Health-related quality of life outcomes in patients with myelodysplastic syndromes with ring sideroblasts treated with luspatercept in the MEDALIST study

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Disclosures and acknowledgments

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Disclosures

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Introduction and objective

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- Patients with MDS experience severe anemia, which is commonly managed with frequent red blood cell transfusions (RBCT) in patients refractory to erythropoiesis-stimulating agents
  - At diagnosis, 85% of patients have anemia[1] and 30–50% depend on RBCT[2–4]
- The administration of RBCT provide transient relief of anemia-related symptoms and can impact health-related quality of life (HRQoL) in patients[5–6]
- Long-term dependence on RBCT may have detrimental clinical consequences, including iron overload and its associated complications of cardiac and hepatic organ failure,[7–9] whereas cessation or reduction of RBCT may increase anemia-related symptoms and negatively impact HRQoL
- Luspatercept is a first-in-class erythroid maturation agent providing clinically meaningful reduction in transfusion burden in patients with transfusion-dependent anemia due to IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with ring sideroblasts in the phase 3 MEDALIST trial (NCT02631070)
- This analysis aimed to evaluate the effect of luspatercept versus placebo on HRQoL of patients treated for MDS from baseline through Week 25 of the MEDALIST trial

IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes.

1. Noël P, Solberg LA Jr. *Crit Rev Oncol Hematol* 1992;12:193–215. 2. Malcovati L, et al. *J Clin Oncol* 2007;25:3503–3510; 3. Malcovati L. *Clin Lymphoma Myeloma* 2009;9 Suppl 3:S305–311. 4. Zeidan AM, et al. *Blood Rev* 2013;27:243–259. 5. Pinchon DJ, et al. *Am J Hematol* 2009;84:671–677. 6. Koutsavlis I. *Anemia* 2016;2016:8494738. 7. Hellström-Lindberg E, et al. *Br J Haematol* 2003;120:1037–1046. 8. Jansen AJG, et al. *Br J Haematol* 2003;121:270–274. 9. Thomas ML. *Eur J Oncol Nurs* 2007;11:151–158.

Methods

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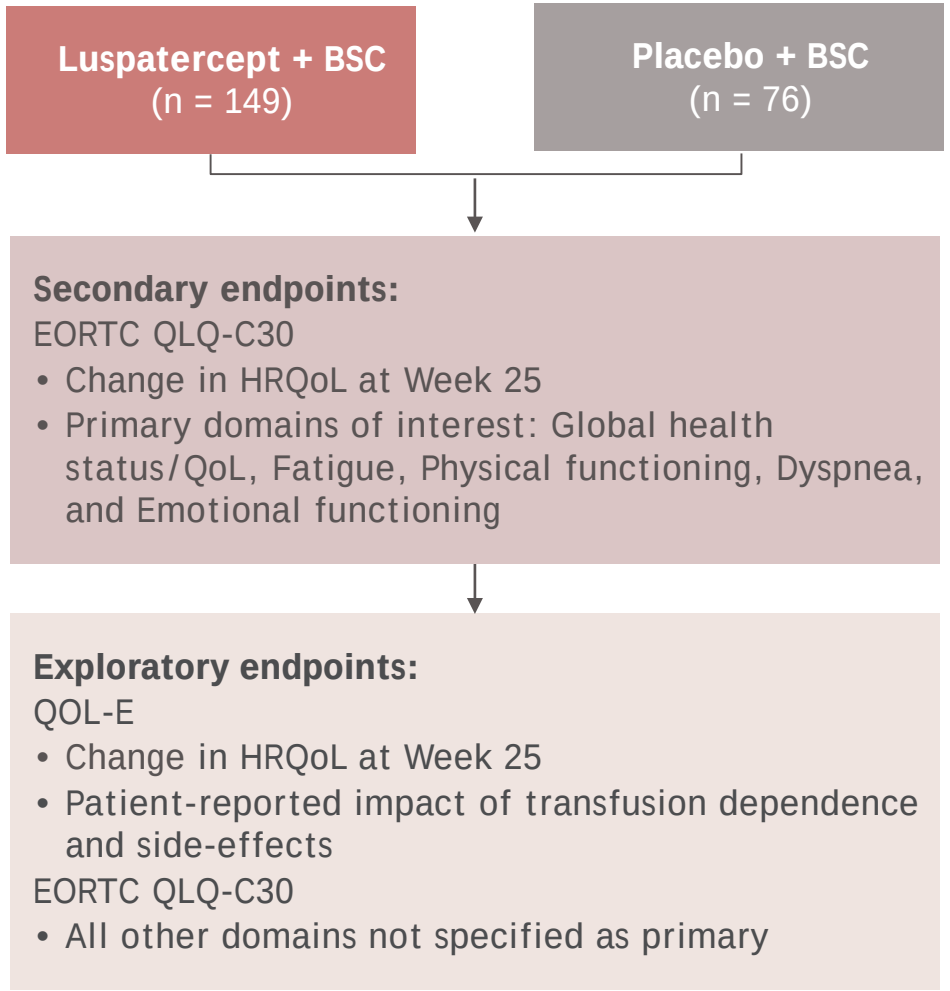
- In the MEDALIST trial, patients received luspatercept or placebo every 3 weeks for 24 weeks plus BSC, including tailored number of RBCT given at the investigator's discretion
- PRO/HRQoL endpoints were determined for the HRQoL-evaluable population (**Figure 1**)
- Mean change from baseline to Week 25 in EORTC QLQ-C30 and QOL-E domains were determined using mixed-effects repeated measures analysis
- Clinically meaningful change within each treatment arm was defined as a ≥ 10-point change in PRO score from baseline for all EORTC QLQ-C30 domains, and ≥ 0.5 SD of the baseline domain score for all QOL-E domains

Figure 1. PRO/HRQoL endpoints[a] in MEDALIST



[a]PRO endpoints were not powered in this study; all analyses were considered descriptive.
BSC, best supportive care; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PRO, patient-reported outcome; QoL, quality of life; QOL-E, quality of life assessment in MDS questionnaire; SD, standard deviation.

Results: Patient population

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Table 1. Patient demographics and clinical characteristics at baseline

Characteristic	Luspatercept + BSC (n = 149)	Placebo + BSC (n = 76)	Total (N = 225)
Age, median (SD), years	70.5 (8.7)	70.7 (10.9)	70.6 (9.4)
≤ 64, n (%)	28 (18.8)	16 (21.1)	44 (19.6)
65–74, n (%)	70 (47.0)	29 (38.2)	99 (44.0)
≥ 75, n (%)	51 (34.2)	31 (40.8)	82 (36.4)
Sex, n (%)			
Male	93 (62.4)	50 (65.8)	143 (63.6)
Race, n (%)			
White	105 (70.5)	51 (67.1)	156 (69.3)
Black	1 (0.7)	0 (0.0)	1 (0.4)
Not collected	42 (28.2)	24 (31.6)	66 (29.3)
Other	1 (0.7)	1 (1.3)	2 (0.9)
IPSS-R risk, n (%)			
Very Low or Low	123 (82.6)	63 (82.9)	186 (82.7)
Intermediate	25 (16.8)	13 (17.1)	38 (16.9)
Missing	1 (0.7)	0 (0.0)	1 (0.4)
Prior ESA use, n (%)			
Yes	144 (96.6)	70 (92.1)	214 (95.1)
Transfusion burden, n (%)			
< 4 units RBCT units/8 weeks	44 (29.5)	20 (26.3)	64 (28.4)
4–5 units RBCT units/8 weeks	40 (26.8)	23 (30.3)	63 (28.0)
≥ 6 units RBCT units/8 weeks	65 (43.6)	33 (43.4)	98 (43.6)

ESA, erythropoiesis-stimulating agent; SD, standard deviation.

Results: Patient population

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Table 2. Baseline EORTC QLQ-C30 scores

EORTC QLQ-C30, mean (SD)	Baseline score in MEDALIST (N = 225)	General population[a] (N = 3,061)	Recurrent/ metastatic cancer patients (N = 4,812)
Global health status/QoL	58.26 (20.14)	67.1	56.3
Physical functioning	**66.31 (21.14)**	82.5	75.8
Role functioning	**65.11 (29.53)**	83.8	60.7
Cognitive functioning	82.07 (20.33)	87.2	80.5
Emotional functioning	76.87 (19.88)	81.6	68.7
Social functioning	**74.33 (27.83)**	89.1	70.5
Fatigue	**42.91 (24.62)**	24.9	41.8
Nausea/vomiting	5.04 (12.17)	2.5	13.1
Pain	18.90 (24.60)	23.2	33.7
Dyspnea	**35.74 (29.48)**	17.0	23.4
Insomnia	27.53 (30.79)	24.0	33.6
Appetite loss	14.37 (23.90)	6.8	28.2
Constipation	17.56 (26.96)	10.7	23.2
Diarrhea	8.93 (18.40)	6.2	10.7
Financial difficulties	11.01 (22.93)	7.6	16.2

Table 3. Baseline QOL-E scores

QOL-E, mean (SD)	Baseline score in MEDALIST (N = 225)
Physical well-being	52.87 (21.52)
Functional well-being	53.70 (32.38)
Social and family life	48.41 (37.63)
Sexual well-being	62.42 (36.25)
Fatigue	74.98 (14.12)
MDS-specific disturbances	57.04 (23.68)
Treatment outcome index	54.71 (20.65)
General	58.69 (21.06)
All	58.07 (21.09)

[a]Nolte S, et al. *Eur J Cancer* 2019;107:153–163. The mean was re-weighted based on the age- and gender-distributions of the MEDALIST patients. A difference of 10 points was considered a clinically meaningful difference. Domains in which MEDALIST patients had a clinically meaningful worse HRQoL compared with the general population are shown in red.

Results: EORTC QLQ-C30 assessment

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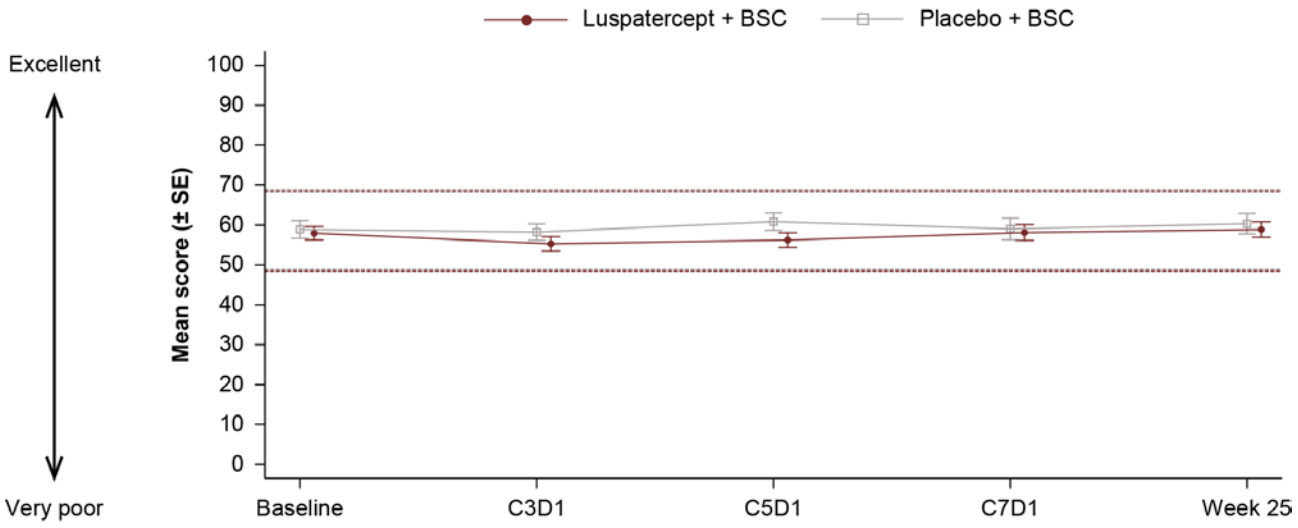
Figure 2. Mean Global health status/QoL score[a] over time on the EORTC QLQ-C30 from baseline through Week 25



	Baseline	C3D1	C5D1	C7D1	Week 25
Number at risk					
Luspatercept + BSC	149	133	129	108	110
Placebo + BSC	75	70	66	60	54
Mean change from baseline					
Luspatercept + BSC		–4.07	–2.39	–2.08	–1.82
Placebo + BSC		0.12	2.18	–0.56	0.16
Median change from baseline					
Luspatercept + BSC		0.00	0.00	0.00	0.00
Placebo + BSC		0.00	0.00	0.00	0.00

Table 4. Relative mean difference in change in EORTC QLQ-C30 domain scores from baseline to Week 25 between luspatercept and placebo[b]

EORTC QLQ-C30 domain[c]	Relative mean difference at Week 25	MCID
Global health status/QoL	–3.76	10
Physical functioning	–7.13	10
Fatigue	6.76	10
Dyspnea	5.55	10
Emotional functioning	–0.51	10
Role functioning	–5.12	10
Cognitive functioning	1.62	10
Social functioning	–3.12	10
Nausea/vomiting	–0.67	10
Pain	–1.07	10
Insomnia	–1.04	10
Appetite loss	0.32	10
Constipation	3.80	10
Diarrhea	–0.86	10
Financial difficulties	0.58	10

[a]Data represent observed change from baseline. Dashed lines indicate threshold for a clinically meaningful difference. Data cutoff: July 1, 2019.
[b]Data from longitudinal mixed model analyses. Data cutoff: July 1, 2019.
[c]Higher scores shown in red domains represent better QoL, higher scores in other domains represent worse QoL.
C, cycle; D, day; MCID, minimal clinically important difference; SE, standard error.

Results: EORTC QLQ-C30 assessment

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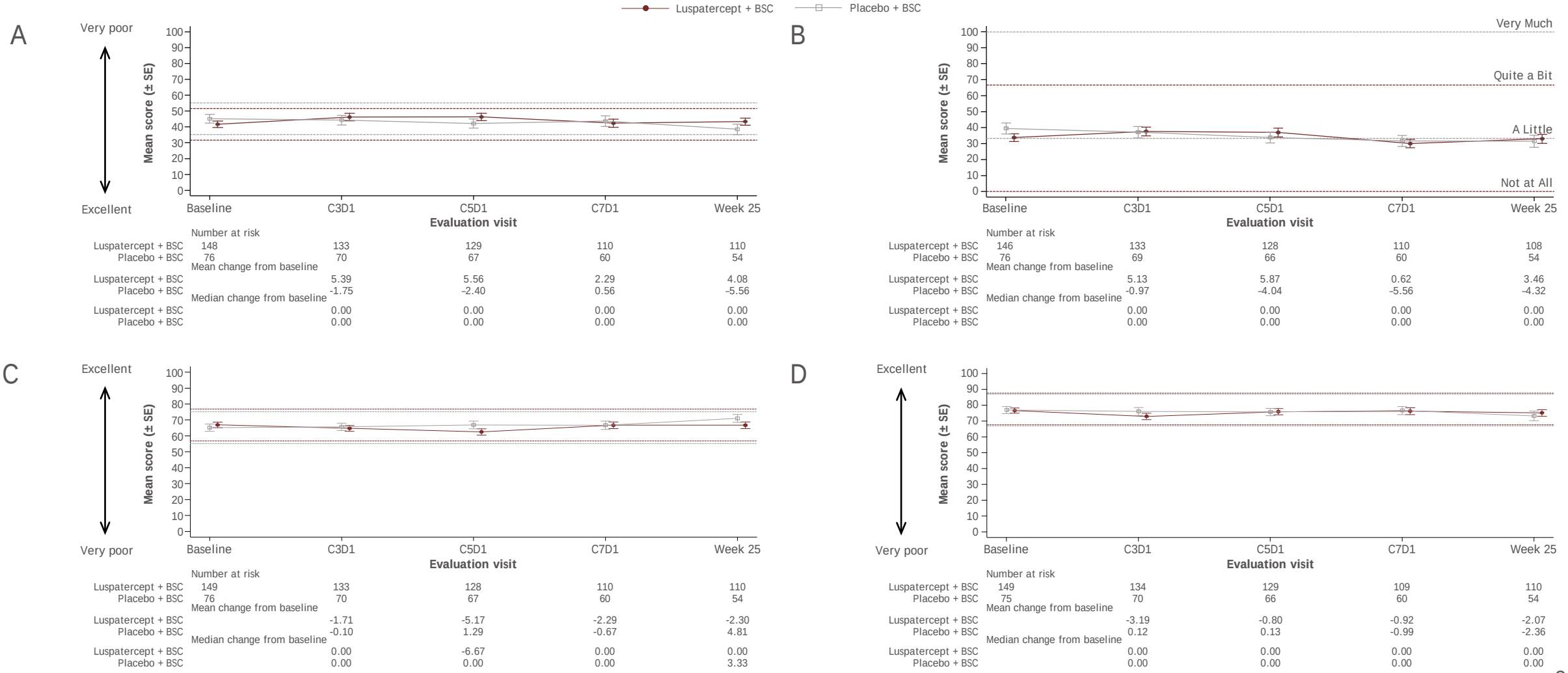
Figure 3. Patient-reported mean (A) Fatigue, (B) Dyspnea, (C) Physical functioning, and (D) Emotional functioning scores[a] over time on the EORTC QLQ-C30 from baseline through Week 25



[a]Data represent observed change from baseline. Dashed lines indicate threshold for a clinically meaningful difference. Data cutoff: July 1, 2019.

Results: QOL-E assessment

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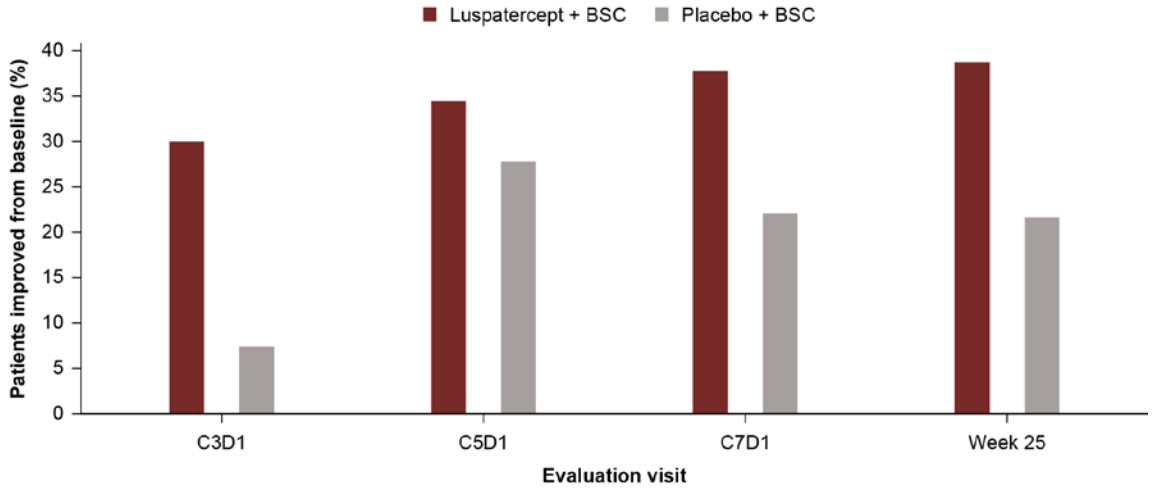
Table 5. Relative mean difference in change in QOL-E domain scores from baseline to Week 25 between luspatercept and placebo[a]

QOL-E domain[b]	Relative mean difference at Week 25	MCID
Physical well-being	−5.28	10.69
Functional well-being	−6.07	16.13
Social and family life	−8.70	18.76
Sexual well-being	0.31	18.14
Fatigue	−5.10	7.14
MDS-specific disturbances	−2.03	11.90
Treatment outcome index	−4.71	10.31
General	−6.30	10.51
All	−5.10	10.57

Figure 4. Patient-reported transfusion burden on QOL-E[c] from treatment initiation through Week 25



	C3D1		C5D1		C7D1		Week 25	
	Luspatercept	Placebo	Luspatercept	Placebo	Luspatercept	Placebo	Luspatercept	Placebo
N	127	68	122	65	106	59	106	51
Improved, %	30	7	34	28	38	22	39	22
Stable, %	59	74	49	52	47	59	49	57
Worsening 1, %	9	13	15	17	14	17	10	20
Worsening 2, %	2	6	2	3	1	2	2	2

[a]Data from longitudinal mixed model analyses. Data cutoff: July 1, 2019.
[b]Higher scores represent better QoL across all domains.
[c]Data cutoff: July 1, 2019. Question from the PRO instrument: What effect of the disease disturbs your daily life? Being dependent on transfusions (response options: "No, not at all", "A little bit", and "Yes, extremely").

Limitations and conclusion

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Limitations

- Patient Hb levels in the MEDALIST trial were maintained at a range where HRQoL may be insensitive to changes in Hb
  - The incremental gain in HRQoL is the largest when Hb levels are 10–12 g/dL, whereas HRQoL improvement appears minimal below 10 g/dL
    - Average Hb level at baseline in the MEDALIST trial was 7.6 g/dL
    - The study design capped Hb concentrations at 11.5 g/dL and change in Hb level at ≤ 2 g/dL from the previous treatment cycle
      - Patients required a dose delay if exceeding these criteria (> 11.5 g/dL Hb or an increase in Hb of > 2 g/dL from previous cycle)
- PRO data collection was on a fixed schedule, independent of RBCT events
  - RBCT provide temporary relief and improvement in HRQoL and symptoms in the days following transfusion
- The majority of concepts covered by EORTC QLQ-C30 (cancer specific) and QOL-E (MDS specific) were not specific to the luspatercept treatment effect (i.e. concepts directly capturing patient experience pertaining to reduction in RBCT)

Conclusion

- Luspatercept with BSC reduced RBCT burden and patient-reported transfusion impact on their daily life, while maintaining other aspects of HRQoL from baseline through Week 25 in the MEDALIST trial

Hb, hemoglobin.