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Poster# **CO58**

Comparative efficacy of iptacopan monotherapy vs danicopan add-on to C5i in paroxysmal nocturnal hemoglobinuria: Results from an indirect treatment comparison

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KEY FINDINGS & CONCLUSIONS

- The results from this ITC suggest that iptacopan monotherapy may provide significantly improved clinical outcomes and decreased fatigue versus danicopan+C5i.
- 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 ITC, with its strengths and limitations.

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INTRODUCTION AND OBJECTIVE

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder characterized by complement-mediated hemolytic anemia and thrombosis.[1]
- Iptacopan is a first-in-class oral monotherapy inhibitor of factor B, targeting the alternative pathway of the complement system.[2]
- Danicopan is a first-in-class oral inhibitor of complement factor D, as an add-on therapy to complement C5 inhibitors (C5i).[3]
- No head-to-head (H2H) trials have compared iptacopan and danicopan + C5i in patients with PNH who have residual anemia despite prior treatment with C5i. In the absence of H2H trials, indirect treatment comparisons (ITC) are commonly conducted to inform Health Technology Assessment.
- **The aim of this ITC was to assess efficacy of iptacopan versus danicopan + C5i among patients with PNH who have residual anemia despite prior treatment with C5i.**

METHODS

- Two relevant phase III clinical trials in the target population were identified: APPLY-PNH (NCT04558918)[4], a randomized open-label trial of iptacopan vs C5i, and ALPHA (NCT04469465)[3], a randomized controlled trial of danicopan + C5i vs placebo + C5i.
- Feasibility assessment determined that anchored matching-adjusted indirect comparison (MAIC) was the most appropriate ITC approach. The MAIC used individual patient data (IPD) from APPLY-PNH and published data from ALPHA.
- **Matching:** Patients not meeting ALPHA eligibility criteria for baseline hemoglobin (Hb) or reticulocyte count were excluded from the APPLY-PNH dataset i.e. patients with Hb> 9.5 g/dL or reticulocyte count < 120 x 109/L. Patients were also excluded from the APPLY-PNH dataset if they were transfusion-free 6 months prior to randomization in APPLY-PNH.
- **Adjusting:** Patients in APPLY-PNH were re-weighted via entropy balancing so that their proportions or both their means and standard deviations (SDs) matched those reported in ALPHA. Base case analysis was adjusted for 2 ranked factors: baseline Hb, sex.
- **Outcomes:** Change from baseline (CFB) in Hb, transfusion avoidance, CFB in lactate dehydrogenase (LDH), CFB in FACIT-Fatigue. Outcome definitions and assessment period in APPLY-PNH were aligned to match ALPHA (84 days).

RESULTS

- The analysis included patients from APPLY-PNH trial (62 patients of iptacopan arm and 35 of C5i arm) and patients from ALPHA trial (42 patients of danicopan + C5i arm and 21 patients of placebo + C5i arm).
- The baseline characteristics of trial populations before and after matching & adjusting are presented in **Table 1**.

Table 1. Key baseline characteristics of both trials

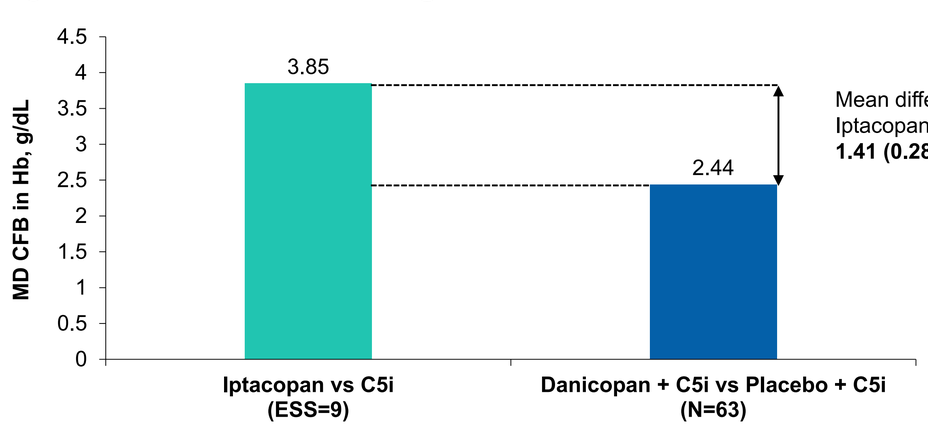
	ALPHA	APPLY-PNH[a]			
	N=63	Unmatched & unadjusted		Matched & adjusted	
		N=97	SMD	ESS=9	SMD
Haemoglobin, g/dL, mean (SD)	7.7 (1.0)	8.9 (0.8)	1.378	7.7 (1.0)	0.005
Sex; % female; n (%)	37 (58.7)	67 (69.1)	0.217	- (58.9)	0.004
Age, years; mean (SD)	54.4 (15.2)	51 (16.8)	0.210	51.2 (13.6)	0.222
LDH, U/L, mean (SD)	291.6 (93.3)	270.4 (75.3)	0.249	282.2 (54.1)	0.123
Reticulocytes (10^{-9}/L), Mean (SD)	244.6 (101)[b, c]	199.2 (83.5)	0.490	191.7 (56.2)	0.648

[a] Missing data varied by outcome at Day 84 in APPLY-PNH. The number of patients in the unmatched and unadjusted by outcome were; 81 for CFB in Hb, 97 for transfusion avoidance, 96 for CFB in LDH, 86 for CFB in FACIT-Fatigue. Baseline characteristics from the transfusion avoidance outcome are presented in this table. [b] Absolute reticulocyte count measured at baseline. [c] Value is only based on n=62.
ESS: effective sample size; LDH: lactate dehydrogenase; SD: standard deviation; SMD: standardized mean difference

Change from Baseline in Hemoglobin

- CFB in Hb was assessed at Day 84. Mean (SD) difference of CFB in Hb between iptacopan and C5i was 3.85 (0.452) g/dL, which was greater than the mean (SD) difference of danicopan + C5i and placebo + C5i: 2.44 (0.385) g/dL (**Figure 1**).
- Iptacopan showed significantly higher increase from baseline in Hb compared to danicopan + C5i with a mean difference of 1.41 g/dL (95% CI: 0.28, 2.55; P = 0.014).

Figure 1. MAIC results in change from baseline in Hb



*Mean difference>0 implies a greater CFB in Hb for iptacopan vs danicopan + C5i.
95% CI which excludes 0 implies the difference is significant. Bold values indicate significance.
CFB: change from baseline; CI: confidence interval; ESS: effective sample size; MD: mean difference.

Transfusion avoidance

- In the matched and adjusted sample, 98.7% of patients on Iptacopan remained transfusion free compared to 20.7% on C5i.
- Iptacopan showed significantly higher odds of being transfusion-free compared to danicopan + C5i (OR: 58.56 [2.82, 1214.72]) (**Table 2**).

Table 2. MAIC results for transfusion avoidance

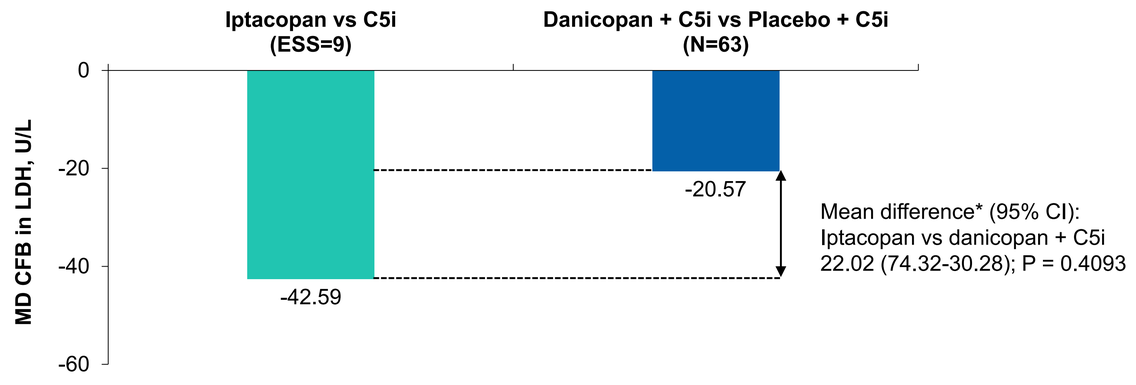
	Proportion of transfusion avoidance				Odds Ratio Iptacopan vs. Danicopan + C5i (95% CI)*	Sample Size (ESS for anchored MAIC)
	APPLY-PNH		ALPHA			
	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i		
Naïve indirect comparison (unmatched & unadjusted)	60/62 (96.8%)	21/35 (60%)	35/42 (83.3%)	8/21 (38%)	2.46 (0.34, 17.63)	N=97
Anchored MAIC; adjusted for baseline Hb, sex	98.7%	20.7%	35/42 (83.3%)	8/21 (38%)	**58.56 (2.82, 1214.72)**	ESS=9

* Odds ratio >1 implies a greater odds of achieving transfusion avoidance for Iptacopan. Bold values indicate significance.
CI: confidence interval; ESS: effective sample size; LDH: lactate dehydrogenase; MAIC: matching-adjusted indirect comparison.

Change from Baseline in LDH

- Mean (SD) difference of CFB in LDH for iptacopan vs C5i was -42.59 (22.302), which was greater than the mean (SD) difference of danicopan + C5i vs. placebo + C5i: -20.57 (14.651) U/L (**Figure 2**).
- Mean difference of CFB in LDH between iptacopan vs. danicopan + C5i was -22.018 U/L (95% CI: -74.319, 30.283; P = 0.4093), suggesting a comparable control of LDH levels.

Figure 2. MAIC results in change from baseline in LDH

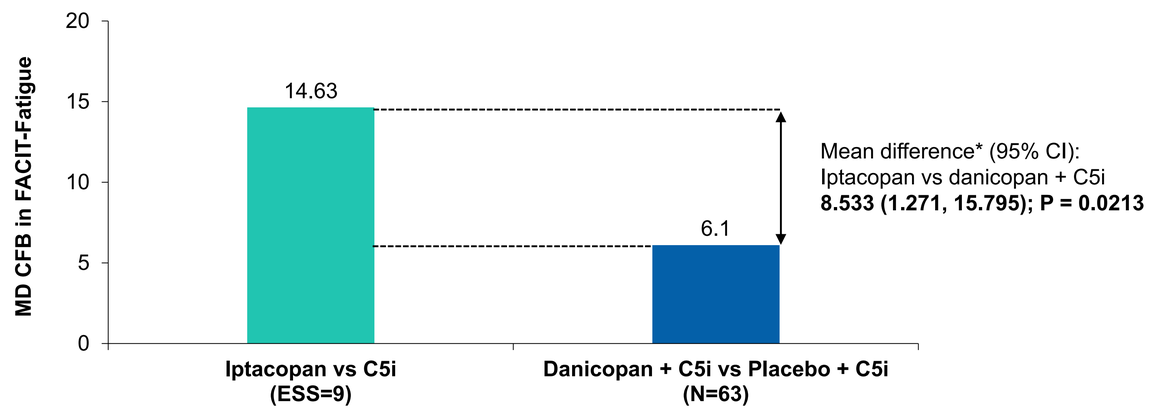


*Mean difference>0 implies a greater change from baseline in LDH for iptacopan vs danicopan + C5i.
95% CI which excludes 0 implies the difference is significant. Bold values indicate significance.
CFB: change from baseline; CI: confidence interval; MD: mean difference.

Change from Baseline in FACIT-Fatigue

- Mean (SD) difference of CFB in FACIT-Fatigue score for iptacopan vs. C5i [14.63 (3.16)] was greater compared to mean (SD) difference of danicopan + C5i vs. placebo + C5i [6.1 (1.9)].
- Iptacopan showed significantly greater improvement from baseline in FACIT-Fatigue score for iptacopan compared to danicopan + C5i (**Figure 3**).

Figure 3. MAIC results in change from baseline in FACIT-Fatigue



*Mean difference>0 implies a greater CFB in FACIT-Fatigue for iptacopan vs danicopan + C5i.
95% CI which excludes 0 implies the difference is significant. Bold values indicate significance.
CFB: change from baseline; CI: confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; MD: mean difference.

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