

PF1303

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Indirect treatment comparison of iptacopan vs. pegcetacoplan in complement inhibitor naïve paroxysmal nocturnal hemoglobinuria patients

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KEY FINDINGS & CONCLUSIONS

- This ITC suggests that iptacopan has a significantly higher increase in Hb, lower transfusion rates, and comparable control of LDH levels when compared to pegcetacoplan.
- In the absence of H2H trials, ITC analyses provides valuable comparative efficacy data to inform health technology assessment and clinical decision-making process.
- These findings should be interpreted within the framework of STC, with its strengths and limitations.



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INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired genetic disorder characterized by complement-mediated hemolysis and subsequent anemia.¹
- Two recently approved monotherapies are: iptacopan, a factor B inhibitor; first oral monotherapy,² and pegcetacoplan, a complement 3 inhibitor; administered as subcutaneous infusion.³
- These drugs have demonstrated efficacy in their respective trials in PNH patients naïve to complement inhibitors and met their primary endpoints.
- Iptacopan and pegcetacoplan have not been compared directly in a head-to-head (H2H) clinical trial.
- The objective of this analysis was to assess the comparative efficacy of iptacopan vs pegcetacoplan in PNH patients naïve to complement inhibitors using an indirect treatment comparison (ITC).

RESULTS

- The analysis included a sample size of 40 for iptacopan and 35 for pegcetacoplan, consistent with their respective trial populations.
- The baseline characteristics of the trial population are listed in **Table 1**.

Table 1. Key baseline characteristics of both trials

	APPOINT-PNH Iptacopan (n = 40)	PRINCE	
		Pegcetacoplan (n = 35)	Standard of care (n = 18)
Age, mean (range), years	42.1 (18.0-81.0)	42.2 (22.0-67.0)	49.1 (20.0-74.0)
Time from PNH diagnosis, median (range), years	3.6 (0.01-23.2)	3.4 (0.1-27.0)	4.7 (0.1-15.1)
Female, n (%)	17 (42.5)	16 (45.7)	8 (44.4)
History of Aplastic Anemia, n (%)	16 (40.0)	5 (14.3)	5 (27.8)
Transfusion in previous 12 months, n (%)	27 (67.5)	29 (82.9)	14 (77.8)
Hb, g/dL, mean (SD)	8.2 (1.1)	9.4 (1.4)	8.7 (0.8)
LDH, U/L, mean (SD)	1698.8 (683.3)	2151.0 (909.4)	1945.9 (1003.7)

Hb: hemoglobin; LDH: lactate dehydrogenase; SD: standard deviation.

Change from baseline in Hb

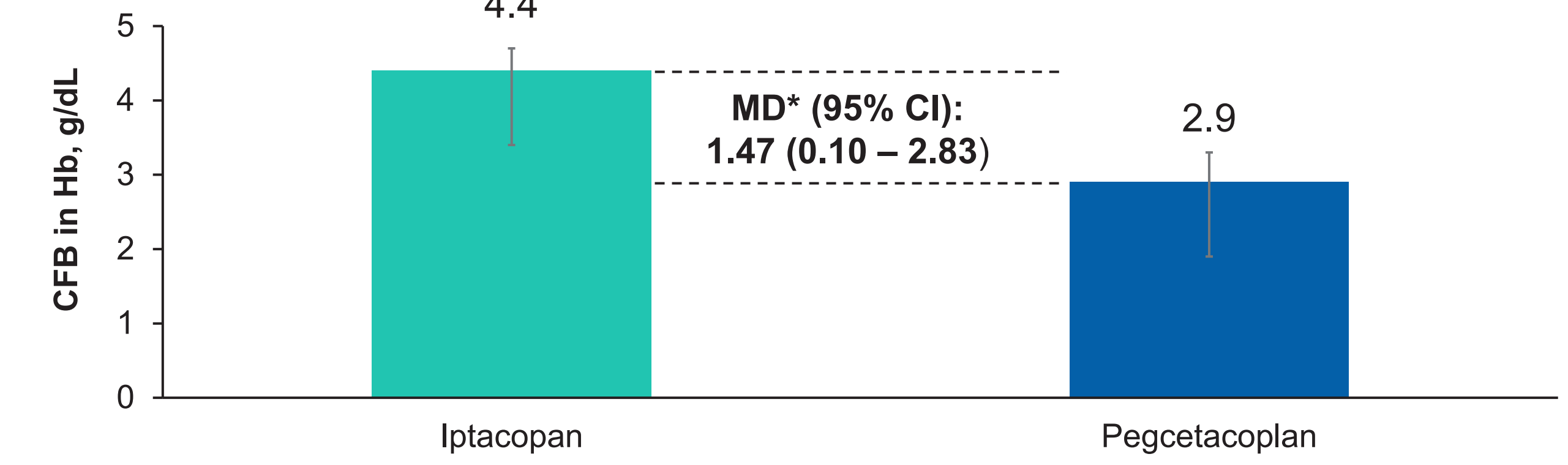
- The published mean (SD) CFB in Hb for iptacopan and pegcetacoplan was 4.41 (0.23) and 2.90 (0.40) g/dL, respectively.

METHODS

- A systematic literature review, identified two phase III clinical trials in the target population which were considered: APPOINT-PNH⁴ (NCT04820530) a single-arm trial of iptacopan; with available individual patient data (IPD), and PRINCE⁵ (NCT04085601), a randomized controlled trial of pegcetacoplan vs supportive care only (excluding complement inhibitors), with published summary data.
- The key eligibility criteria for the trials were generally similar with some differences such as, in hemoglobin (Hb; g/dL) levels (<10 in APPOINT-PNH; <12 in females and <13.5 in males in PRINCE).
- A feasibility assessment was conducted evaluating factors such as trial design, key eligibility criteria, and outcomes. Based on the network diagram (**Figure 1**), an unanchored simulated treatment comparison (STC) was conducted to compare iptacopan and pegcetacoplan.
- A regression model was applied to APPOINT-PNH trial IPD, and the fitted model simulated the effect of iptacopan in the population from the PRINCE trial.

- The predicted outcome for iptacopan for mean (SD) CFB in Hb was 4.37 (0.26), resulting in a significant **mean difference** favoring iptacopan vs pegcetacoplan: 1.47 (95% CI: 0.10, 2.83; P = 0.0348) (**Figure 2**).

Figure 2. Change from baseline in Hb

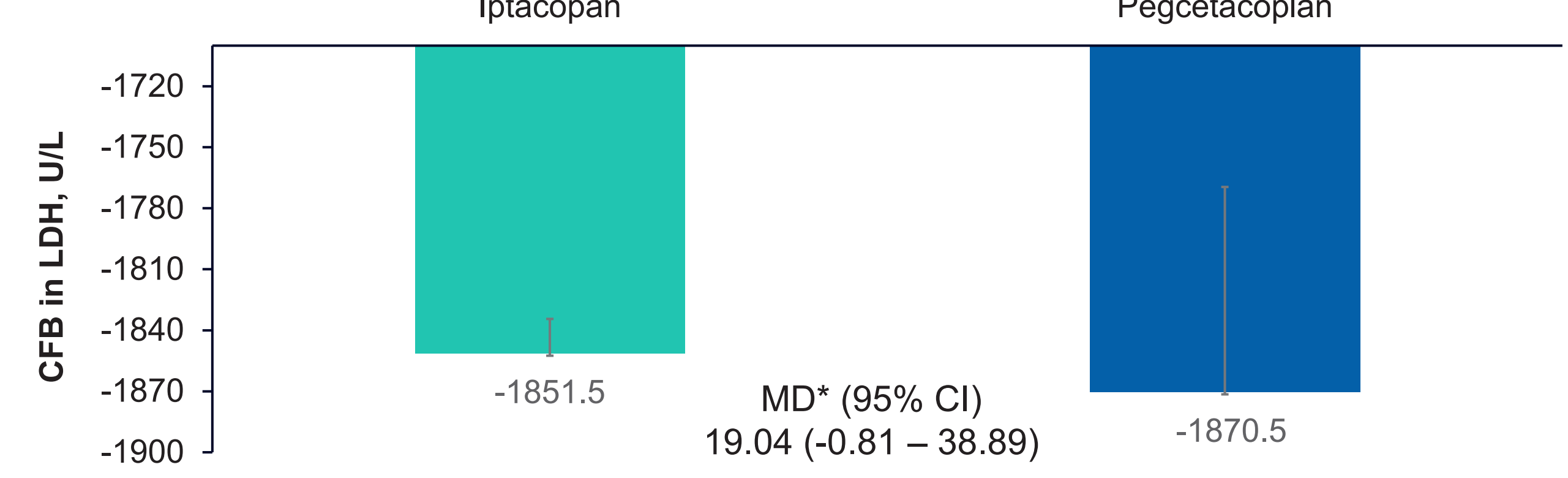


*A mean difference >0 implies the results are in favor of iptacopan vs pegcetacoplan. A 95% CI which excludes 0 implies the difference is significant. Bold values indicate significance. CFB: change from baseline; CI: confidence interval; Hb: hemoglobin; MD: mean difference.

Change from baseline in LDH

- The published mean (SD) CFB in LDH for iptacopan and pegcetacoplan was -1,424.39 (103.53) and -1,870.50 (101.00) U/L, respectively.
- The predicted mean (SD) CFB in LDH for iptacopan was -1,851.46 (17.67) U/L, resulting in a **mean difference** of 19.04 (-0.81, 38.89; P = 0.0601) (**Figure 3**).

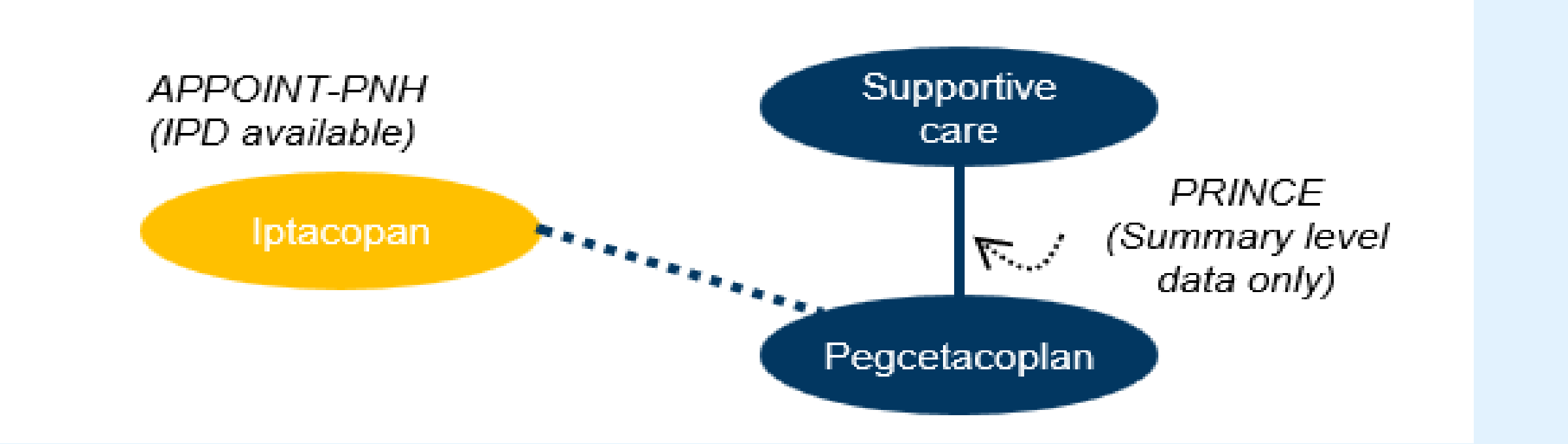
Figure 3. Change from baseline in LDH



*A mean difference >0 implies the results are in favor of pegcetacoplan vs iptacopan. A 95% CI which includes 0 implies the difference is not significant. CFB: change from baseline; CI: confidence interval; LDH: lactate dehydrogenase; MD: mean difference.

- The regression model included 5 prognostic variables and treatment effect modifiers as covariates: age, sex, transfusion avoidance, history of aplastic anemia, and baseline lactate dehydrogenase (LDH).
- The STC analyzed outcomes such as change from baseline (CFB) in Hb, CFB in LDH, and transfusion rate.
- Results were reported using point estimates (mean difference; rate ratio) and 95% confidence intervals (CIs) for each analysis. Nominal significance was ascertained using a two-tailed P-value of <0.05.

Figure 1. Network diagram



IPD: individual patient data

Transfusion rate

- Transfusion rate for pegcetacoplan was calculated using transfusion avoidance endpoint over the study follow-up in the PRINCE trial.
- Upon comparison of transfusion rates, the unadjusted rates were lower for iptacopan (0.003 per patient-month) compared to pegcetacoplan (0.154 per patient-month).
- The predicted transfusion rate for iptacopan was 0.027 per patient-month and the **rate ratio** of iptacopan vs pegcetacoplan was 0.174 (0.133, 0.228; p < 0.0001) (**Table 2**) suggesting a significantly lower rate of transfusion for iptacopan.

Table 2. Summary of transfusion rate results

Transfusion rate	PRINCE (Pegcetacoplan)	APPOINT-PNH (Iptacopan)
Unadjusted indirect comparison		
Transfusion rate per patient-month	0.154 (0.139,0.171)	0.003 (0.000, 7.929)
Simulated Treatment Comparison		
Transfusion rate per patient-month	0.154 (0.139, 0.171)	0.027 (0.0004, 1.789)
Rate Ratio (95% CI)*; P-value (Iptacopan vs. Pegcetacoplan)	-	0.1742 (0.133, 0.228), p < 0.0001

*Rate ratio <1 implies a lower rate of transfusion for iptacopan. A 95% CI which excludes 1 indicates that the rate ratio is significant. Bold values include significance. CI: confidence interval.

Discussion

- Results suggest iptacopan may have improved efficacy versus pegcetacoplan with significant improvement in CFB in Hb and transfusion rates.
- In the absence of H2H trials, this analysis provides valuable comparative efficacy data, by adjusting for potential treatment effect modifiers and prognostic factors identified *a priori* through an STC. Residual confounding bias in the effect estimates cannot be excluded.

Acknowledgements

The authors would like to thank Jahnavi Yenamandra and V.S. Hari Prasad from Novartis Healthcare Pvt. Ltd., India for developing the poster content and layout, respectively. The final responsibility of the content lies with the authors.

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