Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial

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Summary

Background Erythropoiesis-stimulating agents (ESAs) are the standard-of-care treatment for anaemia in most patients with lower-risk myelodysplastic syndromes but responses are limited and transient. Luspatercept promotes late-stage erythroid maturation and has shown durable clinical efficacy in patients with lower-risk myelodysplastic syndromes. In this study, we report the results of a prespecified interim analysis of luspatercept versus epoetin alfa for the treatment of anaemia due to lower-risk myelodysplastic syndromes in the phase 3 COMMANDS trial.

Methods The phase 3, open-label, randomised controlled COMMANDS trial is being conducted at 142 sites in 26 countries. Eligible patients were aged 18 years or older, had a diagnosis of myelodysplastic syndromes of very low risk, low risk, or intermediate risk (per the Revised International Prognostic Scoring System), were ESA-naive, and required red blood cell transfusions (2–6 packed red blood cell units per 8 weeks for ≥8 weeks immediately before randomisation). Integrated response technology was used to randomly assign patients (1:1, block size 4) to luspatercept or epoetin alfa, stratified by baseline red blood cell transfusion burden (<4 units per 8 weeks *vs* ≥4 units per 8 weeks), endogenous serum erythropoietin concentration (≤200 U/L *vs* >200 to <500 U/L), and ring sideroblast status (positive *vs* negative). Luspatercept was administered subcutaneously once every 3 weeks starting at 1·0 mg/kg body weight with possible titration up to 1·75 mg/kg. Epoetin alfa was administered subcutaneously once a week starting at 450 IU/kg body weight with possible titration up to 1050 IU/kg (maximum permitted total dose of 80 000 IU). The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean haemoglobin increase of at least 1·5 g/dL (weeks 1–24), assessed in the intention-to-treat population. Safety was assessed in patients who received at least one dose of study treatment. The COMMANDS trial was registered with ClinicalTrials.gov, NCT03682536 (active, not recruiting).

Findings Between Jan 2, 2019 and Aug 31, 2022, 356 patients were randomly assigned to receive luspatercept (178 patients) or epoetin alfa (178 patients), comprising 198 (56%) men and 158 (44%) women (median age 74 years [IQR 69–80]). The interim efficacy analysis was done for 301 patients (147 in the luspatercept group and 154 in the epoetin alfa group) who completed 24 weeks of treatment or discontinued earlier. 86 (59%) of 147 patients in the luspatercept group and 48 (31%) of 154 patients in the epoetin alfa group reached the primary endpoint (common risk difference on response rate 26·6; 95% CI 15·8–37·4; p<0·0001). Median treatment exposure was longer for patients receiving luspatercept (42 weeks [IQR 20–73]) versus epoetin alfa (27 weeks [19–55]). The most frequently reported grade 3 or 4 treatment-emergent adverse events with luspatercept (≥3% patients) were hypertension, anaemia, dyspnoea, neutropenia, thrombocytopenia, pneumonia, COVID-19, myelodysplastic syndromes, and syncope; and with epoetin alfa were anaemia, pneumonia, neutropenia, hypertension, iron overload, COVID-19 pneumonia, and myelodysplastic syndromes. The most common suspected treatment-related adverse events in the luspatercept group (≥3% patients, with the most common event occurring in 5% patients) were fatigue, asthenia, nausea, dyspnoea, hypertension, and headache; and none (≥3% patients) in the epoetin alfa group. One death after diagnosis of acute myeloid leukaemia was considered to be related to luspatercept treatment (44 days on treatment).

Interpretation In this interim analysis, luspatercept improved the rate at which red blood cell transfusion independence and increased haemoglobin were achieved compared with epoetin alfa in ESA-naive patients with lower-risk myelodysplastic syndromes. Long-term follow-up and additional data will be needed to confirm these results and further refine findings in other subgroups of patients with lower-risk myelodysplastic syndromes, including non-mutated *SF3B1* or ring sideroblast-negative subgroups.

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Introduction

Myelodysplastic syndromes, which are also referred to as myelodysplastic neoplasms,[1] are a heterogeneous group of haematopoietic stem cell disorders characterised by ineffective haematopoiesis, blood cytopenias (predominantly anaemia), and the potential to progress to acute myeloid leukaemia.[2–4] Among patients with lower-risk myelodysplastic syndromes (defined as disease of very low risk, low risk, or intermediate risk per the 2012 Revised International Prognostic Scoring System [IPSS-R][5]), the main goals of therapy are the treatment of anaemia and improvement of quality of life.[2] Treatment of chronic anaemia due to lower-risk myelodysplastic syndromes often necessitates regular red blood cell transfusions, which are associated with increased morbidities, iron overload, and reduced overall survival.[6]

Erythropoiesis-stimulating agents (ESAs) such as epoetin alfa are the standard-of-care treatment for patients with lower-risk myelodysplastic syndromes.[2,7] Key factors associated with a favourable response to ESA treatment include diagnosis of lower-risk myelodysplastic syndromes, low red blood cell transfusion requirement (<4 red blood cell units per 8 weeks) or no transfusion requirement, and endogenous serum erythropoietin concentration lower than 500 U/L;[2,7] patients with high red blood cell transfusion burden (>4 red blood cell units per 8 weeks) and endogenous serum erythropoietin concentration higher than 500 U/L are ineligible for ESA treatment.[2,7] However, in the EPOANE study and Eastern Cooperative Oncology Group E1996 study, response rates to ESAs in patients with endogenous serum erythropoietin at 200–500 U/L were between 0% and 5%;[8,9] in the EPOANE trial, all treatment responders (n=27) had serum erythropoietin concentration lower than 200 U/L with a mean response duration of 27·5 weeks. Furthermore, of the

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2013, and Jan 1, 2023, without language restrictions, using the search terms: "myelodysplastic syndromes" AND "erythropoiesis-stimulating agents" AND "response rate", and we searched ClinicalTrials.gov, for trials comparing erythropoiesis-stimulating agents (ESAs) with other treatments for myelodysplastic syndromes. All clinical trials in adult patients were considered. We identified 134 publications, of which 38 were review articles describing treatment options and management guidelines for anaemia in patients with lower-risk myelodysplastic syndromes, and 18 reported results of clinical trials of treatments for lower-risk myelodysplastic syndromes. We identified no publications reporting on clinical trials that had directly compared ESAs with other treatments for anaemia in ESA-naive patients with lower-risk myelodysplastic syndromes. Apart from the ongoing COMMANDS trial (NCT03682536), there were no other clinical trials (active or completed) on ClinicalTrials.gov in which treatment with ESAs had been compared with another treatment in ESA-naive patients with lower-risk myelodysplastic syndromes.

Added value of this study

The phase 3, randomised COMMANDS trial is the first study to directly compare an alternative treatment for anaemia with an ESA (epoetin alfa) in ESA-naive patients with lower-risk myelodysplastic syndromes. In this interim analysis, a significantly greater proportion of patients treated with luspatercept achieved red blood cell transfusion independence for at least 12 weeks, with a concurrent mean haemoglobin increase of at least 1·5 g/dL (weeks 1–24), than those treated with epoetin alfa. Rates of key secondary endpoints, including haematological improvement–erythroid response and red blood cell transfusion independence for at least 12 weeks and for 24 weeks, were also greater with luspatercept than with epoetin alfa. Furthermore, median duration of red blood cell transfusion independence lasting at least 12 weeks was longer with luspatercept than epoetin alfa (127 weeks *vs* 77 weeks). Luspatercept treatment also showed greater efficacy than epoetin alfa in *SF3B1*-mutated and ring sideroblast-positive subgroups of patients, as well as favourability in non-mutated *SF3B1* and ring sideroblast-negative subgroups and across various somatic mutations associated with myelodysplastic syndromes.

Implications of all the available evidence

In this interim analysis of the COMMANDS trial, response rates and durability achieved by luspatercept in ESA-naive patients with lower-risk myelodysplastic syndromes show that luspatercept can significantly improve anaemia to a greater degree than the currently established standard-of-care treatment in this patient population, who have limited treatment options. These findings suggest that luspatercept might change the current treatment landscape, and reduce patient reliance on red blood cell transfusions, and decrease transfusion-related morbidities. Nevertheless, further testing of long-term data and assessments of other subgroups of patients with lower-risk myelodysplastic syndromes will be needed to refine and validate the present findings.

27 responders, 13 relapsed while on treatment after a median response duration of 19 weeks.

Luspatercept is indicated for the treatment of anaemia after failure of ESA treatment in adults with lower-risk myelodysplastic syndromes (per the IPSS-R) with ring sideroblasts, or with a myelodysplastic or myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, in cases requiring at least 2 red blood cell units per 8 weeks.[10] In the double-blind, placebo-controlled, phase 3 MEDALIST trial, luspatercept reduced the severity of anaemia in transfusion-dependent patients with lower-risk myelodysplastic syndromes with ring sideroblasts who were refractory to or unlikely to respond to ESAs, or who had discontinued ESA treatment previously because of an adverse event.[11] To date, no study has compared the efficacy and safety of luspatercept versus ESAs for the treatment of anaemia in ESA-naive patients with lower-risk myelodysplastic syndromes.

Here, we report data from a prespecified interim analysis of the phase 3 COMMANDS trial, comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anaemia due to lower-risk myelodysplastic syndromes in ESA-naive patients who require red blood cell transfusions.

Methods

Study design and participants

COMMANDS is a global, phase 3, open-label, randomised controlled trial being conducted at 142 sites in 26 countries (appendix pp 3–6). The study sites include academic medical centres and community hospitals and clinics. Two interim analyses were planned, the first for futility and the second for efficacy. Here, we report the results of the second interim analysis, which tested the superiority of the primary endpoint when approximately 300 patients had completed 24 weeks of treatment or had discontinued before reaching 24 weeks of treatment. Patient randomisation started on Jan 2, 2019, and the interim efficacy analysis cutoff date was Aug 31, 2022.

Eligible patients were aged 18 years or older; were ESA-naive; had a documented diagnosis of myelodysplastic syndromes according to WHO 2016 criteria[3] that met IPSS-R classification of very low risk, low risk, or intermediate risk myelodysplastic syndromes[5] with less than 5% blasts in bone marrow, confirmed by a central pathology laboratory at screening; required red blood cell transfusions (2–6 packed red blood cell units per 8 weeks for a minimum of 8 weeks immediately before the date of randomisation); and had an endogenous serum erythropoietin concentration of lower than 500 U/L at screening. Patients were excluded if they had previous treatment with, but not limited to, ESAs, disease-modifying drugs (including lenalidomide), hypomethylating drugs, or luspatercept; or a diagnosis of myelodysplastic syndromes with del(5q) or myelodysplastic syndromes, unclassifiable. Further eligibility criteria are listed in the appendix (pp 7–10). Methods of patient recruitment were according to local site practices, with most patients recruited by referral.

The study protocol was approved by the institutional review board or central ethics committee at each participating institution and was conducted in accordance with the principles of the Declaration of Helsinki and all applicable laws of the relevant regulatory authorities. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) in permuted blocks (block size 4) by a central randomisation procedure with use of integrated response technology to either luspatercept or epoetin alfa. The treatments in this study were open-label and justification for the design is provided in the appendix (pp 10–11). The study centre staff, study team, and enrolled patients were not masked to treatment assignment. Stratification was done according to baseline red blood cell transfusion burden (<4 packed red blood cell units in the 8 weeks immediately preceding randomisation *vs* ≥4 packed red blood cell units in the 8 weeks immediately preceding randomisation), baseline endogenous serum erythropoietin concentration (≤200 U/L *vs* >200 to <500 U/L), and baseline ring sideroblast status (positive *vs* negative, where ring sideroblast positivity was defined as having ring sideroblasts constituting ≥15% erythroid precursors in bone marrow, or ≥5% and <15%, respectively, if a mutation of *SF3B1* was present). Baseline values were defined as the last value measured on or before the date of the first dose of treatment, unless otherwise specified. Baseline transfusion burden was defined as the number of packed red blood cell units received within 8 weeks of the first dose date. Study sites entered the serum erythropoietin results, red blood cell transfusion burden, and ring sideroblast status into the integrated response technology system. Full details on the randomisation procedure are provided in the appendix (p 10). To prevent bias and assess efficacy and safety objectively, an external independent statistician (TechData; King of Prussia, PA, USA) prepared summaries of the unmasked aggregate efficacy and safety data for review by an external independent data monitoring committee. The trial sponsors and study team remained masked to any aggregate analyses by treatment group performed for the data monitoring committee.

See Online for appendix

Procedures

Luspatercept was administered subcutaneously once every 3 weeks, at a starting dose of 1·0 mg/kg body weight that could be increased to 1·33 mg/kg and then to a maximum of 1·75 mg/kg. Epoetin alfa was administered subcutaneously once a week, at a starting dose of 450 IU/kg body weight that could be increased to 787·5 IU/kg and then to a maximum of 1050 IU/kg (maximum permitted total dose of 80 000 IU). Best supportive care (including transfusions, antibiotics, antivirals, and antifungals) was permitted.

Disease assessment was done at day 169 (week 24) of treatment and every 24 weeks thereafter. Patients without clinical benefit (defined for this study as a transfusion reduction of ≥2 packed red blood cell units per 8 weeks *vs* baseline) or who showed disease progression per International Working Group criteria[12] were discontinued from receiving luspatercept or epoetin alfa and entered post-treatment follow-up. Patients who had clinical benefit without disease progression could continue open-label treatment, until discontinuation due to evidence of disease progression, death, unacceptable toxicity, physician decision, or patient's withdrawal of consent, after which patients entered long-term follow-up. Full details on disease assessment and dose modifications are included in the appendix (pp 11–14). Post-treatment follow-up included reporting of treatment-emergent adverse events until 42 days after the last dose, and collection of transfusion data for at least 8 weeks after the last dose or until the end of study treatment, whichever was later. Long-term follow-up included monitoring for other malignancies or pre-malignancies, progression to acute myeloid leukaemia, subsequent therapies for myelodysplastic syndromes, and survival for 5 years from the date of the first dose or for 3 years from the last dose (whichever is later), unless in cases of consent withdrawal, death, or loss to follow-up. Follow-up could be done via telephone contact by the site every 12 weeks for the first 3 years and every 6 months thereafter (if applicable).

Baseline characteristics including sex (self-reported by patients) were presented for all randomly assigned patients. All patients were monitored for treatment-emergent adverse events until 42 days after the last dose of study drug. Most assessments were collected at every study visit (every 21 days) before dosing and included monitoring of patient's clinical symptoms, adverse events, relevant laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests or procedures. Adverse events were recorded in electronic case report forms and in the patient's source documents; patients could also self-report any new adverse events by contacting the local investigator between study visits. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Serious adverse events were defined as any adverse event at any dose that: might result in death, is life-threatening, requires hospitalisation or prolongs existing hospitalisation, results in persistent or significant disability or incapacity, is a birth defect, or constitutes an important medical event. The suspected relationship of adverse events to treatment was judged by the investigator. We defined adverse events of special interest and other relevant safety events on the basis of non-clinical findings or the known safety profile[10,11,13–16] of the study drugs.

Outcomes

The primary endpoint was red blood cell transfusion independence for at least 12 weeks with a concurrent mean haemoglobin increase of at least 1·5 g/dL during weeks 1–24. Laboratory tests were assessed centrally and response status for each patient was derived by the sponsor. Key secondary endpoints analysed during weeks 1–24 included red blood cell transfusion independence for at least 12 weeks, transfusion independence for 24 weeks, and haematological improvement–erythroid (HI–E) response (≥8 weeks) per International Working Group criteria.[12] Other secondary endpoints included red blood cell transfusion independence for at least 8 weeks; time to transfusion independence lasting at least 12 weeks, red blood cell transfusion burden during treatment (weeks 1–24); time to first red blood cell transfusion (week 1 to end of treatment); red blood cell transfusion independence for at least 24 weeks (weeks 1–48); duration of transfusion independence lasting at least 12 weeks (week 1 to end of treatment, defined as the longest transfusion independence period after the first dose date up to the last treatment visit for patients who achieved transfusion independence for ≥12 weeks during weeks 1–24); time to HI–E lasting at least 8 weeks; mean haemoglobin change over 24 weeks (weeks 1–24); progression to acute myeloid leukaemia; and safety in terms of adverse events. Results of other secondary endpoints are not reported herein (appendix pp 19–20, 27–28). Exploratory endpoints and analyses included subgroup analyses by stratification factors and baseline characteristics, and an analysis of the effect of somatic mutations associated with myelodysplastic syndromes on primary endpoint response (appendix pp 16–19). Selected ad-hoc endpoints included duration of red blood cell transfusion independence lasting at least 12 weeks with a concurrent mean haemoglobin increase of at least 1·5 g/dL (week 1 to end of treatment), and reduction by at least 50% in red blood cell units transfused over 12 or more weeks and 24 or more weeks during the entire treatment phase. An ad-hoc safety analysis at 24 weeks of exposure for both treatments was also performed. The rationale for ad-hoc endpoints, and a list of all study endpoints, are provided in the appendix (pp 17, 25, 27–29).

Statistical analysis

The sample size calculation and statistical analyses are described in detail in the appendix (pp 14–19). A total sample size of approximately 350 patients (175 in the luspatercept arm and 175 in the epoetin alfa arm) was calculated to have 90% power to detect a difference of 16 percentage points in response rates of 36% in the luspatercept arm[16] and 20% in the epoetin alfa arm.[9] Response was defined as reaching the primary endpoint (red blood cell transfusion independence for ≥12 weeks with a concurrent mean haemoglobin increase ≥1·5 g/dL during weeks 1–24). Two interim analyses (one for futility

and one for superiority when 30% and 85% patients had contributed data for the primary endpoint, respectively) were planned. The Lan-DeMets (O'Brien-Fleming) spending function was used to derive the futility and superiority boundaries and to control the overall one-sided type I error rate at 0·025.

The planned interim efficacy analysis was done in the intention-to-treat (ITT) population of all randomly assigned patients, regardless of the treatment received, who completed 24 weeks of treatment or discontinued treatment before reaching 24 weeks. Most interim efficacy analyses were performed in 301 patients who completed 24 weeks of treatment or discontinued earlier. Endpoints over 48 weeks were analysed in patients with available data. Progression to acute myeloid leukaemia was assessed in the ITT population of all randomly assigned patients. The percentage of patients with and without a response with regard to the primary and key secondary endpoints were compared with the Cochran–Mantel–Haenszel test to derive common risk difference with 95% CIs, with the stratification factors of baseline red blood cell transfusion burden (<4 packed red blood cell units per 8 weeks *vs* ≥4 units per 8 weeks), ring sideroblast status (positive *vs* negative), and endogenous serum erythropoietin concentration (≤200 U/L *vs* >200 to <500 U/L). A gatekeeping method was used to control the overall type I error rate for key secondary endpoints in the order: HI–E response, red blood cell transfusion independence for 24 weeks, and transfusion independence for at least 12 weeks. Other secondary endpoints were analysed without methods for controlling the type I error rate. Odds ratios (ORs) and 95% CIs are presented for the primary outcome and key secondary outcomes. In addition, risk difference was calculated per stratum, and these estimates were combined to generate a common risk difference to describe overall treatment effect between the treatment arms. To evaluate the robustness of the primary endpoint and HI–E endpoint, sensitivity analyses of these two endpoints were done (appendix pp 16–17). Descriptive statistics were used to describe continuous secondary endpoints and counts, and percentages were used to describe categorical secondary endpoints. Kaplan-Meier analysis was used to estimate curves for time-to-event variables from week 1 to the end of treatment (duration of red blood cell transfusion independence lasting at least 12 weeks; and duration of red blood cell transfusion independence for at least 12 weeks with concurrent mean haemoglobin increase of at least 1·5g/dL). Full details of the Kaplan-Meier analyses are provided in the appendix (p 15). Time to acute myeloid leukemia progression was not estimable due to the small number of patients who progressed. Hazard ratios for progression to acute myeloid leukaemia were obtained from a Cox proportional hazard model stratified by baseline red blood cell transfusion burden, ring sideroblast status, and endogenous serum erythropoietin concentration. Acute myeloid leukaemia incidence rate per 100 person-years was also presented. Subgroup analyses were conducted with unstratified Cochran–Mantel–Haenszel tests for response rate endpoints. Treatment duration was estimated with the Kaplan-Meier method and comparisons between subgroups were done with the log-rank test. The total number of mutated genes for each patient at baseline (hereafter referred to as mutational burden) was calculated, and its association with reaching the primary endpoint was assessed with the Wilcoxon rank-sum test. Risk difference estimates and 95% CIs were used to describe treatment effect in patients with commonly mutated genes. A random-effects meta-analysis model was used to summarise treatment effect across mutations. In addition, the DISCOVER package (version 0.9.4) in R was used to run mutual exclusivity tests on mutations with at least five events across both study arms. p values were adjusted for multiple testing with a Benjamini-Hochberg procedure adapted for discrete test statistics. The analysis with the DISCOVER package was exploratory and post-hoc, and not part of the prespecified study endpoints.

Safety analyses were done in the safety population, comprising all randomly assigned patients who received at least one dose of study drug. For serious adverse events, grade 3–4 adverse events, and adverse events of special interest, exposure-adjusted incidence rates per 100 person-years were calculated.

All statistical analyses were done with SAS (version 9.4) or R (version 4.0.5). ggplot2 (version 3.3.3) in R was used for data visualisation. Subgroup analyses and meta-analysis were done with the meta package (version 4.18-1) in R. Two-sided p values of less than 0·05 were reported as significant. The external independent data monitoring committee evaluated data accrued during the study. The COMMANDS trial was registered with ClinicalTrials.gov, NCT03682536 (active, not recruiting).

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

As of the interim analysis cutoff date (Aug 31, 2022), 356 patients were randomly assigned to treatment: 178 patients to luspatercept and 178 to epoetin alfa (figure 1). Baseline characteristics in the randomly assigned patients were balanced across the treatment groups (table 1). The median age of patients was 74 years (IQR 69–80); 198 (56%) patients were men and 158 (44%) were women. The median transfusion burden in the 8 weeks before baseline was 3 units per 8 weeks (IQR 2–4). The median baseline endogenous serum erythropoietin was 84·5 U/L (IQR 40·9–179·1) and the median baseline haemoglobin concentration (pretransfusion) was 7·8 g/dL (IQR 7–8; table 1). Among patients

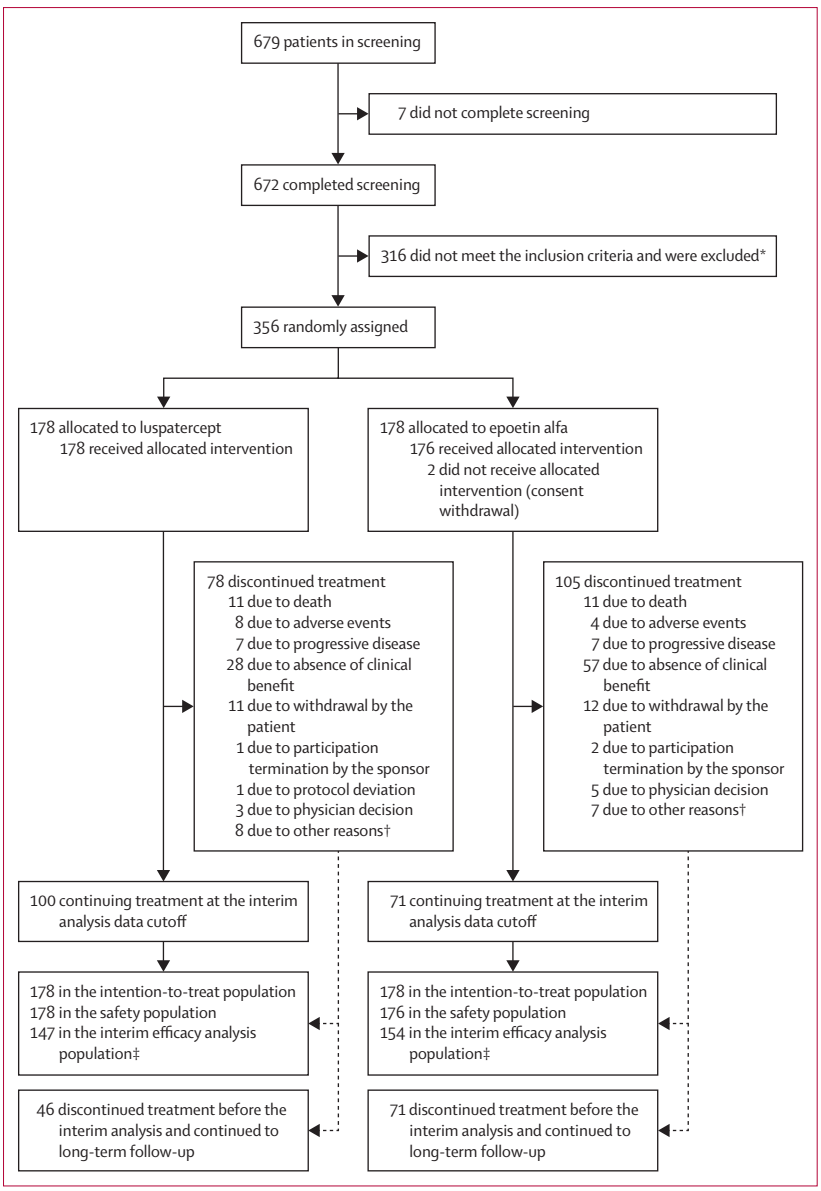

Figure 1: **CONSORT study design and patient disposition**
*The top four reasons for ineligibility were: no documented diagnosis of myelodysplastic syndromes according to WHO 2016 classification that met Revised International Prognostic Scoring System classification of very low risk, low risk, or intermediate risk disease, and less than 5% blasts in bone marrow; an endogenous serum erythropoietin concentration of 500 U/L or higher; no transfusion requirement of 2–6 packed red blood cell units per 8 weeks confirmed for a minimum of 8 weeks immediately before randomisation; and not meeting protocol-defined laboratory criteria in haematology and serum chemistries. †Other reasons for discontinuation from treatment included, but were not limited to, loss of response, diagnosis of malignancy, requirement of treatment prohibited by protocol, and closure of country-level activity. ‡55 patients in the intention-to-treat population were still on treatment at the interim analysis cutoff date (had not yet completed the minimum treatment period of 24 weeks).

with available ring sideroblast data, 258 (73%) of 355 had ring sideroblasts. Median treatment duration was 42 weeks (IQR 20–73) in the luspatercept group and 27 weeks (19–55) in the epoetin alfa group (appendix p 29). 147 patients in the luspatercept group and 154 patients in the epoetin alfa group had been on treatment for at least 24 weeks or had discontinued early and were included in the interim efficacy analyses (85% information for primary endpoint). 55 of the 356 randomly assigned patients were still on treatment and had not yet completed the minimum treatment period of 24 weeks at the data cutoff).

The primary endpoint of red blood cell transfusion independence for at least 12 weeks with a concurrent mean haemoglobin increase of at least 1·5 g/dL (weeks 1–24) was reached in 86 (59%) of 147 patients in the luspatercept group and 48 (31%) of 154 patients in the epoetin alfa group (common risk difference on response rate 26·6 [95% CI 15·8–37·4]; p<0·0001; odds ratio [OR] 3·1 [95% CI 1·9–5·0]; appendix p 38). Additionally, 98 (67%) patients in the luspatercept group and 71 (46%) in the epoetin alfa group achieved red blood cell transfusion independence for at least 12 weeks during weeks 1–24 (common risk difference on response rate 19·1 [8·6–29·6]; nominal p=0·0002; OR 2·4 [1·5–4·0]; figure 2). Red blood cell transfusion independence for 24 weeks during weeks 1–24 was achieved in 70 (48%) patients in the luspatercept group and 45 (29%) in the epoetin alfa group (common risk difference on response rate 17·0 [6·7–27·2]; nominal p=0·0006; OR 2·3 [1·4–3·8]; figure 2). HI–E response was reached in 109 (74%) patients in the luspatercept group and in 79 (51%) patients in the epoetin alfa group (common risk difference on response rate 22·3 [11·8–32·8]; nominal p<0·0001; OR 2·8 [1·7–4·6]; figure 2). Red blood cell transfusion independence for at least 24 weeks during weeks 1–48 was achieved in 74 (58%) of 128 patients in the luspatercept group and 47 (35%) of 136 in the epoetin alfa group (common risk difference on response rate 21·8 [10·9–32·8]; nominal p<0·0001).

We assessed the median duration of red blood cell transfusion independence until the end of treatment in all patients who achieved red blood cell transfusion independence for at least 12 weeks (weeks 1–24). The median duration was 127 weeks (95% CI 108–not estimable) in those patients in the luspatercept group versus 77 weeks (39–not estimable) in those patients in the epoetin alfa group (nominal p=0·0050; appendix p 39). In patients with a HI–E response, mean time to HI–E was 17·1 days (SD 29·3) for patients in the luspatercept group and 27·0 days (33·9) for those in the epoetin alfa group. Other secondary endpoints and outcomes of sensitivity analyses are reported in the appendix (pp 19–21).

In the ITT population, progression to acute myeloid leukaemia occurred in four (2%) of 178 patients in the luspatercept group and five (3%) of 178 patients in the epoetin alfa group (hazard ratio [HR] 0·821 [95% CI 0·214–3·147]; nominal p=0·77). The incidence rate of progression to acute myeloid leukaemia was 1·76 per 100 person-years (95% CI 0·66–4·70) in the luspatercept group and 2·31 per 100 person-years (0·96–5·55) in the epoetin alfa group.

Of the 301 patients included in the efficacy analysis, 295 had baseline mutational data for 82 analysed genes. Of the 82 genes, somatic mutations in 36 genes were reported. Most mutations had a variant allele frequency of 3–50% and the most commonly mutated genes were *SF3B1*, *TET2*, *ASXL1*, *DNMT3A*, *U2AF1*, and *SRSF2* (appendix pp 24, 48). Mutation frequency at baseline did not differ significantly between the luspatercept and epoetin alfa treatment groups (appendix pp 48, 56–57). A pairwise test on mutations with more than five events indicated mutual exclusivity of *SF3B1* with *SRSF2*, *U2AF1*, and *ASXL1* (all adjusted p<0·0001; appendix p 57). Baseline mutational burden was lower in primary endpoint responders versus non-responders in the epoetin alfa group, and was significantly associated with reaching the primary endpoint (p=0·016). In the luspatercept treatment group we found no such association between primary endpoint response and mutational burden (p=0·56; appendix p 50). The risk difference estimates for commonly mutated genes indicated that patients with mutations in *ASXL1*, *TET2*, *SF3B1*, and *SF3B1*α (defined as *SF3B1* mutations with concomitant mutation of *DNMT3A* or *ASXL1* and/or *TET2*) were more likely to have a primary endpoint response with luspatercept than with epoetin alfa (figure 3). Furthermore, in meta-analysis of primary endpoint response in patients with commonly mutated genes, the summarised random-effects model estimate was 0·27 (95% CI 0·18–0·37) in favour of luspatercept. Additionally, in patients with co-occurrence of common mutations (ie, *SF3B1*α), a higher frequency of primary endpoint response was observed with luspatercept than with epoetin alfa.

The distribution of the percentage of ring sideroblasts at baseline did not differ between treatment groups (appendix p 51) and the percentage of ring sideroblasts at baseline was not associated with the primary endpoint response in either the luspatercept group (p=0·064) or epoetin alfa group (p=0·12; appendix p 52). Remaining biomarker results, including the association of baseline mutations with the primary endpoint by ring sideroblast status, are presented in the appendix (pp 24, 54–57).

The proportions of luspatercept responders versus epoetin alfa responders for the primary endpoint were assessed by subgroups (appendix p 59), as follows: the ring sideroblast-positive subgroup (70 [65%] of 108 luspatercept responders *vs* 29 [26%] of 112 epoetin alfa responders) and ring sideroblast-negative subgroup (16 [41%] of 39 *vs* 19 [46%] of 41); mutated *SF3B1* subgroup (64 [70%] of 92 *vs* 27 [31%] of 88) and non-mutated *SF3B1* subgroup (22 [42%] of 53 *vs* 20 [32%] of 62); endogenous serum erythropoietin concentration (≤200 U/L) subgroup (74 [63%] of 118 *vs* 44 [36%] of 121) and endogenous serum erythropoietin concentration (>200 to <500 U/L) subgroup (12 [41%] of 29 *vs* four [12%] of 33); and with baseline transfusion burden less than 4 red blood cell units per 8 weeks (61 [66%] of 92 *vs* 35 [39%] of 90) and baseline

	Luspatercept (n=178)	Epoetin alfa (n=178)	Total (n=356)
Age, years	74 (68–80)	75 (69–80)	74 (69–80)
Sex			
Male	107 (60%)	91 (51%)	198 (56%)
Female	71 (40%)	87 (49%)	158 (44%)
Race			
American Indian or Alaska Native	0	0	0
Asian	19 (11%)	24 (13%)	43 (12%)
Black or African American	2 (1%)	0	2 (1%)
Native Hawaiian or other Pacific Islander	0	0	0
White	142 (80%)	141 (79%)	283 (79%)
Not collected or unknown	15 (8%)	13 (7%)	28 (8%)
Ethnicity			
Hispanic or Latino	11 (6%)	12 (7%)	23 (6%)
Not Hispanic or Latino	151 (85%)	153 (86%)	304 (85%)
Not reported	16 (9%)	11 (6%)	27 (8%)
Unknown	0	2 (1%)	2 (1%)
Time since original diagnosis of myelodysplastic syndromes, months*	8·0 (2·0–28·8)	5·2 (1·6–18·5)	6·2 (1·8–23·6)
WHO 2016 classification of myelodysplastic syndromes			
Myelodysplastic syndromes with single lineage dysplasia	1 (1%)	4 (2%)	5 (1%)
Myelodysplastic syndromes with multiple lineage dysplasia	49 (28%)	46 (26%)	95 (27%)
Myelodysplastic syndromes with single lineage dysplasia and ring sideroblasts	2 (1%)	6 (3%)	8 (2%)
Myelodysplastic syndromes with multiple lineage dysplasia and ring sideroblasts	125 (70%)	117 (66%)	242 (68%)
Myelodysplastic syndromes or myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	1 (1%)	4 (2%)	5 (1%)
Missing†	0	1 (1%)	1 (<1%)
IPSS-R myelodysplastic syndromes risk category			
Very low	16 (9%)	17 (10%)	33 (9%)
Low	126 (71%)	131 (74%)	257 (72%)
Intermediate	34 (19%)	28 (16%)	62 (17%)
High‡	1 (1%)	0	1 (<1%)†
Missing§	1 (1%)	2 (1%)	3 (1%)
Serum erythropoietin concentration, U/L	78·7 (41·7–185·3)	85·9 (40·5–177·8)	84·5 (40·9–179·1)
Serum erythropoietin category, U/L			
≤200	141 (79%)	141 (79%)	282 (79%)
≤100	100 (56%)	103 (58%)	203 (57%)
>100 and ≤200	41 (23%)	38 (21%)	79 (22%)
>200 and <500	37 (21%)	37 (21%)	74 (21%)
Ring sideroblasts¶	130/178 (73%)	128/177 (72%)	258/355 (73%)
Mutated *SF3B1*‖	111/176 (63%)	99/171 (58%)	210/347 (61%)
Red blood cell transfusion burden, units per 8 weeks**	3 (2–4)	3 (2–4)	3 (2–4)
Red blood cell transfusion burden category			
<4 units per 8 weeks	114 (64%)	109 (61%)	223 (63%)
2 units per 8 weeks	80 (45%)	79 (44%)	159 (45%)
≥4 units per 8 weeks	64 (36%)	69 (39%)	133 (37%)

(Table 1 continues on next page)

	Luspatercept (n=178)	Epoetin alfa (n=178)	Total (n=356)
(Continued from previous page)			
Pretransfusion haemoglobin concentration, g/dL	7·8 (7–8)	7·8 (7–8)	7·8 (7–8)
Haemoglobin category			
<8 g/dL	107 (60%)	106 (60%)	213 (60%)
≥8 g/dL	71 (40%)	72 (40%)	143 (40%)
Platelet count, 10^9/L	230 (155–304)	235 (140–324)	232 (144–310)

Data are n (%), median (IQR). IPSS-R=Revised International Prognostic Scoring System. *Time since original myelodysplastic syndrome diagnosis was defined as the number of months from the date of original diagnosis to the date of informed consent. †While most patients had their myelodysplastic syndromes diagnosis confirmed via the WHO classification, one patient included in the analysis had their diagnosis confirmed by a bone marrow biopsy rather than a bone marrow aspirate. ‡For one patient in the luspatercept group, the central pathology laboratory confirmed the patient's myelodysplastic syndrome diagnosis with an IPSS-R risk score of intermediate at screening. At the next bone marrow assessment, the central laboratory sent the report with an IPSS-R score of high and confirmed that the high score was also applicable at the time of screening. §Reason for missing IPSS-R risk score was the absence of one component, however based on the other four components, the patients were determined to have lower-risk myelodysplastic syndromes; these patients were not included in the subgroup analyses by IPSS-R score. Relevant protocol deviations were filed. ¶The analysis included only patients with available baseline ring sideroblast data. ||The analysis included only patients with available gene mutation data. **The protocol transfusion requirement for patients' eligibility was 2–6 packed red blood cell units per 8 weeks, confirmed for a minimum of 8 weeks immediately before randomisation. In statistical analysis, the number of units transfused within 8 weeks on or before first dose date was considered as the baseline measurement. In addition, the protocol allowed a 3-day window between randomisation and the first dose date. Based on these criteria, some patients who met protocol-defined eligibility criteria for baseline transfusion did not have any transfusions recorded within 8 weeks before or on the first dose date; for these patients, baseline transfusion burden in statistical analysis was defined with respect to the randomisation date. Three patients in the randomly assigned (intention-to-treat) population did not meet protocol-defined eligibility criteria for baseline transfusions, which were recorded as protocol deviations (one patient on one unit per 8 weeks, one patient on 0 units per 8 weeks, and one patient on 7 units per 8 weeks).

Table 1: **Baseline demographics and disease characteristics in randomly assigned patients**

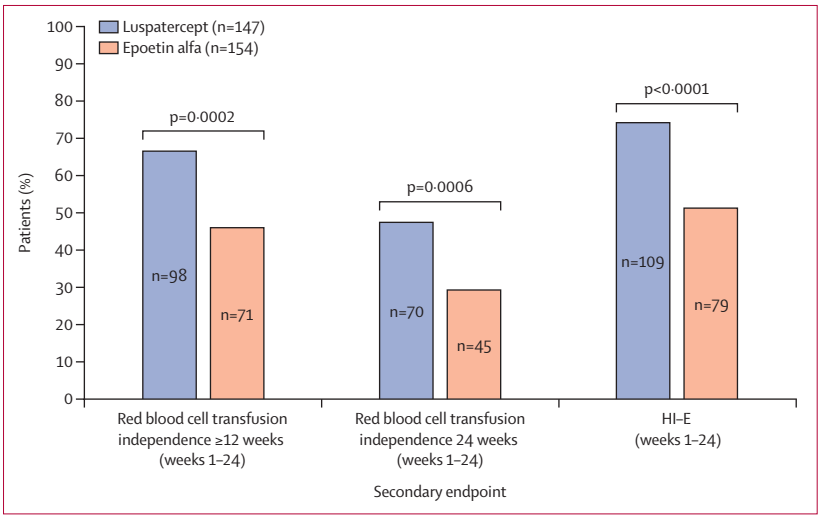

Figure 2: **Red blood cell transfusion independence and HI–E response during weeks 1–24**
Only patients who received their first dose of treatment at least 24 weeks (169 days) before the data cutoff (Aug 31, 2022), including those who discontinued treatment, were included in the analysis. HI–E=haematological improvement–erythroid.

transfusion burden of at least 4 red blood cell units per 8 weeks (25 [45%] of 55 *vs* 13 [20%] of 64). Corresponding risk differences are provided in the appendix (p 59). The median duration of red blood cell transfusion independence lasting at least 12 weeks was longer in patients in the luspatercept group than in those in the epoetin alfa group for all analysed subgroups, including the ring sideroblast-positive and ring sideroblast-negative subgroups, although resulting HR values were broad due to the small numbers of patients (appendix pp 21–22, 39–47). Remaining subgroup analyses are presented in the appendix (pp 23–24, 59–62).

In ad-hoc efficacy analyses, we assessed the duration of red blood cell transfusion independence in patients with transfusion independence lasting at least 12 weeks with a mean haemoglobin increase of at least 1·5 g/dL. The median duration was 75 weeks (95% CI 47–96) in the luspatercept group, compared with 64 weeks (35–75) in the epoetin alfa group (nominal p=0·26). Additionally, reduction of at least 50% in red blood cell units transfused over 12 weeks or more was reported in 120 (82%) of 147 patients in the luspatercept group versus 101 (66%) of 154 in the epoetin alfa group (common risk difference on response rate 14·5 [95% CI 4·9–24·2]; nominal p=0·0016). Reduction of at least 50% in red blood cell units transfused over 24 weeks or more was reported in 109 (74%) patients in the luspatercept group versus 73 (47%) in the epoetin alfa group (common risk difference on response rate 25·4 [15·1–35·8]; nominal p<0·0001).

All 178 patients randomly assigned to the luspatercept group received treatment, whereas 176 of 178 patients randomly assigned to the epoetin alfa group received epoetin alfa (two patients discontinued the study immediately after randomisation; figure 1). Thus, 354 patients were included in the safety population. The median duration of treatment was longer in the luspatercept group than in the epoetin alfa group (42 weeks *vs* 27 weeks), thus providing a longer reporting period for treatment-emergent adverse events. Overall, 164 (92%) of 178 patients treated with luspatercept and 150 (85%) of 176 treated with epoetin alfa had at least one treatment-emergent adverse event (appendix pp 30–31). The most frequently reported treatment-emergent adverse events (all grades, occurring in ≥10% of patients in either group) were diarrhoea, fatigue, peripheral oedema, hypertension, asthenia, nausea, dyspnoea, and COVID-19, which occurred at higher frequency in the luspatercept group than in the epoetin alfa group except for asthenia (table 2). Suspected treatment-related adverse events were reported by 54 (30%) patients treated with luspatercept and 31 (18%) treated with epoetin alfa. The most common suspected treatment-related adverse events in the luspatercept group (≥3% patients, with the most common event occurring in 5% patients) were fatigue (nine events in seven patients), asthenia (seven events in five patients), nausea (11 events in nine patients), dyspnoea (six events in six patients), headache (six events in five patients), and hypertension (nine events in six patients). These events were grade 1 or 2 in severity except for seven events of hypertension rated as grade 3 severity. There were no suspected treatment-related adverse events reported in 3% or more patients in the epoetin alfa group. 97 (54%) patients treated with

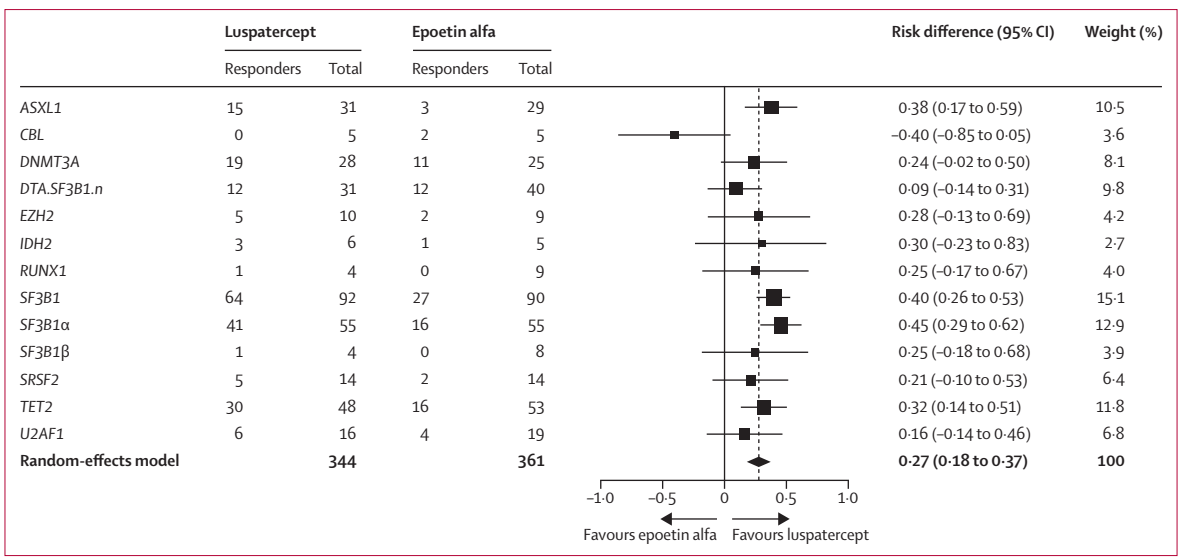

Figure 3: **Comparison of primary endpoint responder status in patients with common genetic mutations**
The vertical line at zero represents absence of treatment effect. The dashed line shows the overall summary effect. *DTA.SF3B1.n* is a wild-type *SF3B1* with concomitant mutations in *ASXL1* and/or *TET2* or *DNMT3A*; *SF3B1α* corresponds to mutated *SF3B1* with concomitant mutations in *DNMT3A* or *ASXL1* and/or *TET2; SF3B1β* is mutated *SF3B1* with concomitant mutations in any of *BCOR, BCORL1, NRAS, RUNX1, SRSF2*, or *STAG2*.[19]

luspatercept and 75 (43%) treated with epoetin alfa had at least one grade 3 or 4 treatment-emergent adverse event (appendix pp 30–31). The most frequently reported grade 3 or 4 treatment-emergent adverse events with luspatercept (≥3% patients) were hypertension, anaemia, dyspnoea, neutropenia, thrombocytopenia, pneumonia, COVID-19, myelodysplastic syndromes, and syncope; and with epoetin alfa were anaemia, pneumonia, neutropenia, hypertension, iron overload, COVID-19 pneumonia, and myelodysplastic syndromes. There were no notable differences in grade 3 or 4 adverse events when adjusting for exposure (luspatercept *vs* epoetin alfa, 85 per 100 patient-years *vs* 73 per 100 patient years; appendix pp 34–35).

Serious treatment-emergent adverse events were reported in 68 (38%) patients treated with luspatercept and 60 (34%) treated with epoetin alfa. In both treatment groups, the most common serious treatment-emergent adverse events were in the category of infections and infestations; primarily COVID-19 (nine [5%] patients in each group) and pneumonia (six [3%] treated with luspatercept and nine [5%] treated with epoetin alfa). Full details of serious treatment-emergent adverse events are reported in the appendix (pp 30, 33–34). The overall rate of serious treatment-emergent adverse events and the exposure-adjusted incidence rate were similar between the groups. Suspected treatment-related serious adverse events were reported in one patient in the luspatercept group (acute myeloid leukaemia) and in three patients in the epoetin alfa group (acute coronary syndrome, acute febrile neutrophilic dermatosis with pyrexia, and hepatitis with asthenia). Eight (4%) patients receiving luspatercept and four (2%) receiving epoetin alfa discontinued treatment due to a treatment-emergent adverse event. Two of these events were considered as suspected treatment-related adverse events: a non-serious grade 3 event of dyspnoea on exertion, and a serious grade 4 event of transformation to acute myeloid leukaemia, in one patient each in the luspatercept group.

Treatment-emergent adverse events of special interest and other relevant safety events included malignancies, premalignant disorders, thromboembolic events, kidney injury, hypertension, liver toxicity, extramedullary haemopoiesis masses, immunogenicity reactions (local and hypersensitivity-type reactions), and asthenia (appendix pp 26–27, 31), and most of these events were of grade 1 or 2 in severity. Incidence rates of malignancies, premalignant disorders, liver toxicity, and immunogenicity hypersensitivity-type reactions were similar in both treatment groups; whereas, asthenia, kidney injury, immunogenicity local-type reactions, hypertension, and thromboembolic events were more frequent with luspatercept. Findings were similar during the first 24 weeks of treatment in ad-hoc analysis (appendix p 32). However, after adjusting for exposure, the incidence rates of asthenia, kidney injury, and thromboembolic events were similar between treatment groups, although the frequencies of hypertension and immunogenicity local-type reactions remained higher in the luspatercept treatment group. No cases of extramedullary haemopoiesis masses were detected in the study.

In this study, five (3%) of 178 patients in the luspatercept group and seven (4%) of 176 in the epoetin alfa group had progressed to high-risk myelodysplastic syndromes (per IPSS-R criteria[5]). 32 (18%) patients in the luspatercept group and 32 (18%) in the epoetin alfa

	Luspatercept (n=178)		Epoetin alfa (n=176)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
General disorder or administration site conditions				
Fatigue	26 (15%)	1 (1%)	12 (7%)	1 (1%)
Peripheral oedema	23 (13%)	0	12 (7%)	0
Asthenia	22 (12%)	0	25 (14%)	1 (1%)
Infections and infestations				
COVID-19	19 (11%)	6 (3%)	17 (10%)	2 (1%)
Gastrointestinal disorders				
Diarrhoea	26 (15%)	2 (1%)	20 (11%)	1 (1%)
Nausea	21 (12%)	0	13 (7%)	0
Respiratory, thoracic, or mediastinal disorders				
Dyspnoea	21 (12%)	7 (4%)	13 (7%)	2 (1%)
Vascular disorders				
Hypertension	23 (13%)	15 (8%)	12 (7%)	8 (5%)
Blood and lymphatic system disorders				
Anaemia	17 (10%)	13 (7%)	17 (10%)	12 (7%)

Data are n (%), where n=number of patients. Events of grade 1–4 severity (Common Terminology Criteria for Adverse Events version 4.03) occurring in at least 10% of patients in either group are shown. System organ classes and preferred terms were coded with the Medical Dictionary for Regulatory Activities (version 25.0). Treatment-emergent adverse events were defined as adverse events that started on or after the first treatment of study medication until 42 days after the last dose of any study drug. A patient was counted only once for the maximum severity for multiple events under the same preferred term within system organ class.

Table 2: **Adverse events of any grade severity occurring in at least 10% of patients (safety population)**

group died during the trial (appendix pp 30–31). In the luspatercept group, treatment-emergent adverse events resulting in death (total n=8 [5%]) were multiple organ dysfunction (one patient), infections and infestations (two patients), nervous system disorders (two patients), coronary artery insufficiency (one patient), intestinal ischaemia (one patient), and acute myeloid leukaemia (one patient). The one case of acute myeloid leukaemia (diagnosed after receiving three doses of 1·0 mg/kg luspatercept) leading to death occurred in a 78-year-old patient, and was considered by the investigator to be related to study treatment. This patient was on luspatercept treatment for 44 days. In the epoetin alfa group, treatment-emergent adverse events resulting in death (total n=12 [7%]) were pyrexia (one patient), infections and infestations (five patients), cardiac disorders (five patients), and malnutrition (one patient). Other causes of death and remaining safety findings are reported in the appendix (pp 25–27, 30–32).

Discussion

This planned interim analysis of the phase 3, open-label, randomised COMMANDS trial showed greater efficacy with use of luspatercept than with epoetin alfa for the treatment of anaemia in ESA-naive patients with lower-risk myelodysplastic syndromes who require red blood cell transfusions. Additionally, treatment with luspatercept was associated with clinically meaningful and statistically significant improvements in red blood cell transfusion independence and its durability, erythroid response, and reduction of transfusion burden, compared with epoetin alfa treatment. To our knowledge, this trial is the first to show improved benefit with luspatercept over an established standard-of-care treatment for lower-risk myelodysplastic syndromes-associated anaemia.

The safety profile of luspatercept in the COMMANDS trial was generally consistent with the known safety profile[10,11] of luspatercept in the approved myelodysplastic syndromes indication. Frequently reported adverse events were mainly low grade, and incidence rates of grade 3 or 4 adverse events and serious adverse events were similar between the treatment groups. In both treatment groups, the most common grade 3 or 4 adverse events were anaemia, neutropenia, pneumonia, and hypertension, and the most commonly reported serious adverse events were COVID-19 and pneumonia. These are consistent with previous trials of luspatercept, including the phase 3 MEDALIST and phase 2 PACE trials.[11,13] The efficacy and safety of epoetin alfa were consistent with the phase 3 EPOANE3021 trial of patients with low-risk or intermediate-1-risk myelodysplastic syndromes defined by IPSS criteria.[9] Overall, most adverse events of special interest were grade 1 or 2. In each treatment group, a small number of patients progressed to high-risk myelodysplastic syndromes or acute myeloid leukaemia, and no trends in the type of malignancies or pre-malignant disorders were identified. Thromboembolic events were balanced between the two groups when adjusting for exposure and at 24 weeks, and were reported only in patients with increased risks for thromboembolic events (ie, age ≥60 years, multiple comorbidities, and pre-existing cardiovascular or cerebrovascular disease); they were not associated with an increase in haemoglobin concentration, platelet count, or hypertension (data not shown). In addition, no cases of serious systemic hypersensitivity, extramedullary haemopoiesis masses, or liver toxicity meeting Hy's law criteria were reported in either group. Although no new safety signals of luspatercept were identified, a longer follow-up will be needed to fully assess safety in this patient population.

The COMMANDS study, and this interim analysis, have some limitations. Firstly, the trial was designed as an open-label study. Nevertheless, the study team was masked to the aggregated data analyses, which were evaluated independently by the data monitoring committee. Secondly, the results reported are from a prespecified interim analysis. Although the presented data show significantly greater efficacy with luspatercept than with epoetin alfa, we acknowledge that the results will be further evaluated with longer follow-up and with a fully mature dataset. Thirdly, the proportions of patients with ring sideroblasts and patients with *SF3B1* mutations enrolled in this study are higher than expected in the overall population of patients with lower-risk myelodysplastic syndromes.[17] In the COMMANDS study,

258 (73%) of 355 patients were positive for ring sideroblasts and 210 (61%) of 347 had mutated *SF3B1*. These higher frequencies might be partly influenced by the indolent nature of myelodysplastic syndromes with ring sideroblasts, which could increase the potential time interval for recruitment to the study (compared with myelodysplastic syndromes without ring sideroblasts, which is more prone to a faster disease evolution). This point is supported by the median time from myelodysplastic syndromes diagnosis in patients enrolled in the study: 8 months (IQR 2–27) for the ring sideroblast-positive subgroup versus 4 months (1–9) for the ring sideroblast-negative subgroup (data not shown). Furthermore, patients without ring sideroblasts included in the COMMANDS trial had similar primary endpoint response rates in both treatment groups, but a longer duration of red blood cell transfusion independence lasting at least 12 weeks was observed for those patients in the luspatercept group versus those in the epoetin alfa group. In addition, the high frequency of patients with mutated *SF3B1* in the COMMANDS study might be partly explained by the selection of a study population enriched for these gene mutations (patients with lower-risk myelodysplastic syndromes with <5% bone marrow blasts and with transfusion-dependent anaemia).[18] Nevertheless, the primary endpoint response rate observed with luspatercept versus epoetin alfa in this interim analysis was higher in patients with mutated *SF3B1* (70% *vs* 31%) than in patients with non-mutated *SF3B1* (42% *vs* 32%). We acknowledge that although activity of luspatercept was observed in all pre-defined subgroups of patients, the response rate in the subgroup of patients with mutated *SF3B1* is higher than in the non-mutated subgroup. These findings suggest that additional data will be needed to further characterise the efficacy and mechanism of action of luspatercept in other, less frequent subgroups of patients or subtypes of lower-risk myelodysplastic syndromes. Future research is recommended to evaluate luspatercept intervention earlier in the disease course, treatment at a higher starting dose, or treatment-combination strategies.

Patients in the luspatercept and epoetin alfa treatment groups had similar baseline mutational burden, with mutations associated with gene splicing found to be mutually exclusive, which was consistent with published literature.[19,20] An unfavourable association between mutational burden and primary endpoint response was observed with epoetin alfa in this interim analysis, in accordance with previous reports showing that patients with increased mutational burden had a reduced likelihood of having a primary endpoint response with epoetin alfa treatment.[21] However, no such association was found in the luspatercept treatment group, suggesting broad activity of luspatercept across various baseline mutational burden. Mutations in *SF3B1, SF3B1α, ASXL1,* and *TET2* were favourably associated with reaching the primary endpoint with luspatercept over epoetin alfa. Subgroup analysis of treatment effect in ring sideroblast-negative patients for the association of baseline mutations with the primary endpoint did not show a significant association in either treatment group, suggesting similar benefit with both drugs in the ring sideroblast-negative subgroup (appendix pp 54–55); however, patient numbers were low, precluding statistical analyses and meaningful conclusions at this time.

Luspatercept is currently approved for the treatment of anaemia in adult patients with lower-risk myelodysplastic syndromes with ring sideroblasts who require red blood cell transfusions (≥2 red blood cell units per 8 weeks) after failure of ESA treatment. Interestingly, the higher response rates observed with luspatercept compared with epoetin alfa in ESA-naive patients in this interim analysis suggest that altering the therapeutic approach and treating patients with luspatercept earlier in the disease course might be beneficial. However, further longer-term studies will be needed to fully understand the consequences of such a treatment approach. Additionally, evaluation of patient-reported quality of life and pharmaco-economic data from COMMANDS will help in understanding the full potential of luspatercept and how it can affect future clinical decision making. Enrolment of patients is complete in the COMMANDS trial, with follow-up ongoing. The findings from this planned interim analysis suggest that luspatercept could provide an alternative to the current standard-of-care treatment for anaemia in patients with lower-risk myelodysplastic syndromes with or without ring sideroblasts who require red blood cell transfusions.

Contributors

MGDP, VS, ACG, SR, SK, VP, KLK, JKS, and GG-M designed the trial and PF is the chief investigator. UP, MGDP, VS, AMZ, RSK, JS, DV, AJ, SD-S, IST, C-CL, AD, SP, TC, PF, and GG-M contributed to data acquisition. JL and JZ did the statistical analysis and SH and SV contributed to biomarker data acquisition and analysis. All authors contributed to data interpretation. All authors critically reviewed and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors accessed and verified the data. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

Declaration of interests

UP reports receiving grant support, paid to GWT-TUD, from Amgen; lecture fees and grant support, paid to the University of Leipzig, from Amgen; fees for serving on a steering committee, consulting fees, and travel support from Bristol Myers Squibb; grant support, paid to GWT-TUD, from Janssen Biotech; grant support, paid to University Dresden, from Merck and Novartis; lecture and consulting fees from Novartis; and consulting fees from AbbVie, Curis, and Geron. UP is also a member of the Medical and Scientific Advisory Board of the MDS Foundation. VS reports receiving research funding, paid to University of Florence, from Bristol Myers Squibb; honoraria from Bristol Myers Squibb; honoraria and travel support from Janssen; advisory board fees from AbbVie, Bristol Myers Squibb, CTI BioPharma, Geron, Gilead, Novartis, Otsuka, Servier, and Syros; and serving as the President of the Scientific Committee of the Italian Foundation of Myelodysplastic Syndromes. AMZ reports receiving grant support from AbbVie, ADC Therapeutics, Amgen, Aprea, Astex, AstraZeneca, Boehringer-Ingelheim, Cardiff Oncology, Bristol Myers Squibb, Incyte, Medimmune, Novartis, Otsuka, Pfizer, Takeda, and Trovagene;

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Data sharing

Bristol Myers Squibb will honour legitimate requests for our clinical trial data from qualified researchers with a clearly defined scientific objective. We consider data sharing requests for phase 2–4 interventional clinical trials that completed on or after Jan 1, 2008. In addition, primary results from these trials must have been published in peer-reviewed journals and the medicines or indications approved in the USA, EU, and other designated markets. Sharing is also subject to protection of patient privacy and respect for the patient's informed consent. Data considered for sharing may include non-identifiable patient-level and study-level clinical trial data, and full clinical study reports and protocols. Bristol Myers Squibb reserves the right to update and change criteria at any time. Other criteria may apply, for details please visit Bristol Myers Squibb at https://vivli.org/ourmember/bristol-myers-squibb/.

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