

(PF687) EFFICACY AND SAFETY OF HRS-5965 VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED PHASE 3 TRIAL

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare complement-mediated hemolytic anemia. While the C5 inhibitor eculizumab controls intravascular hemolysis, many patients (pts) remain anemic due to persistent extravascular hemolysis. HRS-5965 is a novel, oral factor B inhibitor of the alternative complement pathway designed to control both hemolytic pathways and improve anemia.

Aims

The objective was to evaluate the efficacy and safety of HRS-5965 compared with eculizumab in pts with PNH.

Methods

In this multicenter, randomized, open-label, active-controlled phase 3 trial, complement-inhibitor-naïve PNH pts were randomized (1:1) to oral HRS-5965 (50 mg twice daily) or intravenous eculizumab for 24 weeks. The primary endpoint was the proportion of pts achieving Hb ≥ 12 g/dL on at least 3 of 4 measurements between Weeks 18 and 24 without red blood cell (RBC) transfusions (after Week 2). The key secondary endpoint was the proportion achieving a ≥ 2 g/dL Hb increase from baseline under the same conditions.

Results

Of the 78 randomized pts, 76 received treatment (HRS-5965, n=40; eculizumab, n=36) and were included in efficacy and safety analysis (Table 1). The proportion of pts meeting the primary endpoint was significantly higher with HRS-5965 than with eculizumab (70.0% [28/40] vs. 11.1% [4/36]; rate difference 57.4%, 95% CI: 39.6-75.2; $P < 0.0001$). The key secondary endpoint was also significantly superior for HRS-5965 (95.0% [38/40] vs. 55.6% [20/36]; rate difference 39.2%, 95% CI: 20.9-57.4; $P < 0.0001$). A significantly higher proportion of pts in the HRS-5965 group were transfusion-free after Week 2 (100% vs. 86.1%, $P = 0.0149$). The mean Hb increase from baseline (Weeks 18-24) was greater with HRS-5965 (LS mean difference: 2.61 g/dL, 95% CI: 1.72-3.49; $P < 0.0001$), and FACIT-Fatigue score improvement was superior (LS mean difference: 4.19, $P = 0.0001$). Reticulocyte counts decreased significantly with HRS-5965 versus an increase with eculizumab (LS mean difference: $-161.37 \times 10^9/L$, $P < 0.0001$). No major adverse vascular events (MAVEs) occurred. Treatment-related adverse events (TRAEs) occurred in 72.5% (HRS-5965) and 55.6% (eculizumab) of pts. Treatment-related serious AEs occurred in 2 patients (5.0%) receiving HRS-5965 (one case each of upper respiratory infection and infectious pneumonia, both moderate in severity).

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Summary/Conclusion

In pts with PNH, oral HRS-5965 was superior to eculizumab in improving hemoglobin levels, reducing transfusion dependence, and enhancing quality of life, with a manageable safety profile, offering a promising new oral treatment for PNH.

Table 1. Efficacy and Safety Outcomes

	HRS-5965 (N=40)	Eculizumab (N=36)	Difference (95% CI)	P value
Primary endpoints				
Hb ≥ 12 g/dL [#] , n (%)	28 (70.0%)	4 (11.1%)	57.4% (39.6-75.2)	<0.0001
Secondary endpoints				
Hb increase ≥ 2 g/dL [#] , *, n (%)	38 (95.0%)	20 (55.6%)	39.2% (20.9-57.4)	<0.0001
Transfusion-free (after Wk 2), n (%)	40 (100%)	31 (86.1%)	13.7% (2.4-24.9)	0.0149
Mean Hb change from baseline [#] , g/dL, LS Mean (SE)	5.47 (0.31)	2.86 (0.32)	2.61 (1.72-3.49)	<0.0001
FACIT-Fatigue score improvement [#] , LS Mean (SE)	8.62 (0.70)	4.43 (0.74)	4.19 (2.15-6.23)	0.0001
Reticulocyte count change from baseline [#] , $\times 10^9/L$, LS Mean (SE)	-118.97 (9.41)	42.40 (9.93)	-161.37 (-188.62, -134.13)	<0.0001
Safety				
MAVEs, n (%)	0	0	—	—
TRAEs, n (%)	29 (72.5%)	20 (55.6%)	—	—
Treatment-related serious AEs, n (%)	2 (5.0%)	0	—	—

[#]Assessed over Weeks 18-24 in the absence of RBC transfusions after Week 2.

*Hb increase ≥ 2 g/dL was the key secondary endpoint.

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