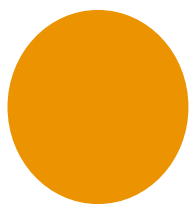


Renal Safety of Pegcetacoplan in Paroxysmal Nocturnal Hemoglobinuria (PNH): Findings from Clinical Trials and Global Real-World Experience

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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a complement-mediated hematologic disorder associated with substantial risk of kidney impairment^{1,2}. Both acute kidney injury (AKI) and chronic kidney disease (CKD) occur frequently in untreated PNH patients as a consequence of acute and chronic hemolysis, iron deposition, microvascular thrombosis, and other factors^{1–5}
- In retrospective analyses, kidney failure accounted for 2–18% of deaths in untreated PNH patients^{5,6}
- Pegcetacoplan, a targeted C3/C3b inhibitor, demonstrated sustained hematologic and clinical benefits in the Phase 3 PEGASUS and PRINCE studies in patients with PNH, with follow-up from their long-term extension (LTE) study supporting maintained efficacy and a favorable safety profile^{7–9}
- Pegcetacoplan is approved in the EU and the US for the treatment of adult patients with PNH and adult and adolescent patients (aged ≥12 years) with C3G or primary IC-MPGN, where it has been shown to reduce proteinuria and stabilize kidney function^{10,11}

AIMS

This analysis evaluated renal safety outcomes in combined data from PEGASUS, PRINCE, their LTE, and in real-world post-marketing data

METHODS

- The Phase 3 trials PEGASUS (C5 inhibitor-experienced patients; NCT03500549) and PRINCE (C5 inhibitor-naïve patients; NCT04085601), included a 16-week randomized controlled period (RCP) followed by a 32-week open-label period or a 26-week RCP, respectively. Upon completion, patients were eligible to roll over into the LTE study (NCT03531255). Patients were followed for up to 5 additional years in the LTE. Combined data from the Phase 3 trials and the LTE are displayed for the total safety set
- Baseline for this combined analysis was defined as the start of treatment with pegcetacoplan monotherapy. The mean estimated glomerular filtration rate (eGFR) over time is presented for the overall safety set, and in patients subgrouped by comorbidities known to affect kidney function (hypertension and diabetes). Analyses also included patients with eGFR decline of ≥30% and ≥50% and KDIGO (Kidney Disease: Improving Global Outcomes) eGFR category¹² change over time between first and last visit. All data are presented descriptively
- Renal adverse events (AEs) were defined as those within the MedDRA High Level Term of renal failure and impairment by Preferred Terms. Post-marketing real-world data were renal events reported to the Sobi global safety database before the predetermined data lock point on 11 February 2026

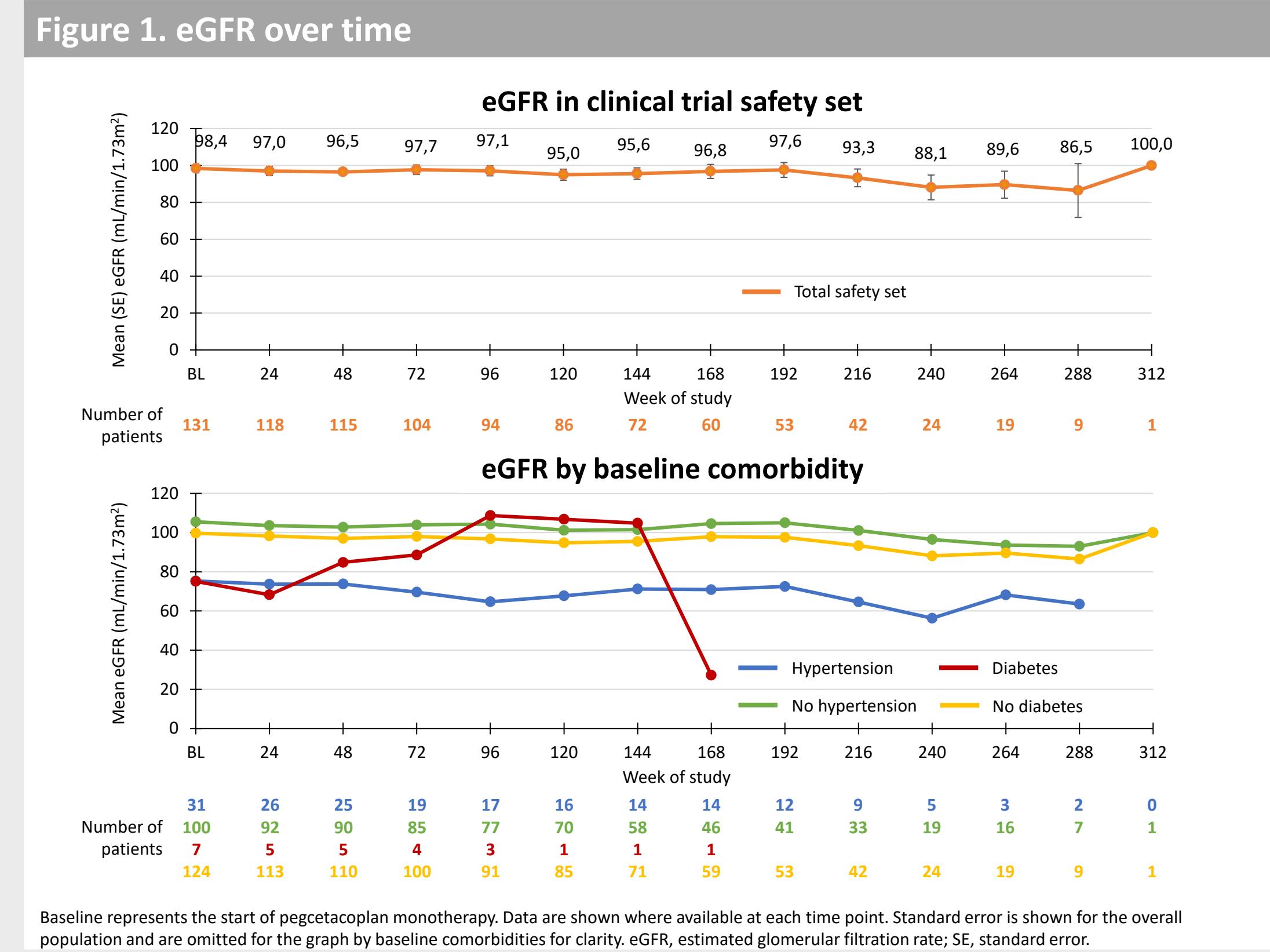
RESULTS

132 patients were included in the combined clinical trial safety set. Baseline characteristics at the start of pegcetacoplan treatment are shown in **Table 1**⁹

Table 1. Baseline characteristics at the initiation of pegcetacoplan		
	PEGASUS (n=80)	PRINCE (n=52)
Age, mean (SD), years	49 (16.0)	44 (14.0)
Time since PNH diagnosis, mean (SD), years	10.2 (8.6)	5.7 (5.7)
eGFR, mean (SD), mL/min/1.73 m ²	97.7 (24.4)	99.3 (31.2)*
* Available in n=51 patients. eGFR, estimated glomerular filtration rate; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation.		

Kidney function by eGFR in pegcetacoplan-treated PNH patients

- Overall, there was no evidence of progressive kidney function decline as assessed by mean eGFR over up to 312 weeks of follow up in patients treated with pegcetacoplan. eGFR in the subgroup of patients who had baseline hypertension or diabetes also remained relatively stable where sufficient sample size was available (**Figure 1**) and eGFR category tended to remain stable from baseline to last study visit (**Table 2**)
- eGFR decline of ≥30% or ≥50% was recorded in 6.3% (n=7/112) and 1.8% (n=2/112) of patients at Week 60, 4.7% (n=4/86) and 2.3% (n=2/86) at Week 120, and 8.3% (n=2/24) and 4.2% (n=1/24) at Week 240 (n=24), respectively



eGFR category at last visit*	Baseline eGFR (mL/min/1.73 m ²)			
	≥90 (n=89)	≥60 to <90 (n=29)	≥30 to <60 (n=11)	≥15 to <30 (n=2)
≥90 mL/min/1.73 m ² , n (%)	80 (89.9)	7 (24.1)	0	0
≥60 to <90 mL/min/1.73 m ² , n (%)	8 (9.0)	16 (55.2)	2 (18.2)	0
≥30 to <60 mL/min/1.73 m ² , n (%)	0	6 (20.7)	5 (45.5)	0
≥15 to <30 mL/min/1.73 m ² , n (%)	1 (1.1)	0	3 (27.3)	1 (50.0)
<15 mL/min/1.73 m ² , n (%)	0	0	1 (9.1)	1 (50.0)

* Last visit for n=131 patients was median (min, max) 160.4 (7.1, 312.1) weeks.
eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

- Overall, most patients had no decline in eGFR category from baseline to the last study visit; interpretation of the lowest baseline eGFR stratum is limited by the small sample size

Long-term renal safety in pegcetacoplan-treated PNH patients

- In the PNH clinical development program (PEGASUS, PRINCE, and LTE), renal AEs were infrequent, reported in 17 (12.9%) patients. The most common renal AEs were of AKI (n=9; 6.8%) and CKD (n=3; 2.3%) (**Table 3**); long-term exposure did not increase the incidence rate of renal AEs
- AKI events occurred in contexts typical of the PNH population. Detailed case narratives show AKI occurring with severe breakthrough hemolysis and hemoglobinuria, sepsis (including COVID-19), cellulitis-related sepsis, or acute gastroenteritis with vomiting and diarrhea, sometimes in patients with pre-existing CKD
- Serious renal AEs reported in the post-marketing setting were consistent with those observed in clinical trials, predominantly not related or unlikely related to pegcetacoplan, and resolved without dose change

Table 3. Treatment-emergent renal adverse events

	PEGASUS + LTE (n=80)	PRINCE + LTE (n=52)	Total safety set (n=132)
Any renal failure or impairment, n (%) / patients with AEs per 100 patient-years	11 (13.8) / 5.9	6 (11.5) / 3.1	17 (12.9) / 4.5
Acute kidney injury, n (%) / patients with AEs per 100 patient-years	6 (7.5) / 3.1	3 (5.8) / 1.5	9 (6.8) / 2.3
Chronic kidney disease, n (%) / patients with AEs per 100 patient-years	2 (2.5) / 1.0	1 (1.9) / 0.5	3 (2.3) / 0.7
End stage renal disease, n (%) / patients with AEs per 100 patient-years	0 / 0	1 (1.9) / 0.5	1 (0.8) / 0.2
Renal failure, n (%) / patients with AEs per 100 patient-years	2 (2.5) / 1.0	0 / 0	2 (1.5) / 0.5
Renal impairment, n (%) / patients with AEs per 100 patient-years	1 (1.3) / 0.5	1 (1.9) / 0.5	2 (1.5) / 0.5

Renal events are listed according to AEs within MedDRA under the High-Level Term of Renal failure and impairment, by Preferred Term. AE, adverse event; LTE, long-term extension.

Limitations

- During the LTE, patients with acute hemolysis could transfer into a dedicated substudy. At that time, they were censored and no further data were included in the main LTE analyses
- Results from week 264 onwards are based on a limited number of patients
- Urine protein-to-creatinine ratio was not available for this analysis and there are limited information on the renal safety of pegcetacoplan in patients with pre-existing CKD
- Post-marketing data are submitted by external reporters and may contain incomplete clinical information; although follow-up is routinely performed, additional details may not always be obtained

CONCLUSIONS

- In these PNH clinical trials, eGFR remained broadly stable among patients with available measurements over approximately 5 years of follow-up, as well as in a limited sample size at later time points; no evidence of progressive kidney function decline with long-term use was observed in the overall population or in those with baseline comorbidities
- Across PNH clinical trials and in the post-marketing environment , reported renal AEs were consistent with PNH and typical intercurrent illnesses; no new safety signals were observed and no increased risk of renal failure was identified over long-term experience
- These data identify no renal safety concerns with pegcetacoplan supportive of the overall favorable benefit:risk profile of pegcetacoplan in PNH. Kidney function stability from the PRINCE and PEGASUS studies in PNH patients suggests broad, long-term haemolysis control with pegcetacoplan

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