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Zeidan AM et al. ASH 2025 [Abstract 789]

Luspatercept initiated at the maximum-approved dose in transfusion-dependent lower-risk myelodysplastic syndromes: interim analysis from MAXILUS

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MAXILUS: background and objective

- Luspatercept is approved to treat anemia in patients with TD LR-MDS who are ESA-naive or have experienced ESA therapy failure[1]
- Luspatercept improved RBC-TI in patients with LR-MDS in the phase 3 COMMANDS and MEDALIST trials[2-4]
  - In these trials, the starting luspatercept dose was 1.0 mg/kg; patients may have had their dose titrated to 1.33 mg/kg and subsequently to 1.75 mg/kg[2,4]
  - Two-thirds of patients in COMMANDS were titrated to the maximum-approved luspatercept dose (1.75 mg/kg) to help them achieve or maintain their clinical response[2]; however, as observed in routine clinical practice, many physicians do not titrate to the full dose per the prescribing information due to concerns about potential side effects
- This phase 3b, open-label MAXILUS trial evaluates the efficacy and safety of luspatercept initiated at the maximum-approved dose in patients with TD LR-MDS
  - Preliminary results from MAXILUS indicated that luspatercept was well tolerated, with no new safety signals observed[5]

Objective: to report the updated efficacy and safety outcomes from the preplanned interim analysis (data cutoff: April 14, 2025) of the MAXILUS study, with > 75% of the overall study population evaluable after the 24-week treatment phase

ESA, erythropoiesis-stimulating agent; LR-MDS, lower-risk myelodysplastic syndromes; RBC-TI, red blood cell-transfusion independence; TD, transfusion-dependent.

1. Reblozyl® (luspatercept-aamt). Package insert. Bristol Myers Squibb; May 2024. 2. Della Porta MG et al. *Lancet Haematol*. 2024;11:E646–E658. 3. Garcia-Manero G et al. *Blood*. 2024;144(suppl 1):350. 4. Fenaux P et al. *N Engl J Med*. 2020;382:140–151. 5. Della Porta MG et al. Poster presentation at EHA; June 12–15, 2025; Milan, Italy; Poster PF634.

MAXILUS: study design

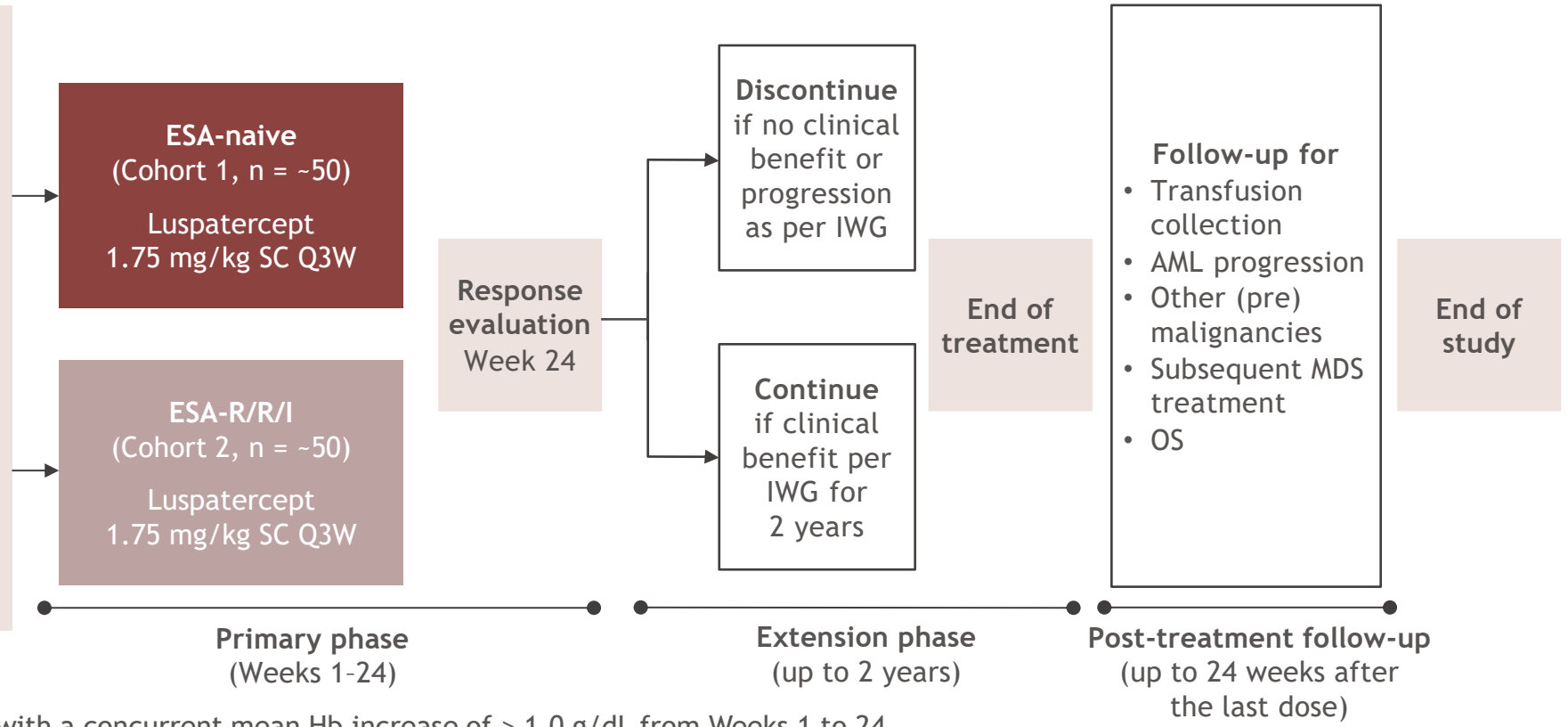
MAXILUS (NCT06045689) is a phase 3b, open-label, non-randomized, 2-cohort trial

Key patient eligibility criteria

- ≥ 18 years of age
- MDS diagnosis (WHO 2018 criteria)
- IPSS-R very low-, low-, or intermediate-risk MDS
- ESA-naive[a] and ESA-R/R/I allowed
- RS+ and RS−
- Hb ≤ 10 g/dL
- ECOG PS score of 0–2
- ≥ 1 U of RBCs within 8 weeks prior to treatment

TB central enrollment control

- ≥ 20% of patients with baseline low TB (< 4 U/8 weeks) and high TB (≥ 4 U/8 weeks) per cohort



- Primary endpoint: RBC-TI for ≥ 8 weeks with a concurrent mean Hb increase of ≥ 1.0 g/dL from Weeks 1 to 24
- Secondary endpoints: RBC-TI for ≥ 8 weeks from Weeks 1 to 24, RBC-TI for ≥ 12 weeks from Weeks 1 to 24, disease progression to AML, and safety
- At this preplanned interim analysis (data cutoff date April 14, 2025), ~40% of the ESA-naive cohort and ~80% of the ESA-R/R/I cohort were expected to be eligible for the primary efficacy analysis
- At the primary analysis, ~90% of patients in both cohorts are expected to be eligible for the primary efficacy analysis

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; IPSS-R, International Prognostic Scoring System-Revised; IWG, International Working Group; MDS, myelodysplastic syndromes; OS, overall survival; Q3W, every 3 weeks; RBC, red blood cell; R/R/I, relapsed/refractory/intolerant; RS, ring sideroblast; SC, subcutaneous; TB, transfusion burden; U, unit; WHO, World Health Organization.
[a]Maximum of 2 doses.

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MAXILUS: patient demographics and disease characteristics[a]

Characteristic	ESA-naive (n = 52)	ESA-R/R/I (n = 53)
Age, median (IQR), years	76.0 (70.5-81.0)	76.0 (71.0-81.0)
Sex, female, n (%)	15 (28.8)	19 (35.8)
Region, n (%)		
Europe	38 (73.1)	48 (90.6)
North America	14 (26.9)	5 (9.4)
Time since original MDS diagnosis,[b] median (IQR), months	1.9 (0.1-9.5)	24.8 (7.8-64.5)
Baseline TB, median (IQR), RBC U/8 weeks	2.0 (1.0-4.0)	3.0 (2.0-6.0)
Baseline TB category, n (%), RBC U/8 weeks		
< 4	38 (73.1)	27 (50.9)
4 to < 6	11 (21.2)	7 (13.2)
≥ 6	3 (5.8)	19 (35.8)
Baseline Hb, median (IQR), g/dL	8.1 (7.1-8.5)	7.5 (6.8-7.7)
Baseline sEPO category,[c] n (%), IU/L		
≤ 200	38 (73.1)	23 (43.4)
> 200	12 (23.1)	27 (50.9)
> 500	4 (7.7)	15 (28.3)
IPSS-R risk classification,[d] n (%)		
Very low	1 (1.9)	5 (9.4)
Low	38 (73.1)	36 (67.9)
Intermediate	12 (23.1)	12 (22.6)
RS status, n (%)		
RS+	31 (59.6)	32 (60.4)
RS−	21 (40.4)	21 (39.6)
***SF3B1* mutation status,[e] n (%)**		
Mutated	27 (51.9)	30 (56.6)
Non-mutated	23 (44.2)	23 (43.4)

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 5.8 (3.3-8.2) months for the ESA-naive cohort and 7.4 (5.6-9.2) months for the ESA-R/R/I cohort.
IQR, interquartile range; IU/L, international units per liter; sEPO, serum erythropoietin.
[a]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention. [b]Data cleaning issues may exist for some data that report time since diagnosis, as the ranges for the ESA-naive cohort (−7.3 to 312.6 months) and the ESA-R/R/I cohort (−0.5 to 199.5 months) include negative values. [c]Baseline sEPO was not reported for 2 (3.8%) patients in the ESA-naive cohort and 3 (5.7%) patients in the ESA-R/R/I cohort. [d]IPSS-R risk classification was by institutional analysis. IPSS-R risk classification was not reported for 1 (1.9%) patient in the ESA-naive cohort. [e]*SF3B1* mutation status was not reported for 2 (3.8%) patients in the ESA-naive cohort.

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MAXILUS: treatment exposure[a]

Patients, n (%)	ESA-naive (n = 52)	ESA-R/R/I (n = 53)
Patients still on active treatment at data cutoff	45 (86.5)	32 (60.4)
Patients who discontinued treatment	7 (13.5)	21 (39.6)
Primary reason for discontinuation[b]		
Withdrawal by patient	3 (5.8)	4 (7.5)
Lack of efficacy	2 (3.8)	7 (13.2)
Death[c]	1 (1.9)	2 (3.8)
Progressive disease	0	5 (9.4)
Patients with ≥ 1 dose delay	19 (36.5)	21 (39.6)
Primary reason for dose delay[d]		
Predose Hb level ≥ 12.0 g/dL	11 (21.2)	3 (5.7)
Other	4 (7.7)	11 (20.8)
Related adverse event, grade 2	3 (5.8)	3 (5.7)
Patients with ≥ 1 dose reduction	6 (11.5)	7 (13.2)
Primary reason for dose reduction[e]		
Hb increase > 2.0 g/dL compared with previous dose	4 (7.7)	2 (3.8)
Adverse event	1 (1.9)	1 (1.9)

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 5.8 (3.3–8.2) months for the ESA-naive cohort and 7.4 (5.6–9.2) months for the ESA-R/R/I cohort. The median (range) duration of treatment exposure was 25.5 (2.1–50.0) weeks in the ESA-naive cohort and 27.1 (2.1–72.9) weeks in the ESA-R/R/I cohort.

[a]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention. [b]An additional reason for discontinuation was reported as "other" (ESA-naive cohort, n = 1 [1.9%]; ESA-R/R/I cohort, n = 3 [5.7%]). [c]In the ESA-naive cohort, cause of death was adverse event (septic shock) and occurred during the post-treatment period (defined as occurring > 42 days after the last dose date of luspatercept). In the ESA-R/R/I cohort, causes of death were unknown (n = 1) and death from new malignancy or complication from new malignancy (n = 1), and occurred during the treatment period (defined as occurring on or after the first dose of luspatercept until 42 days after the last dose of luspatercept). [d]In the ESA-naive cohort, additional reasons for dose delay were investigator decision (n = 3 [5.8%]), presence of ≥ 1% blasts in the peripheral blood (n = 2 [3.8%]), related adverse event, grade ≥ 3 (n = 2 [3.8%]), and "not reported" (n = 1 [1.9%]). In the ESA-R/R/I cohort, additional reasons for dose delay were presence of ≥ 1% blasts in the peripheral blood (n = 3 [5.7%]), related adverse event, grade ≥ 3 (n = 3 [5.7%]), investigator decision (n = 2 [3.8%]), and "not reported" (n = 1 [1.9%]). [e]In the ESA-naive cohort, additional reasons for dose reduction were reported as "other" (n = 1 [1.9%]) and "not reported" (n = 2 [3.8%]). In the ESA-R/R/I cohort, an additional reason for dose reduction was "not reported" (n = 4 [7.5%]).

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MAXILUS: safety in the ESA-naive cohort[a]

Patients, n (%)	ESA-naive (n = 52)
Any-grade TEAE	41 (78.8)
Treatment-related	10 (19.2)
Grade 3/4 TEAE	18 (34.6)
Treatment-related	2 (3.8)
Grade 5 TEAE	0
Treatment-related	0
Serious TEAE	12 (23.1)
Treatment-related	1 (1.9)
TEAE leading to drug interruption	3 (5.8)
TEAE leading to dose reduction	1 (1.9)
TEAE leading to permanent discontinuation of study intervention	1 (1.9)
Progression to AML	0
Patients with ≥ 1 treatment-emergent EOI[b]	17 (32.7)
Asthenia (including fatigue)	6 (11.5)
Hypertension	4 (7.7)
Fractures	4 (7.7)
Acute renal failure	4 (7.7)
Malignancies[c]	2 (3.8)
Premalignant disorders	1 (1.9)

- The rates of grade 3/4 treatment-related TEAEs were low
- There were no grade 5 TEAEs
- No patients experienced disease progression to AML
- No thromboembolic events or infusion reactions were reported

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 5.8 (3.3–8.2) months for the ESA-naive cohort.
EOI, event of interest; TEAE, treatment-emergent adverse event.
[a]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention. [b]No patients experienced EOIs of extramedullary hematopoiesis, immunogenicity-type reactions, or thromboembolic events.
[c]Malignancies were basal cell carcinoma and prostate cancer (n = 1 each).

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MAXILUS: safety in the ESA-R/R/I cohort[a]

Patients, n (%)	ESA-R/R/I (n = 53)
Any-grade TEAE	49 (92.5)
Treatment-related	20 (37.7)
Grade 3/4 TEAE	25 (47.2)
Treatment-related	3 (5.7)
Grade 5 TEAE	2 (3.8)
Treatment-related	0
Serious TEAE	16 (30.2)
Treatment-related	0
TEAE leading to drug interruption	9 (17.0)
TEAE leading to dose reduction	1 (1.9)
TEAE leading to permanent discontinuation of study intervention	2 (3.8)
Progression to AML	0
Patients with ≥ 1 treatment-emergent EOI[b]	30 (56.6)
Asthenia (including fatigue)	16 (30.2)
Hypertension	6 (11.3)
Fractures	5 (9.4)
Acute renal failure	5 (9.4)
Malignancies[c]	2 (3.8)
Immunogenicity-type reactions	1 (1.9)
Premalignant disorders	1 (1.9)

- The rates of grade 3/4 treatment-related TEAEs were low
- There were no treatment-related grade 5 TEAEs
- No patients experienced disease progression to AML
- No thromboembolic events were observed

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 7.4 (5.6–9.2) months for the ESA-R/R/I cohort.
[a]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention. [b]No patients experienced EOIs of extramedullary hematopoiesis or thromboembolic events. [c]Malignancies were nasopharyngeal cancer and non-small cell lung cancer (n = 1 each).

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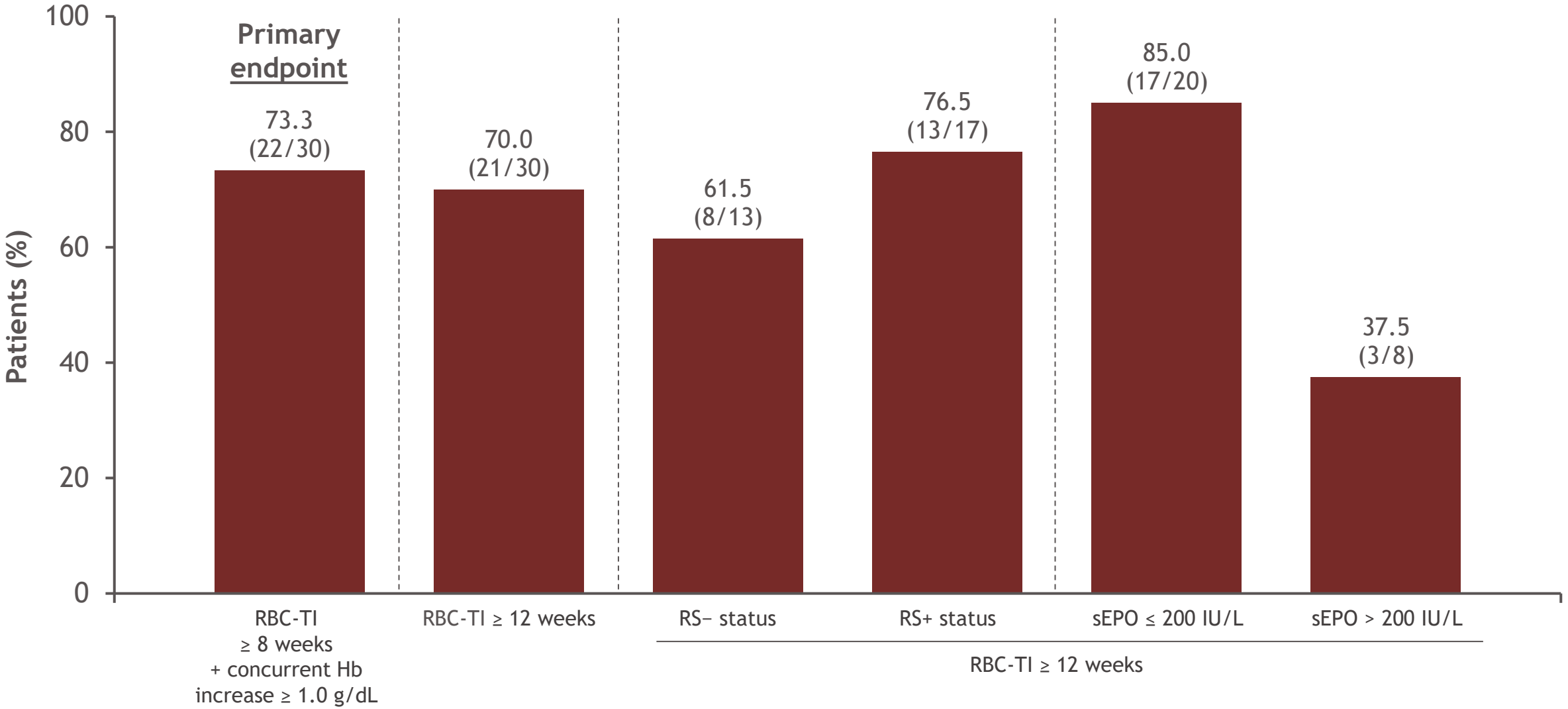
MAXILUS: RBC-TI (Weeks 1-24)[a] in the ESA-naive cohort



Data cutoff date: April 14, 2025. Median (IQR) follow-up was 5.8 (3.3–8.2) months for the ESA-naive cohort.
[a]Data are among the efficacy-evaluable population, which included patients who received their first treatment ≥ 24 weeks prior to data cutoff (ESA-naive, n = 30).

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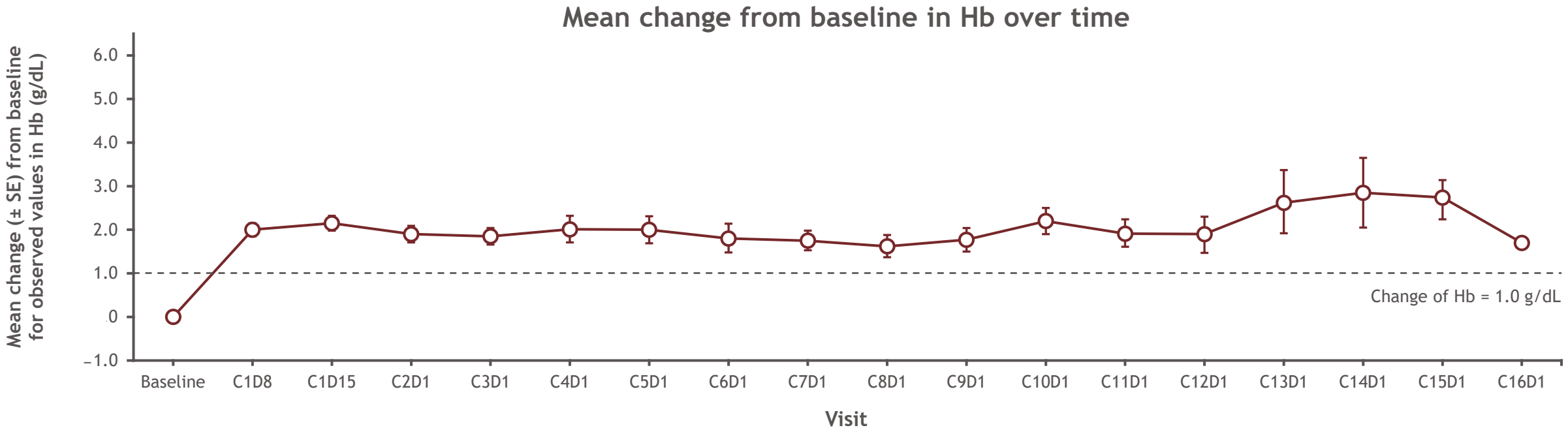
MAXILUS: Hb levels in the ESA-naive cohort



No. of patients	52	41	43	46	43	39	35	35	31	28	24	20	14	12	9	6	3	1

	Median (IQR), g/dL
Baseline Hb,[a] (n = 52)[b]	8.1 (7.1-8.5)
Baseline Hb,[c] primary endpoint responders (n = 22)[d]	8.0 (7.1-8.4)
Change from baseline to maximum Hb value,[c] (n = 30)[e]	3.0 (2.0-3.8)
Change from baseline to maximum Hb value,[c] primary endpoint responders (n = 22)[d]	3.2 (2.3-4.1)

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 5.8 (3.3–8.2) months for the ESA-naive cohort.
C, cycle; D, day.
[a]After applying the 14/3-day rule, the baseline Hb value is defined as the lowest Hb value from the central, local laboratory, or pretransfusion Hb value from transfusion records that is within 56 days on or prior to the first dose of investigational product. If a patient is missing Hb records after the 14/3-day rule, a 7/3-day rule is applied. [b]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention (ESA-naive, n = 52). [c]Only Hb values that are ≤ 14 days after a transfusion may be used unless there is another transfusion ≤ 3 days after the Hb assessment. Only patients with both baseline and post-baseline values are included. [d]Data are among patients who achieved RBC-TI ≥ 8 weeks (Weeks 1-24) with a concurrent mean Hb increase of ≥ 1.0 g/dL (ESA-naive, n = 22). [e]Data are among the efficacy-evaluable population who had both baseline and post-baseline values (ESA-naive, n = 30).

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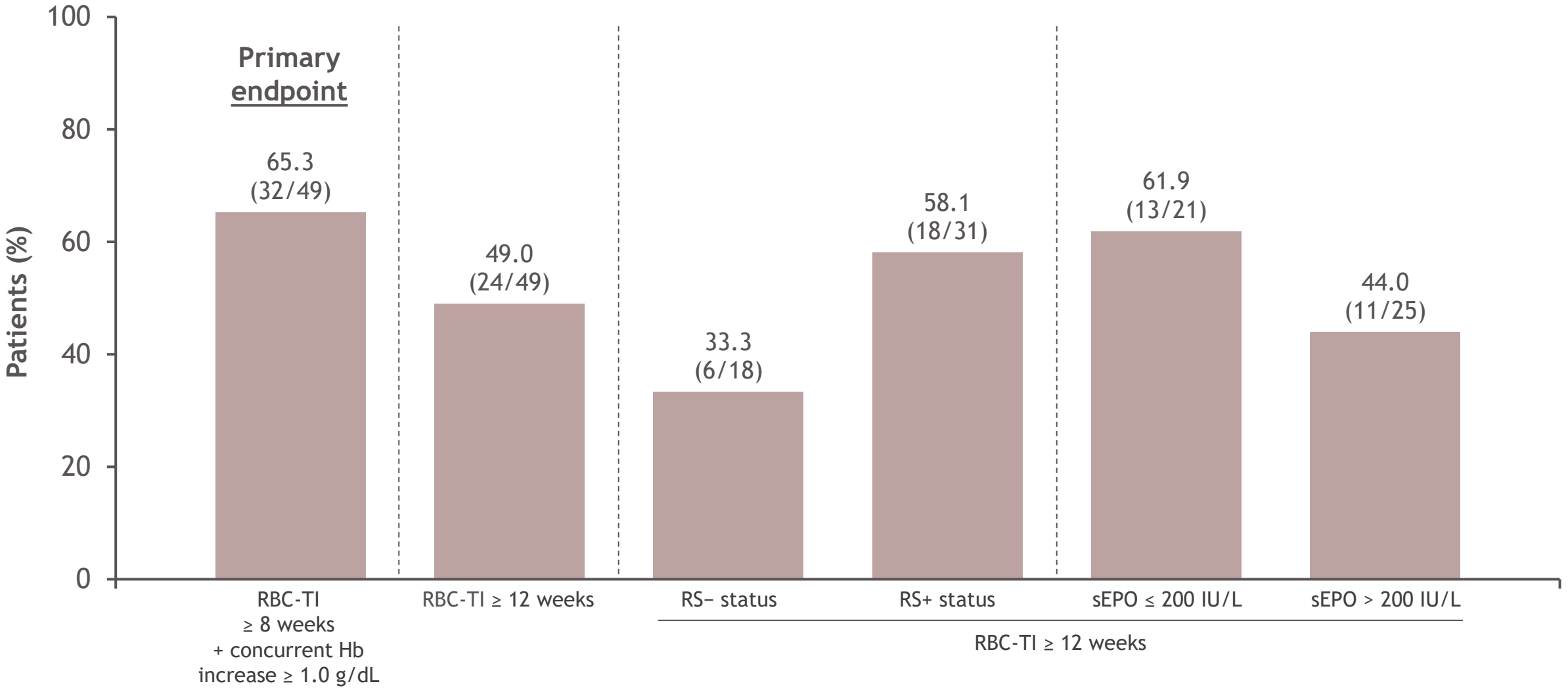
MAXILUS: RBC-TI (Weeks 1-24)[a] in the ESA-R/R/I cohort



Data cutoff date: April 14, 2025. Median (IQR) follow-up was 7.4 (5.6–9.2) months for the ESA-R/R/I cohort.
[a]Data are among the efficacy-evaluable population, which included patients who received their first treatment ≥ 24 weeks prior to data cutoff (ESA-R/R/I, n = 49).

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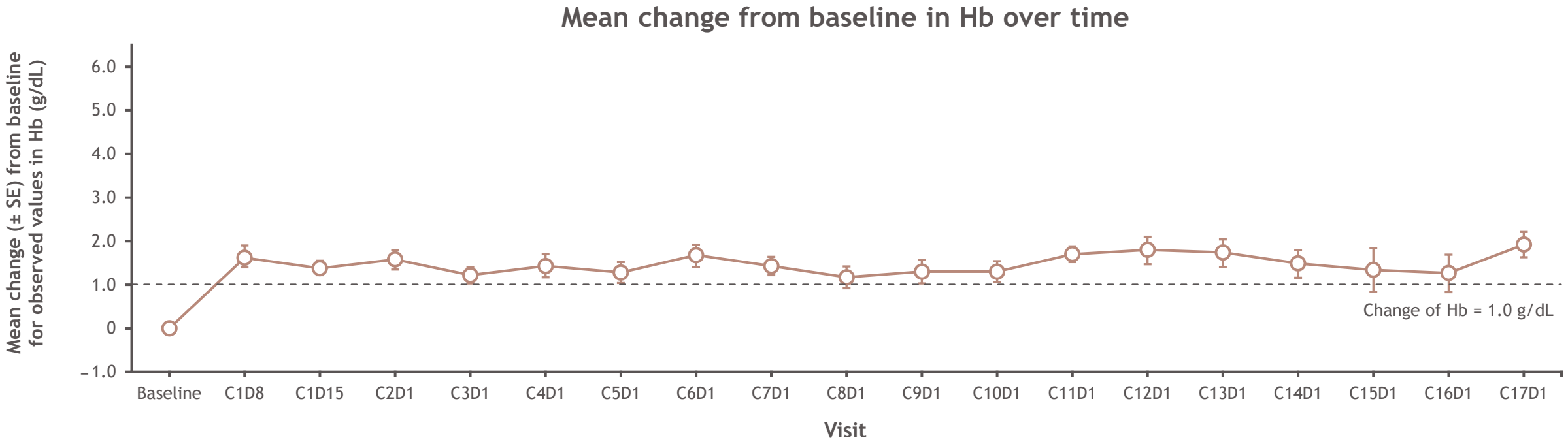
MAXILUS: Hb levels in the ESA-R/R/I cohort



	Median (IQR), g/dL
Baseline Hb,[a] (n = 53)[b]	7.5 (6.8-7.7)
Baseline Hb,[c] primary endpoint responders (n = 32)[d]	7.2 (6.6-7.7)
Change from baseline to maximum Hb value,[c] (n = 49)[e]	2.6 (1.8-3.6)
Change from baseline to maximum Hb value,[c] primary endpoint responders (n = 32)[d]	2.9 (2.1-3.8)

Data cutoff date: April 14, 2025. Median (IQR) follow-up was 7.4 (5.6–9.2) months for the ESA-R/R/I cohort.
[a]After applying the 14/3-day rule, the baseline Hb value is defined as the lowest Hb value from the central, local laboratory, or pretransfusion Hb value from transfusion records that is within 56 days on or prior to the first dose of investigational product. If a patient is missing Hb records after the 14/3-day rule, a 7/3-day rule is applied. [b]Data are among the all-treated population, defined as all patients who received ≥ 1 dose of study intervention (ESA-R/R/I, n = 53). [c]Only Hb values that are ≤ 14 days after a transfusion may be used unless there is another transfusion ≤ 3 days after the Hb assessment. Only patients with both baseline and post-baseline values are included. [d]Data are among patients who achieved RBC-TI ≥ 8 weeks (Weeks 1-24) with a concurrent mean Hb increase of ≥ 1.0 g/dL (ESA-R/R/I, n = 32). [e]Data are among the efficacy-evaluable population who had both baseline and post-baseline values (ESA-R/R/I, n = 49).

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MAXILUS: summary

- In this preplanned interim analysis, initiating luspatercept at the maximum-approved dose (1.75 mg/kg) resulted in high and sustained RBC-TI ≥ 8 weeks with concurrent Hb increase ≥ 1.0 g/dL in the ESA-naive (> 70%) and ESA-R/R/I (> 60%) cohorts
  - Although patient numbers were small, RBC-TI ≥ 12 weeks was sustained in a majority of patients in the ESA-naive cohort with either RS− status or low sEPO (62% and 85%, respectively), with numerically higher response rates in the ESA-naive setting compared with ESA-R/R/I
- Luspatercept at the maximum dose was well tolerated, with a low incidence of treatment-related adverse events reported in both the ESA-naive and ESA-R/R/I cohorts
  - Discontinuation and dose modification rates remained low
  - No thromboembolic events occurred
  - No patients experienced disease progression to AML, and the incidence of progression to HR-MDS was low (n = 1 in the ESA-R/R/I cohort, potentially due to natural disease progression)

These interim analysis data from MAXILUS demonstrate continued clinical efficacy of luspatercept in LR-MDS, including RS− and low sEPO subgroups, with no new safety signals reported

HR-MDS, higher-risk myelodysplastic syndromes.

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- All authors contributed to and approved the presentation
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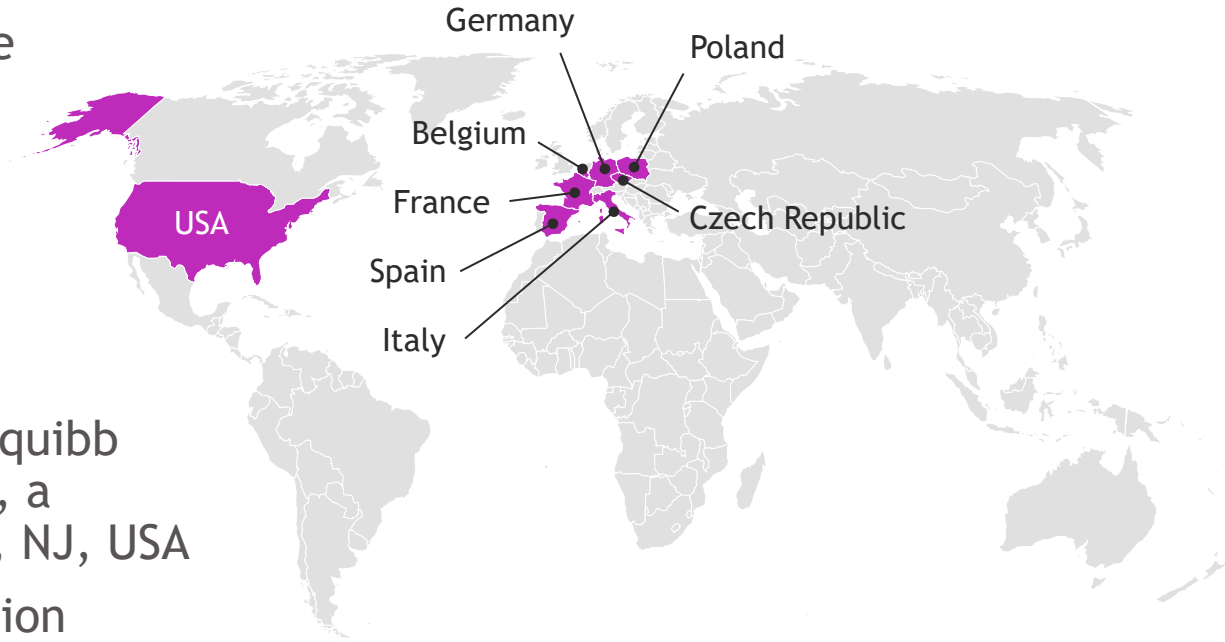

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