Evaluating Luspatercept as a Superior Treatment for Enhancing Clinical and HRQoL Outcomes in Transfusion-dependent Patients with Lower-risk MDS: Results from Phase 3 COMMANDS Study

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Objectives

- This post hoc analysis of data from the phase-3 COMMANDS trial investigated whether luspatercept or epoetin alfa was superior for achieving a clinical response while maintaining or improving health-related quality of life in transfusion-dependent patients with lower-risk myelodysplastic syndromes.

Conclusions

- Luspatercept treatment led to significantly more clinical responses than epoetin alfa treatment while maintaining or improving HRQoL in transfusion-dependent patients with lower-risk MDS.
- The superiority of luspatercept over epoetin alfa was statistically significant across all analyzed HRQoL domains.
- These findings support the first-line use of luspatercept treatment in patients with lower-risk MDS who have anemia.

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Introduction

- Myelodysplastic syndromes (MDS) are bone marrow disorders characterized by ineffective hematopoiesis that can lead to anemia, the need for transfusions, and impaired health-related quality of life (HRQoL).[1-2]
- Per the International Prognostic Scoring System-Revised (IPSS-R), patients with MDS are classified as: very low, low, intermediate, high, or very high risk.[3]
- For transfusion-dependent patients with lower-risk MDS, key treatment goals are to increase hemoglobin (Hb) levels and achieve red blood cell transfusion independence (RBC-TI) while maintaining or improving HRQoL.[4]
- The clinical efficacy of two treatments—luspatercept and epoetin alfa—was compared in the phase 3 COMMANDS clinical trial.[5]
- Luspatercept was found to significantly increase Hb levels and improve the rate of RBC-TI in transfusion-dependent patients with lower-risk MDS (IPSS-R intermediate or lower) and no prior treatment for anemia.[5]
- However, clinical response in conjunction with HRQoL outcomes in this patient population have not yet been analyzed or compared.

Methods

COMMANDS study design

- Adult patients with MDS were randomized 1:1 to receive luspatercept (1.0 mg/kg subcutaneously Q3W with titration, up to 1.75 mg/kg if needed to achieve response) or epoetin alfa (450 IU/kg weekly) for at least 24 weeks.
- The primary endpoint in COMMANDS was concurrently achieving RBC-TI ≥12 weeks and a mean Hb increase of ≥1.5 g/dL within 24 weeks of treatment.
- A secondary endpoint was remaining RBC-TI from week 1 to week 24 (this definition of clinical response was used for the present study sensitivity analysis).

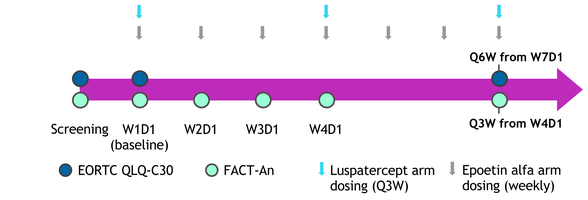
HRQoL endpoints

- HRQoL was measured with two patient-reported outcome (PRO) instruments:
  - European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 (QLQ-C30)
  - Functional Assessment of Cancer Therapy - Anemia (FACT-An)
- Questionnaires were administered at prespecified timepoints (**Figure 1**).
- Maintaining or improving HRQoL from baseline was defined using clinically meaningful thresholds identified in the literature.[6-8]

Post-hoc statistical analysis

- All analyses, including the sensitivity analysis, were conducted on patients in the intent-to-treat (ITT) population with an available baseline HRQoL assessment, defined separately for each instrument.
- Rates at which patients achieved both clinical and HRQoL goals were estimated for each arm.
- Arms were compared using the Cochran-Mantel-Haenszel method, stratified by the randomization stratification factors.
- Odds ratios (OR), 95% confidence intervals (CI), and p-values for between-arm comparisons were estimated.
- Patients with missing HRQoL data were assumed not to have an HRQoL response.

Figure 1. Timeline of dosing and PRO assessments



Questionnaires were also administered as part of MDS assessment visits at week 24, week 48, and the end-of-treatment visit; data from week 48 and the end-of-treatment visit were excluded from the current analysis.
Abbreviations: D, day; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT-An, Functional Assessment of Cancer Therapy-Anemia Questionnaire; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; W, week.

Results

Analysis populations

- Each HRQoL-evaluable population included 346 patients, comprising 95% of the COMMANDS ITT population (n=363).
- The QLQ-C30-evaluable population had a median age of 74 years, was 54% male, and included 174 patients in the luspatercept treatment arm and 172 in the epoetin alfa arm (**Table 1**).
- The FACT-An-evaluable population had similar characteristics, with 173 patients in each treatment arm.

Clinical response

- Clinical responses from the analysis populations were consistent with clinical responses reported from the COMMANDS trial.[5]
- Patients in the QLQ-C30 analysis population receiving luspatercept achieved the primary clinical response at a significantly higher rate than those receiving epoetin alfa (61% vs. 35%; OR=3.1 [95% CI: 2.0, 4.9]; p <0.001).
- In the sensitivity analysis, patients receiving luspatercept remained RBC-TI through week 24 at a higher rate than those receiving epoetin alfa (48% vs. 31%; OR=2.3 [95% CI: 1.4, 3.8]; $p = 0.001$).
- Patients in the FACT-An analysis population showed similar results for both the base case and sensitivity analyses.

Concurrent clinical response and HRQoL outcomes

- Across all QLQ-C30 and FACT-An domains, patients receiving luspatercept had more than double the odds (OR >2) as those receiving epoetin alfa to achieve a concurrent clinical and HRQoL response at week 24 (**Figure 2**).
- Results from the sensitivity analysis (RBC-TI through week 24) were similar to the base case across all domains (**Figure 3**).

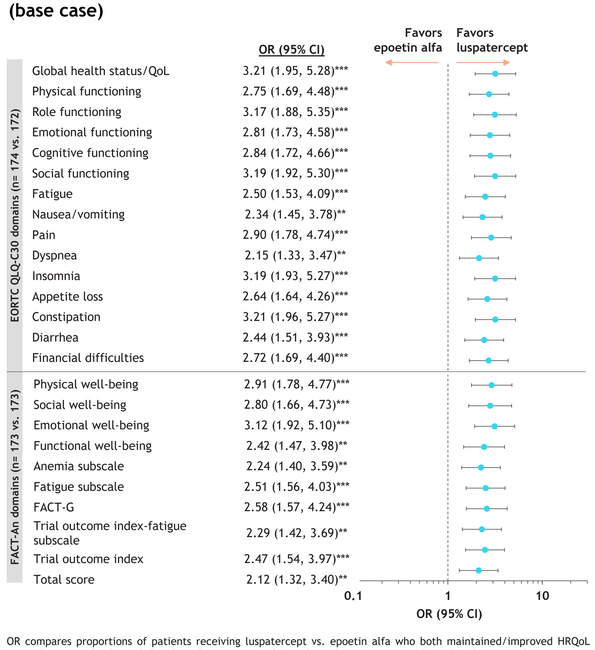
Results (cont.)

Table 1. QLQ-C30-evaluable population baseline characteristics [a]

Characteristic	Luspatercept (n = 174)	Epoetin alfa (n = 172)	Overall (n = 346)
Age (years), median (range)	74 (46-93)	75 (31-91)	74 (31-93)
Male, n (%)	103 (59.2)	84 (48.8)	187 (54.0)
Time since MDS diagnosis (months), median (range) [b]	8.0 (-0.4, 243.1)	5.1 (-0.3, 171.6)	6.2 (-0.4, 243.1)
IPSS-R risk classification at baseline, n (%)			
Very low	15 (8.6)	16 (9.3)	31 (9.0)
Low	123 (70.7)	126 (73.3)	249 (72.0)
Intermediate/High/Missing	36 (20.7)	30 (17.4)	66 (19.1)
Baseline transfusion burden (pRBC units per 8 weeks), median (range)	3 (1-10)	3 (0-14)	3 (0-14)
Baseline transfusion burden category, n (%)			
<4 pRBC units per 8 weeks	113 (64.9)	104 (60.5)	217 (62.7)
≥4 pRBC units per 8 weeks	61 (35.1)	68 (39.5)	129 (37.3)
Hb, median, g/dL	7.7	7.7	7.7
Hb, categorical, n (%)			
<8 g/dL	107 (61.5)	106 (61.6)	213 (61.6)
≥8 g/dL	67 (38.5)	66 (38.4)	133 (38.4)
RS status, n (%)			
RS+	129 (74.1)	122 (70.9)	251 (72.5)
RS−	45 (25.9)	49 (28.5)	94 (27.2)
Missing	0 (0.0)	1 (0.6)	1 (0.3)
sEPO, n (%)			
≤200 U/L	139 (79.9)	136 (79.1)	275 (79.5)
>200 U/L	35 (20.1)	36 (20.9)	71 (20.5)

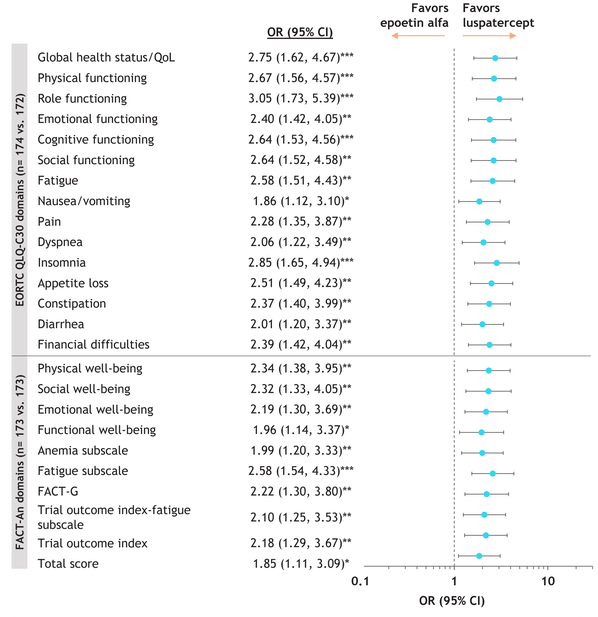
[a] Characteristics were similar for the FACT-An analysis population.
[b] Number of months from date of original diagnosis to date of enrollment in COMMANDS trial.
Abbreviations: Hb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic neoplasms; pRBC, packed red blood cells; RS, ring sideroblast; SD, standard deviation; sEPO, serum erythropoietin.

Figure 2. ORs for concurrent clinical and HRQoL responses at week 24 (base case)



OR compares proportions of patients receiving luspatercept vs. epoetin alfa who both maintained/improved HRQoL in the given domain and achieved the clinical response (RBC-TI ≥12 weeks concurrent with ≥1.5 g/dL mean Hb increase within 24 weeks). OR >1 indicates that patients receiving luspatercept had superior odds of meeting these criteria.
**Nominal P < 0.01; ***nominal P < 0.001.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30; FACT-An, Functional Assessment of Cancer Therapy - Anemia; FACT-G, Functional Assessment of Cancer Therapy-General; HRQoL, health-related quality of life; OR, odds ratio; QoL, quality of life; RBC-TI, red blood cell transfusion independence.

Figure 3. ORs for concurrent clinical and HRQoL responses at week 24 (sensitivity analysis)



OR compares proportions of patients receiving luspatercept vs. epoetin alfa who both maintained/improved HRQoL in the given domain and achieved the clinical response (RBC-TI from week 1 to week 24). OR >1 indicates that patients receiving luspatercept had superior odds of meeting these criteria.
*Nominal P < 0.05; **nominal P < 0.01; ***nominal P < 0.001.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30; FACT-An, Functional Assessment of Cancer Therapy - Anemia; FACT-G, Functional Assessment of Cancer Therapy-General; Hb, hemoglobin; HRQoL, health-related quality of life; OR, odds ratio; QOL, quality of life; RBC-TI, red blood cell transfusion independence.

Strengths and Limitations

- By assessing concurrent HRQoL outcomes and clinical responses, this study provided a more comprehensive view on patient experiences of luspatercept vs. epoetin alfa than afforded by previous data analyses of the COMMANDS trial.
- The sensitivity analysis demonstrated that, even with different definitions of clinical response, the superiority of luspatercept remained significant across all HRQoL domains.
- Patients with missing HRQoL data at week 24 were assumed not to have a response (i.e., non-responder imputation).
  - This conservative assumption was required only for a small proportion of patients from the HRQoL-evaluable populations (8.1%-12.6% receiving luspatercept and 6.4%-10.5% receiving epoetin alfa) who achieved a clinical response but had missing HRQoL data at week 24.

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