Longer-term red blood cell transfusion reduction in the phase 3 MEDALIST study of luspatercept in patients with lower-risk myelodysplastic syndromes with ring sideroblast

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Objective

- To evaluate long-term transfusion burden reduction in patients treated with luspatercept in the MEDALIST trial

Results

Patients

- 229 patients were randomized; 153 to receive luspatercept and 76 to receive placebo **(Table 1)**
- As of data cutoff (July 1, 2019), the median follow-up time in the luspatercept and placebo arms was 26.4 and 26.1 months, respectively
- The median (range) transfusion burden at baseline was 5 (1-15) and 5 (2-20) RBC units over 8 weeks in the luspatercept and placebo arms, respectively
- The mean (standard deviation) transfusion burden at baseline was 5.5 (2.76) and 5.8 (2.95) RBC units over 8 weeks in the luspatercept and placebo arms

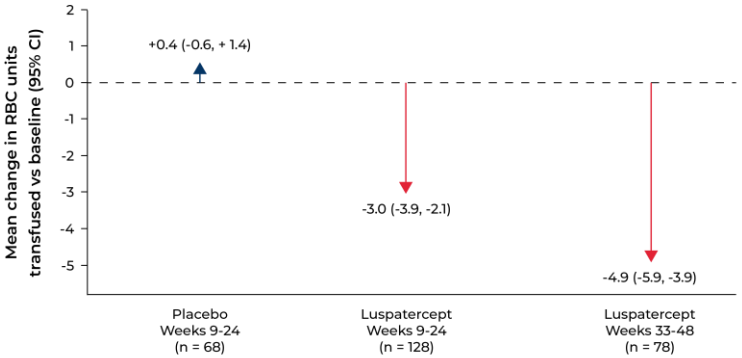
Long-term transfusion burden reduction

- The primary endpoint (RBC-TI ≥ 8 weeks during Weeks 1-24) was achieved by 58 of 153 (37.9%) and 10 of 76 (13.2%) patients receiving luspatercept and placebo, respectively ($P < 0.0001$)
- 73 of 153 (47.7%) and 12 of 76 (15.8%) patients receiving luspatercept and placebo, respectively, achieved RBC-TI ≥ 8 weeks any time during the treatment period ($P < 0.0001$)
- 77 of 153 (50.3%) patients receiving luspatercept and 11 of 76 (14.5%) patients receiving placebo achieved ≥ 50% reduction in RBC transfusion burden from baseline for ≥ 24 weeks ($P < 0.0001$)
  - The median longest episode of RBC transfusion burden reduction ≥ 50% was 131.6 weeks in the luspatercept arm and not estimable in the placebo arm

Change in RBC transfusions on treatment

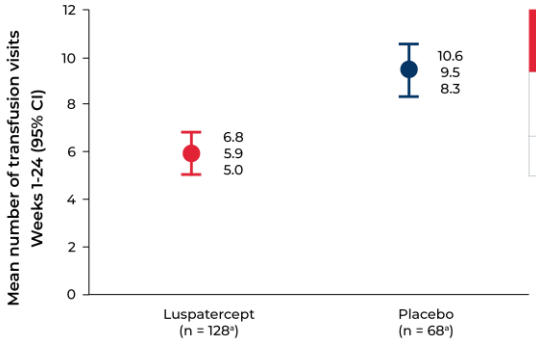
- In Weeks 9-24, mean change from baseline in RBC units transfused was -3.0 (95% confidence interval [CI] -3.9, -2.1) versus +0.4 (95% CI -0.6, +1.4) in the luspatercept versus placebo arms **(Figure 2)**
  - In Weeks 33-48, mean change from baseline in RBC units transfused was -4.9 (95% CI -5.9, -3.9) in patients receiving luspatercept
- In Weeks 1-24, mean number of transfusion visits was 5.9 versus 9.5 in the luspatercept versus placebo arms **(Figure 3)**

Figure 2. Mean change from baseline in RBC units transfused



CI, confidence interval; RBC, red blood cell.

Figure 3. Mean number of transfusion visits in Weeks 1-24



Risk of recurrent transfusion visits during Weeks 1-24[a,b]	
Luspatercept vs placebo	Hazard ratio (95% CI)
Overall population	0.699 (0.597, 0.819)

[a]83.7% (128/153) patients treated with luspatercept and 89.5% (68/76) placebo patients completed 24 weeks of treatment and were considered having complete data for this analysis. [b]A Cox model using the Andersen-Gill model[b] to assess the recurrence of transfusion visits during the primary treatment phase (Weeks 1-24). CI, confidence interval.

Total transfusions over 48 weeks

- The mean number of RBC units transfused during Weeks 1-48 was 22.89 versus 35.98 in the luspatercept versus placebo arms (*P* < 0.0001) (**Table 2**)
- The mean number of RBC transfusion visits during Weeks 1-48 was 12.95 versus 19.54 in the luspatercept versus placebo arms (*P* < 0.0001) (**Table 2**)

Table 2. Number of RBC units transfused and transfusion visits over 48 weeks

	Luspatercept (N = 153)	Placebo (N = 76)
Number of RBC units transfused over 48 weeks		
Mean	22.89	35.98
LS mean	23.28	35.20
LS mean difference (95% CI)	-11.92 (-15.55, -8.28)	
P value	< 0.0001	
Number of RBC transfusion visits over 48 weeks		
Mean	12.95	19.54
LS mean	13.14	19.15
LS mean difference (95% CI)	-6.00 (-8.16, -3.85)	
P value	< 0.0001	

CI, confidence interval; LS, least squares; RBC, red blood cell.

Change in serum ferritin

- Least squares (LS) mean change in serum ferritin from baseline to Weeks 9-24 was -2.7 µg/L and +226.5 µg/L in the luspatercept and placebo arms, respectively (LS mean difference -229.1 µg/L; *P* = 0.0024) **(Table 3)**
  - The mean change in serum ferritin in Weeks 33-48 was -72.0 µg/L and +247.4 µg/L in the luspatercept and placebo arms, respectively (LS mean difference -319.5 µg/L; *P* = 0.0294)

Table 3. Mean change from baseline in serum ferritin

	Averaged over Weeks 9-24		Averaged over Weeks 33-48	
	Luspatercept (N = 153)	Placebo (N = 76)	Luspatercept (N = 153)	Placebo (N = 76)
LS mean (SE), µg/L	-2.7 (54.05)	+226.5 (68.02)	-72.0 (74.76)	+247.4 (140.96)
LS mean difference (95% CI), µg/L	-229.1 (74.43)		-319.5 (144.57)	
***P* value**	0.0024		0.0294	

CI, confidence interval; LS, least squares; SE, standard error.

Achievement of HI-E

- In Weeks 1-24, 81 of 153 (52.9%) patients in the luspatercept arm and 9 of 76 (11.8%) patients in the placebo arm achieved modified HI-E response per IWG 2006 criteria

Conclusions

- Luspatercept produced clinically meaningful and durable reductions in RBC transfusions in patients with LR MDS with RS

- Luspatercept also resulted in statistically significant reductions in serum ferritin in patients with LR MDS with RS