Supplementary Materials

Supplementary Table 1. Designs of Trials for Pegcetacoplan (PRINCE) and Crovalimab (COMMODORE 2 and COMMODORE 3) in C5i Treatment-Naïve Patients with PNH

PRINCE (NCT04085601) Phase 3, randomized, multicentre, open-label, controlled trial[1]	
Study periods	• 4 weeks screening • 26 weeks randomised controlled • Standard of care escape anytime if Hb decreased by ≥2 g/dL from baseline
Population	53 adults (≥18 years of age) with PNH and Hb < the LLN (males: ≤13.6 g/dL; females: ≤12.0 g/dL) 2:1 randomised to pegcetacoplan (n=35) or best supportive care (n=18)
Key eligibility criteria	• Hb levels below the LLN (males: ≤13.6 g/dL; females: ≤12.0 g/dL) • LDH levels ≥1.5 times the ULN (1.5x ULN; ≥339 U/L) • No complement-inhibitor (i.e., eculizumab, ravulizumab) treatment within 3 months prior to screening
Co-primary endpoints	• Hb stabilization (avoidance of a >1 g/dL decrease in Hb levels in the absence of transfusions through Week 26) • Change from baseline in LDH levels at Week 26
Selected secondary endpoints	• Change from baseline in Hb levels at Week 26 • Transfusion avoidance (defined as the proportion of patients who did not require a transfusion through Week 26) • Incidence and severity of adverse events (including study deaths) through Week 26
COMMODORE 2 (NCT04434092 Phase 3, randomized, multicentre, open-label, active-controlled trial[2]	
Study periods	• 4 weeks screening • 24 weeks core treatment • Post-24 weeks extended crovalimab treatment • Week 25 analysis of co-primary and secondary endpoints
Population	204 adult C5i naïve patients with PNH and LDH ≥2 × ULN randomised 2:1 to crovalimab or eculizumab
Key eligibility criteria	• Weight ≥40 kg • Granulocyte or monocyte clone size ≥10% • Presence of one or more PNH-related signs or symptoms within 3 months prior to screening • LDH levels ≥2 times the ULN (2x ULN) • Platelet count ≥3x10^4/mm3

	• Absolute neutrophil count ≥500/ul • No history of treatment with a complement inhibitor
Co-primary endpoints	• Mean proportion of patients with hemolysis control measured by central LDH ≤1.5×ULN from Week 5 through Week 25 • Proportion of patients who achieve transfusion avoidance from baseline through Week 25
Selected secondary endpoints	• Proportion of patients with breakthrough hemolysis (BTH) from baseline through Week 25 • Proportion of patients with stabilized Hb from baseline through Week 25 • Mean change from baseline to Week 25 in fatigue (FACIT-Fatigue score) (patients aged ≥18 years)
COMMODORE 3 trial (NCT04654468) Phase 3, single-arm, open-label, Chinese multicentre trial[3]	
Study periods	• 24 weeks core treatment • Post-24 weeks extended crovalimab treatment • Week 25 analysis of co-primary and secondary endpoints
Population	51 patients (15-58 years old) treated with crovalimab
Key eligibility criteria	• Weight ≥40 kg • At least 4 transfusions of packed RBCs during the 12 months prior to screening • LDH levels ≥2 times the ULN (2x ULN; ≥468 U/L for adults, ≥460 U/L for adolescents) • No history of allogeneic bone marrow transplantation • No known or suspected hereditary complement deficiency
Co-primary endpoints	• Mean proportion of patients with hemolysis control (LDH ≤1.5x ULN) from Weeks 5 through 25 • Difference in the proportion of patients who achieved transfusion avoidance from baseline through Week 25 versus the proportion of patients with transfusion avoidance within 24 weeks prior to screening
Selected secondary endpoints	• Proportion of patients with stabilized Hb (avoidance of ≥2 g/dL decrease in Hb level from baseline, in the absence of transfusion) • Proportion of patients with breakthrough hemolysis • Mean change from baseline to Week 25 in FACIT-Fatigue score (in adults; assessed from baseline to Week 17) • Incidence and severity of adverse events (including study deaths) through Week 25

C5i, complement component 5 inhibitor; FACIT, Functional Assessment of Chronic Illness Therapy; Hb; hemoglobin; IV, intravenous; LDH; lactate dehydrogenase; LLN, lower limit of normal; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous; ULN; upper limit of normal.

Supplementary Table 2. Designs of Trials for Pegcetacoplan (PEGASUS) and Crovalimab (COMMODORE 1) in C5i Treatment-Experienced Patients with PNH

PEGASUS trial (NCT03500549) Phase 3, multi-centre, open-label, randomised, active-comparator controlled study[4]	
Study periods	• 4 weeks run in of pegcetacoplan+eculizumab • 16 weeks randomised controlled • 32 weeks open label
Population	80 patients ≥ 18 years of age, with PNH receiving eculizumab, but continue to have Hb levels <10.5 g/dL
Key Eligibility Criteria	• On treatment with eculizumab • Hb <10.5g/dL • ARC >1.0 xULN • Platelet count >50,000/μL
Exclusion Criteria	• Active bacterial infection • History of bone marrow transplantation • History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product
Primary Endpoint	• Change in Hb from baseline to week 16
Selected Secondary Endpoints	• Freedom from transfusion • Reticulocyte count • LDH level • FACIT-fatigue score
COMMODORE 1 (NCT04432584) Phase 3, multi-centre, open-label, randomised, active-comparator controlled study[5]	
Study periods	• 4 weeks screening • 25 weeks core treatment • Post-24 weeks extended crovalimab treatment
Population	89 patients ≥18 years of age with PNH
Key Eligibility Criteria	• Body weight ≥40 kg • PNH diagnosis confirmed by high-sensitivity flow cytometry with granulocyte or monocyte GPI-deficient clone size ≥10% • LDH levels of ≤1.5x ULN, Platelet count >30 000/mm3

	• Absolute neutrophil count of >500/mm3 • Receiving approved dosing of eculizumab (900 mg every 2 weeks) for ≥24 weeks prior to first study drug administration
Exclusion Criteria	• Major adverse vascular event within 6 months prior to first drug administration • Pre-enrolment hemoglobin value ≤7 g/dL, or pre-enrolment hemoglobin value >7 g/dL and ≤9 g/dL with concurrent signs and symptoms of anemia • History of allogeneic bone marrow transplantation
Primary Endpoints	• Percentage of participants with AEs and by severity • Percentage of participants with injection-site reactions, infusion-related reactions, hypersensitivity and infections (including meningococcal meningitis); AEs leading to study drug discontinuation
Selected Secondary Endpoints	• Serum concentrations of crovalimab over time • Change over time in CH50, total C5 and free C5 concentration

AEs, adverse events; ARC, absolute reticulocyte count; FACIT, Functional Assessment of Chronic Illness Therapy; Hb; hemoglobin; LDH, LDH; lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SC, subcutaneous; ULN; upper limit of normal.

Supplementary Table 3. Baseline Data From PRINCE, COMMODORE 2 and COMMODORE 3

Characteristics	PRINCE	COMMODORE 2	COMMODORE 3
	Pegcetacoplan (n=35)	Crovalimab (n=135)	Crovalimab (n=51)
Median age, years (range)	39 (22-67)	36 (18–76)	31 (15-58)
<18 years of age, n (%)	0	0	3 (5.8)
Female, n (%)	16 (45.7)	58 (43)	29 (56.9)
Median weight, kg (range)	63.0 (41.0-95.0)	66.1 (42.0–140.3)	60.0 (48.9-96.0)
Median time since PNH diagnosis, years (range)	3.4 (0.1-27.0)	-	7.1 (0.7-18.2)
Aplastic anemia, n (%)	5 (14.3)	53 (39)	19 (37.3)
Major vascular events, n (%)	-	21 (16)	5 (10)
RBC transfused in prior ≤12 months (units)	Mean (SD)	7.1 (8.2)	6.5 (8.3)
	Median (range)	5 (0.0-34.0)	-
Patients who received RBCs ≤12 months prior to randomization, n (%)	29 (82.9)	103 (76)*	51 (100)
Hb (g/dL)	Mean (SD)	9.4 (1.4)	-
	Median (range)	9.2 (6.5-13.1)	8.5 (6.3-13.5)
Central LDH (× ULN), mean (SD)	9.2 (3.9)	7.6 (3.4)	9.3 (2.8)
LDH >4 × ULN, n (%)	33 (94.3)	-	50 (98.0)
FACIT-Fatigue score, mean (SD) or [95% CI]	36.3 [32.8; 39.9]	36.0 (10.4)	31.8 [29.3; 34.3]
Platelet count (10^9/L), mean (SD)	189.8 (119.2)	-	143.9 (80.7)
Neutrophil count (10^9/L), mean (SD)	2.91 (1.57)	-	2.70 (1.64)
Reticulocyte count (10^9/L), mean (SD)	218.9 (80.9)	-	217.9 (81.3)

CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, packed red blood cell; SD, standard deviation; SoC, standard of care; ULN, upper limit of normal.

Supplementary Table 4. Indirect Treatment Comparison Methodology Applied in Pegcetacoplan Versus Crovalimab in C5i Treatment-Naïve Patients with PNH

MAIC method	The MAIC approach has specific requirements to harmonise study populations and selection and weighting of confounding variables (i.e., predictors and effect modifiers) following recommendations by the UK National Institute of Health and Care Excellence (NICE) to minimize the risk of bias within indirect comparisons.[6,7]
	
	While the eligibility criteria for COMMODORE 2 and PRINCE were comparable with no restriction on transfusions history, there was no need for harmonization of the inclusion/exclusion criteria between the two trials. However, to control for confounding factors, two models were applied separately for the regressions of clinical outcomes and for the FACIT-Fatigue score, respectively:
	
	• For clinical outcomes, the regressions applied all patient characteristics and baseline clinical variables:
	  • **Age** (% patients >36 years of age
	  • **Sex** (% female)
	  • **Weight** (% patients >66 kg)
	  • **Race** (% Asian)
	  • **Baseline Hb** (% patients >8.5 g/dL)
	  • **Baseline LDH** (ULN)
	  • **Baseline aplastic anemia** (% patients with aplastic anemia)
	• For FACIT-Fatigue score the regression included baseline FACIT-Fatigue, age and baseline Hb as key variables for assessing outcomes related to FACIT-Fatigue score.

Comparative analysis methodology applied	Meta-analysis compared respective outcomes between PRINCE versus COMMODORE 2 and COMMODORE 3. Applying both fixed-effects (inverse variance) and random-effects approaches, standard errors of the study-specific estimates were adjusted to incorporate a measure of study heterogeneity (i.e., Tau-squared [τ^2]).[8,9]

FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; SD, standard deviation.

Supplementary Table 5. ITC Methodology Applied in Pegcetacoplan Versus Crovalimab in C5i Treatment-Experienced Patients with PNH

Bucher's (anchored) ITC method	Though data from head-to-head randomised controlled trials would provide the gold-standard level of evidence,[10–13] an evaluation through ITC is a pragmatic solution when such data are not available.[14] ITC is also recommended by healthcare reimbursement authorities worldwide as an acceptable methodology to address the lack of head-to-head data.[10–13] Moreover, in lieu of unadjusted methods or naïve comparisons, an anchored ITC approach is recommended based on the benefits provided through preserving the randomised features of the trial and compensating for imbalances in prognostic factors between studies.[12,13,15] The anchored analytic approach has distinct advantages over unanchored comparisons (such as standard matching-adjusted indirect comparisons), which cannot account for unobserved confounders and are, thus, inherently associated with high risk of bias. This approach, also known as Bucher's ITC, is a method noted for robustness, reproducibility and high transparency.[16]
Comparative analysis methodology applied	For the comparative analysis, mean change from baseline with the corresponding SD are required, and thus for the present ITC, required estimation for ~~iptacopan~~pegcetacoplan. The SDs for mean change-from-baseline were estimated using data reported at baseline and at EOS,[14] with the correlation coefficients for active and reference arms derived from the PRINCE trial: $$SD_{Change} = \sqrt{SD_{baseline}^2 + SD_{EoS}^2 - (2 \times Corr \times SD_{baseline} \times SD_{EoS})}$$
Sensitivity analysis	The confirmatory analysis for Bucher's ITC used a harmonised patient population; however, the approach relied on assumptions that cannot be verified. Eligibility criteria harmonization in Bucher's ITC is not standard approach as it may affect randomization which is a key assumption for Bucher's method.

Corr, correlation; EOS, end of study; FACIT, Functional Assessment of Chronic Illness Therapy; ITC, indirect treatment comparison; SD, standard deviation.

Supplementary Table 6. Matching-Adjusted Indirect Comparison Between PRINCE and COMMODORE 2

Variables used in the model	Unit	PRINCE baseline			COMMODORE 2 baseline		PRINCE after matching			
		Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Age	% >36 years of age	60	n/a	35	50	n/a	50	n/a	10.6	30.2%
Sex	% female	45.7	n/a		43	n/a	43	n/a		
Weight	% >66 kg	42.9	n/a		50	n/a	50	n/a		
Race	% Asian	65.7	n/a		64	n/a	63.7	n/a		
Baseline Hgb	% >8.5 g/dL	82.9	n/a		50	n/a	50	n/a		
Baseline LDH	ULN	9.2	3.9		7.6	3.4	7.6	3.5		
Aplastic anemia	%	14.3	n/a		39	n/a	39.3	n/a		

ESS; effective sample size; LDH; lactate dehydrogenase; SD; standard deviation; ULN; upper limit of normal.

Supplementary Table 7. Matching-Adjusted Indirect Comparison Between PRINCE and COMMODORE 3

Variables used in the model	Unit	PRINCE baseline			COMMODORE 3 baseline		PRINCE after matching			
		Estimate	SD	N	Estimate	SD	Estimate	SD	ESS	ESS %
Age	% below 31 years	0.23	n/a	35	0.50	n/a	0.50	n/a	8.4	24.0%
Sex	% female	45.7	n/a		56.9	n/a	56.9	n/a		
Time since diagnosis	% below 7.1 years	0.63	n/a		0.50	n/a	0.50	n/a		
Race	% Asian	65.7	n/a		100.0	n/a	100.0	n/a		
Baseline Hb	g/dL	9.4	1.4		8.4	1.0	8.4	1.1		
Baseline LDH	ULN	9.2	3.9		9.3	2.8	9.3	1.0		
Baseline reticulocytes	10^9/L	218.9	80.9		217.9	81.3	217.9	76.0		
% with aplastic anemia	%	14.3	n/a		37.3	n/a	37.3	n/a		
% with baseline LDH >4 × ULN	%	94.3	n/a		98.0	n/a	98.0	n/a		

ESS; effective sample size; Hb; hemoglobin; LDH; lactate dehydrogenase; SD; standard deviation; ULN; upper limit of normal.

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