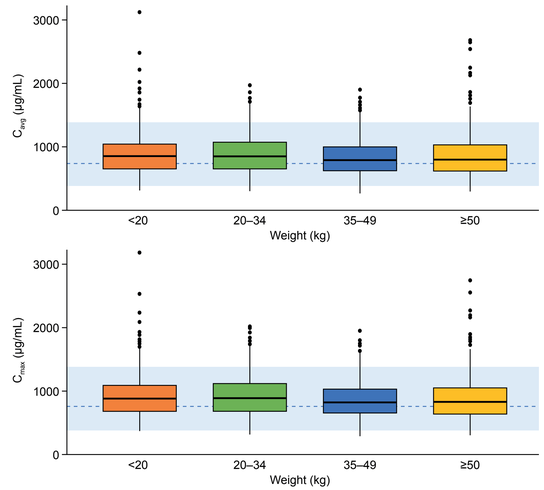


The blue and orange vertical dashed lines are the median average serum concentration for C3G and primary IC-MPGN patient populations, respectively. The blue and orange shaded regions are the 5th to 95th percentiles for pegcetacoplan 1080 mg SC BIW (or corresponding weight-adjusted regimen) at steady state for C3G and primary IC-MPGN patients, respectively. The black line represents the E-R curve.
BIW, twice weekly; $C_{avg,ss}$, average concentration at steady state; C3G, complement 3 glomerulopathy; E-R, exposure-response; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; SC, subcutaneous; UPCR, urine protein-to-creatinine ratio.

Paediatric dosing

- The following weight-stratified paediatric SC dosing regimens are predicted to match early and steady-state exposure (average and maximum concentration) of adults, across age and body weight (**Figure 5**): ≥50 kg, 1080 mg BIW; 35–49 kg, 648 mg ×1 dose then 810 mg BIW; 20–34 kg, 540 mg BIW ×2 doses then 648 mg BIW; and <20 kg, 324 mg BIW ×4 doses then 486 mg BIW.
- Dosing for patients <12 years old, or weighing <30 kg, is predicted for potential future studies.

Figure 5. Simulated steady-state pegcetacoplan exposure in paediatric patients by weight group



Lower and upper boundaries of the box represent the 1st quartile (Q1) and 3rd quartile (Q3), respectively. Median is shown as the horizontal line inside the box. Whiskers represent the minimum and maximum values within 1.5 IQR below Q1 or above Q3. The blue shaded region represents 90% prediction interval for the adult C3G or primary IC-MPGN population. The blue dashed line represents the adult C3G or primary IC-MPGN population median.
C3G, complement 3 glomerulopathy; C_{avg}, average concentration; C_{max}, maximum concentration; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IQR, interquartile range.

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1. Bomback AS et al. Efficacy and safety of pegcetacoplan in kidney transplant recipients with recurrent complement 3 glomerulopathy or primary immune complex membranoproliferative glomerulonephritis. *Kidney Int Rep.* 2024;10(1):87-98. **2.** Mastrangelo A et al. Clinical and pathophysiological insights into immunological mediated glomerular diseases in childhood. *Front Pediatr.* 2020;8:205. **3.** Kirpalani A et al. Long-term outcomes of C3 glomerulopathy and immune-complex membranoproliferative glomerulonephritis in children. *Kidney Int Rep.* 2020;5(12):2313-2324. **4.** Caravaca-Fontán F et al. Update on C3 glomerulopathy: a complement-mediated disease. *Nephron.* 2020;144(6):272-280. **5.** Fakhouri F, et al. Trial of pegcetacoplan in C3 glomerulopathy and immune-complex MPGN. 2025;393(22):2210–2220. **6.** ASPAVELI 1080 mg solution for infusion. Summary of Product Characteristics. Updated January 2026.

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