Assessment of longer-term efficacy, safety, and haematological improvement in the phase 3, randomised, double-blind, placebo-controlled MEDALIST trial of luspatercept to treat anaemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts who require red blood cell transfusions

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Introduction

- Chronic anaemia is the most common cytopenia in lower-risk myelodysplastic syndromes (LR-MDS), with complications including fatigue, falls, and decreased quality of life[1,2]
- Additional cytopenias in patients with LR-MDS may complicate treatment and contribute to infections and bleeding events[3,4]
- Treatments for anaemia include erythroid-stimulating agents (ESAs) and red blood cell (RBC) transfusions; however, RBC transfusion dependence is associated with reduced survival[5] and responses to ESAs are limited[2]
- Treatment options are lacking for patients with transfusion-dependent LR-MDS for whom ESA treatment is ineffective or is not an option[2,6]
- Luspatercept is a first-in-class erythroid maturation agent that binds select TGF-ß superfamily ligands to diminish SMAD2/3 signaling and enhance late-stage erythropoiesis[7]
  - In the primary analysis of the MEDALIST trial, the primary endpoint of RBC transfusion independence (RBC-TI) ≥ 8 weeks (during Weeks 1-24) was achieved by 37.9% of patients in the luspatercept arm and 13.2% in the placebo arm ($P < 0.0001$)[8]
  - Luspatercept is approved by the European Medicines Agency for the treatment of adult patients with transfusion-dependent anaemia due to Revised International Prognostic Scoring System (IPSS-R)-defined Very low-, Low-, and Intermediate-risk MDS with ring sideroblasts (RS), who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy

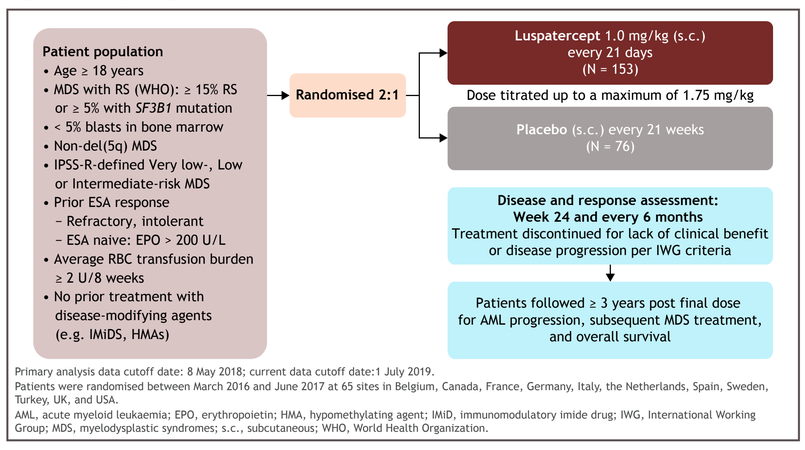
Objective

- To report longer-term efficacy, safety, and haematological improvement (HI) outcomes for patients in the MEDALIST trial

Methods

- MEDALIST (NCT02631070) is an ongoing phase 3, randomised, double-blind, placebo-controlled trial (**Figure 1**)

Figure 1. Study design of the MEDALIST trial



Primary analysis data cutoff date: 8 May 2018; current data cutoff date:1 July 2019.
Patients were randomised between March 2016 and June 2017 at 65 sites in Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, Sweden, Turkey, UK, and USA.
AML, acute myeloid leukaemia; EPO, erythropoietin; HMA, hypomethylating agent; IMiD, immunomodulatory imide drug; IWG, International Working Group; MDS, myelodysplastic syndromes; s.c., subcutaneous; WHO, World Health Organization.

- Patients were randomised between March 2016 and June 2017 at 65 sites
- Eligible patients had anaemia due to IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with RS; were refractory to, intolerant of, or unlikely to respond to (serum erythropoietin > 200 U/L) ESAs; and required RBC transfusions
- Patients were randomised 2:1 to receive luspatercept (starting dose 1.0 mg/kg, with titration up to 1.75 mg/kg, if needed) or placebo subcutaneously every 3 weeks for ≥ 24 weeks
- Disease and response assessments were conducted at Week 24 and every 6 months, with patients followed up for at least 3 years post final dose
- Platelet and neutrophil counts were assessed by the central laboratory
- Study endpoints in the current analysis (data cutoff date: 1 July 2019) included:
  - Achievement of RBC-TI ≥ 8 weeks over the entire treatment period and number of individual response periods
  - Cumulative duration of RBC-TI ≥ 8 weeks in all responders (defined as the sum of all durations of RBC-TI ≥ 8 weeks for all patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase)
  - Clinical benefit (defined as achieving RBC-TI ≥ 8 weeks and/or modified haematological improvement-erythroid [mHI-E] according to International Working Group [IWG] 2006 criteria[9])
  - Total duration of clinical benefit (defined as the time from achieving clinical benefit to end of treatment)
  - HI-E response, HI-neutrophil (HI-N) response, and HI-platelet (HI-P) response during Weeks 1–24 and Weeks 1–48
  - Mean neutrophil and platelet changes from baseline, and absolute increases in neutrophil and platelet counts

Results

Patients

- Of 229 patients, 99 received ≥ 6 RBC units/8 weeks, 64 received ≥ 4 to < 6 RBC units/8 weeks, and 66 received < 4 RBC units/8 weeks, in the 16 weeks prior to randomisation (**Table 1**)
- Baseline neutropenia (per IWG 2006 criteria,[9] baseline neutrophils < 1 × 10^9/L) was confirmed in 15 (9.8%) and 10 (13.2%) patients in the luspatercept and placebo arms, respectively (**Table 1**)
- Baseline thrombocytopenia (per IWG 2006 criteria,[9] baseline platelets < 100 × 10^9/L) was confirmed in 8 (5.2%) and 6 (7.9%) patients in the luspatercept and placebo arms, respectively (**Table 1**)

RBC-TI ≥ 8 weeks over the entire treatment period

- Of 153 luspatercept-treated patients, 73 (47.7%) achieved RBC-TI ≥ 8 weeks any time over the entire treatment period versus 12 (15.8%) of 76 placebo patients ($P < 0.0001$) (**Figure 2**)
  - Higher RBC-TI ≥ 8 weeks any time over the entire treatment period for luspatercept patients versus placebo patients was achieved regardless of the baseline transfusion burden (**Figure 2**)
  - Of the 73 luspatercept-treated patients achieving RBC-TI ≥ 8 weeks during the entire treatment period, 51 (69.9%) had ≥ 2 separate response periods, 28 (38.4%) had ≥ 3 separate response periods, and 15 (20.5%) had ≥ 4 separate response periods (**Figure 3**)

Cumulative duration of RBC-TI ≥ 8 weeks in all responders

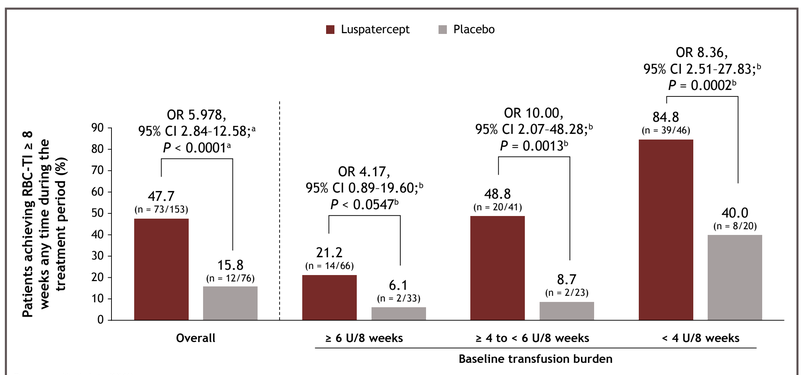
- Of the 153 luspatercept-treated patients, 12 (7.8%) remained transfusion-free after the first dose through Week 48
- Patients receiving luspatercept had longer duration of treatment, duration of the longest single period of RBC-TI ≥ 8 weeks, and cumulative duration of RBC-TI ≥ 8 weeks (**Table 2**)

Table 1. Baseline patients characteristics

Characteristic	Luspatercept (N = 153)	Placebo (N = 76)
Age, median (range), years	71 (40-95)	72 (26-91)
Male, n (%)	94 (61.4)	50 (65.8)
RBC transfusion burden, median (range),[a] U/8 weeks	5 (1-15)	5 (2-20)
≥ 6 U/8 weeks, n (%)	66 (43.1)	33 (43.4)
≥ 4 to < 6 U/8 weeks, n (%)	41 (26.8)	23 (30.3)
< 4 U/8 weeks, n (%)	46 (30.1)	20 (26.3)
IPSS-R,[b] n (%)		
Very low	18 (11.8)	6 (7.9)
Low	109 (71.2)	57 (75.0)
Intermediate	25 (16.3)	13 (17.1)
SF3B1 mutation,[c] n (%)	138 (93.2)	64 (86.5)
Serum EPO,[d] n (%)		
< 200 U/L	88 (57.5)	50 (65.8)
≥ 200 U/L	64 (41.8)	26 (34.2)
Baseline Hb,[e] median (range), g/dL	7.6 (6-10)	7.6 (5-9)
Serum ferritin, mean (SD), µg/L	1,348.0 (971.24)	1,503.8 (1,242.94)
MDS WHO 2008 classification of RCMD-RS, n (%)	145 (94.8)	74 (97.4)
ANC, mean (SD), × 10^9/L	2.8 (2.1)	2.7 (2.0)
ANC category, n (%)		
< 0.5 × 10^9/L	1 (0.7)	0
0.5 to < 1.0 × 10^9/L	14 (9.2)	10 (13.2)
≥ 1.0 × 10^9/L	138 (90.2)	66 (86.8)
Platelet count, mean (SD), × 10^9/L	259.3 (122.6)	251.7 (123.9)
Platelet count category, n (%)		
< 100 × 10^9/L	8 (5.2)	6 (7.9)
100-400 × 10^9/L	128 (83.7)	61 (80.3)
> 400 × 10^9/L	17 (11.1)	9 (11.8)
Patients with baseline neutropenia,[f] n (%)	15 (9.8)	10 (13.2)
Patients with baseline thrombocytopenia,[g] n (%)	8 (5.2)	6 (7.9)
Prior therapy with G-CSF,[h] n (%)	51 (33.3)	22 (28.9)

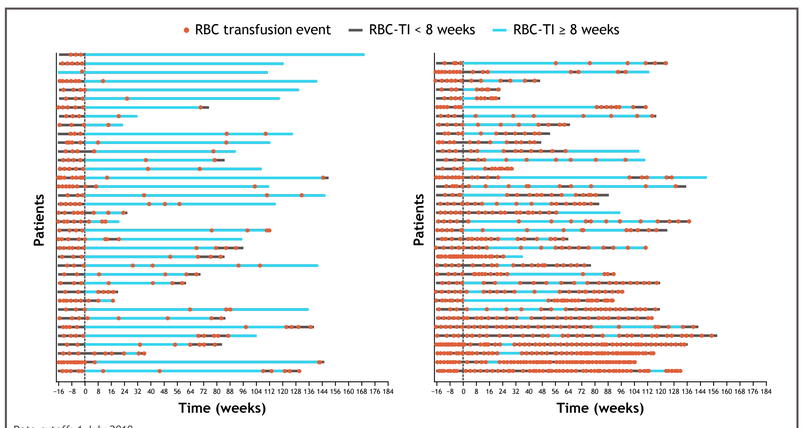
[a]In the 16 weeks prior to randomisation; [b]1 patient in luspatercept arm classified as IPSS-R High risk; [c]Of patients with available baseline gene mutation data (luspatercept, n = 148; placebo, n = 74); no patients with *SF3B1* mutation had RS < 15%; [d]Data missing for 1 patient in luspatercept arm; [e]Baseline Hb defined as the last value measured on/before date and time of first dose; [f]Baseline neutrophil count < 1 × 10^9/L; [g]Baseline platelet count < 100 × 10^9/L; [h]In combination with ESAs.
ANC, absolute neutrophil count; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; RCMD-RS, refractory cytopenia with multilineage dysplasia with ring sideroblasts; RS, ring sideroblasts; SD, standard deviation; WHO, World Health Organization.

Figure 2. RBC-TI ≥ 8 weeks achieved any time during treatment period



Data cutoff: 1 July 2019.
[a]Determined using a Cochran-Mantel-Haenszel test stratified for average baseline transfusion requirement (≥ 6 U/8 weeks vs < 6 U/8 weeks) and baseline IPSS-R score (Very low or Low vs Intermediate); [b]Determined using a Cochran-Mantel-Haenszel test; luspatercept minus placebo.
CI, confidence interval; IPSS-R , Revised International Prognostic Scoring System; OR, odds ratio; RBC-TI, red blood cell transfusion independence.

Figure 3. Analysis of multiple response periods among luspatercept-treated patients achieving RBC-TI ≥ 8 weeks (n = 73)



Data cutoff: 1 July 2019.
Response according to IWG 2006 criteria.
Transfusion events are not representative of changes in RBC units transfused.
IWG, International Working Group; RBC, red blood cell; RBC-TI, red blood cell transfusion independence.

Table 2. Cumulative duration of response

Parameter	Luspatercept (N = 153)	Placebo (N = 76)
Treatment duration, median (range), weeks	50.9 (6.0-172.0)	24.0 (7.0-103.0)
In patients achieving RBC-TI ≥ 8 weeks during the entire treatment period	109.1 (18.0-172.0)[a]	53.6 (24.0-103.0)[b]
Patients remaining on treatment as of 1 July 2019 data cutoff, n (%)	41 (26.8)	0
Cumulative duration of RBC-TI ≥ 8 weeks (sum of all periods of RBC-TI ≥ 8 weeks),[c] median (95% CI), weeks	79.9 (53.7-112.3)[a]	21.0 (10.9-NE)[b]

Data cutoff: 1 July 2019.
[a]In the 73 patients in the luspatercept arm who achieved RBC-TI ≥ 8 weeks during the entire treatment period. [b]In the 12 patients in the placebo arm who achieved RBC-TI ≥ 8 weeks during the entire treatment period. [c]Cumulative duration of RBC-TI ≥ 8 weeks defined as the sum of all durations of RBC-TI for patients achieving RBC-TI ≥ 8 weeks during the entire treatment period.
CI, confidence interval; NE, not estimable; RBC-TI, red blood cell transfusion independence.

Clinical benefit

- Clinical benefit with luspatercept was achieved by 98 (64.1%) patients, regardless of baseline transfusion burden (**Table 3**)
- The median duration of clinical benefit was 92.3 weeks in the luspatercept arm versus 26.8 weeks in the placebo arm (**Table 3**)

Haematological improvement

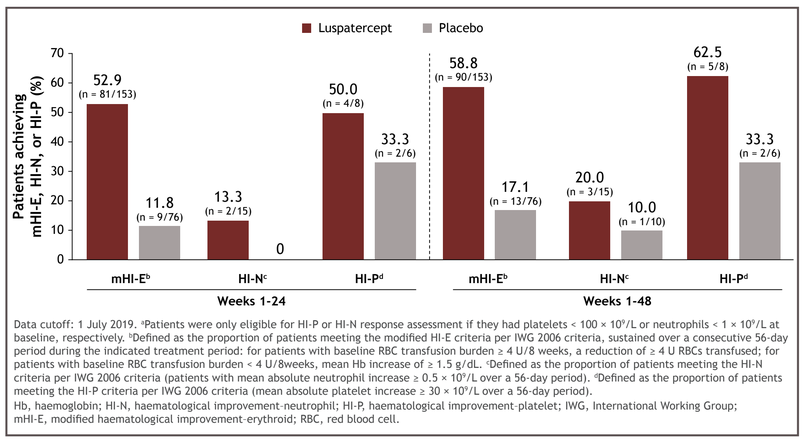
- mHI-E was achieved in 90 of 153 (58.8%) patients in the luspatercept arm and 13 of 76 (17.1%) patients in the placebo arm during Weeks 1–48 (**Figure 4**)
- Of patients evaluable for HI-N (baseline neutrophil count < 1 × 10^9/L), 3 of 15 (20.0%) patients receiving luspatercept and 1 of 10 (10.0%) patients receiving placebo achieved HI-N during Weeks 1–48 (**Figure 4**)
- Of patients evaluable for HI-P (baseline platelet count < 100 × 10^9/L), 5 of 8 (62.5%) receiving luspatercept and 2 of 6 (33.3%) receiving placebo achieved HI-P during Weeks 1–48 (**Figure 4**)
  - None of the patients in the luspatercept arm who achieved HI-P received platelet transfusions

Table 3. Achievement and duration of clinical benefit over the entire treatment period

Clinical benefit and duration	Luspatercept	Placebo
Clinical benefit[a] - all patients, n/N (%)	**98/153 (64.1)**	**20/76 (26.3)**
Baseline transfusion burden ≥ 6 U/8 weeks	37/66 (56.1)	9/33 (27.3)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	22/41 (53.7)	3/23 (13.0)
Baseline transfusion burden < 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)
Duration of clinical benefit[b] - all patients, median (range), weeks	**92.3 (8-172)**	**26.8 (8-103)**
Baseline transfusion burden ≥ 6 U/8 weeks	66.0 (8-148)	23.9 (8-103)
Baseline transfusion burden ≥ 4 to < 6 U/8 weeks	96.1 (13-150)	45.7 (45-51)
Baseline transfusion burden < 4 U/8 weeks	91.7 (21-172)	26.8 (18-76)

Data cutoff: 1 July 2019.
[a]Defined as achieving RBC-TI ≥ 8 weeks and/or mHI-E per IWG 2006 criteria over the entire treatment period.
[b]Duration of clinical benefit is defined as the time from start of response (RBC-TI ≥ 8 weeks and/or mHI-E) to end of treatment.
IWG, International Working Group; mHI-E, modified haematological improvement-erythroid; RBC-TI, red blood cell transfusion independence.

Figure 4. Patients achieving mHI-E, HI-N, and HI-P[a]



Data cutoff: 1 July 2019. [a]Patients were only eligible for HI-P or HI-N response assessment if they had platelets < 100 × 10^9/L or neutrophils < 1 × 10^9/L at baseline, respectively. [b]Defined as the proportion of patients meeting the modified HI-E criteria per IWG 2006 criteria, sustained over a consecutive 56-day period during the indicated treatment period: for patients with baseline RBC transfusion burden ≥ 4 U/8 weeks, a reduction of ≥ 4 U RBCs transfused; for patients with baseline RBC transfusion burden < 4 U/8weeks, mean Hb increase of ≥ 1.5 g/dL. [c]Defined as the proportion of patients meeting the HI-N criteria per IWG 2006 criteria (patients with mean absolute neutrophil increase ≥ 0.5 × 10^9/L over a 56-day period). [d]Defined as the proportion of patients meeting the HI-P criteria per IWG 2006 criteria (mean absolute platelet increase ≥ 30 × 10^9/L over a 56-day period).
Hb, haemoglobin; HI-N, haematological improvement-neutrophil; HI-P, haematological improvement-platelet; IWG, International Working Group; mHI-E, modified haematological improvement-erythroid; RBC, red blood cell.

Safety

- Adverse events (AEs) occuring more frequently in the luspatercept arm: fatigue (1.3%), asthenia (0.7%), and headache (0.7%), did not often lead to treatment discontinuation; no discontinuations due to these TEAEs occurred in the placebo arm
- 1 patient in the luspatercept arm who achieved HI-N or HI-P progressed to higher-risk MDS
- None of the patients who achieved HI-N or HI-P progressed to acute myeloid leukaemia
- Infection was reported in 4 of 9 luspatercept-treated patients and 3 of 7 placebo-treated patients experiencing neutropenia on study
- Bleeding was not reported in any luspatercept- or placebo-treated patients experiencing thrombocytopenia on study

Table 4. Safety summary

Summary of TEAEs, n (%)	Luspatercept (N = 153)	Placebo (N = 76)
Patients with ≥ 1 TEAE	134 (87.6)	63 (82.9)
Patients with ≥ 1 TEAE resulting in discontinuation	21 (13.7)	6 (7.9)
Treatment-emergent grade 3 or 4 neutropenia	7 (4.6)	6 (7.9)
Treatment-emergent grade 3 or 4 thrombocytopenia	0	0
Progression to HR-MDS or AML	8 (5.2)	4 (5.3)
HR-MDS	5 (3.3)	2 (2.6)
AML	3 (2.0)	2 (2.6)

Data cutoff: 1 July 2019
AML, acute myeloid leukaemia; HR-MDS, higher-risk myelodysplastic syndromes; TEAE, treatment-emergent adverse event.

Conclusions

- In this longer-term analysis of the MEDALIST trial, more luspatercept-treated patients achieved RBC-TI ≥ 8 weeks any time during treatment versus placebo (47.7% vs 15.8%, respectively)
- Approximately 70% of responders in the luspatercept arm had multiple response periods
- Luspatercept-treated patients had durable cumulative duration of RBC-TI and clinical benefit regardless of baseline transfusion burden
- A greater proportion of patients in the luspatercept arm achieved mHI-E during Weeks 1–48 than those in the placebo arm (58.8% vs 17.1%, respectively)
- Of patients evaluable for HI-N (n = 25), 20.0% achieved HI-N during Weeks 1–48 in the luspatercept arm versus 10.0% in the placebo arm
- Of patients evaluable for HI-P (n = 14), 62.5% achieved HI-P during Weeks 1–48 in the luspatercept arm compared with 33.3% in the placebo arm
- Those TEAEs occurring more frequently with luspatercept resulted in very few discontinuations

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