Luspatercept (myelodysplastic syndromes, treatment-naive and pretreated without ring sideroblasts)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSH	British Society for Haematology
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
del(5q)	deletion of the q-arm of chromosome 5
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACT-An	Functional Assessment of Cancer Therapy-Anaemia
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hb	haemoglobin
IPSS-R	International Prognostic Scoring System-Revised
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IWG	International Working Group
MDS	myelodysplastic syndromes
MDS-U	myelodysplastic syndromes unclassifiable
MMRM	mixed-effects model with repeated measures
NCCN	National Comprehensive Cancer Network
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
sEPO	serum erythropoietin
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug luspatercept. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 April 2024.

Research question

The aim of the present report is to assess the added benefit of luspatercept in comparison with the appropriate comparator therapy (ACT) in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) who either have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy, or without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of luspatercept

Therapeutic indication	**ACT[a]**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk[d] MDS[b, c] ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy[e]	Individualized treatment[f, g] selected from ▪ erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L) ▪ transfusion therapy with packed red blood cells as needed in combination with chelation therapy ▪ lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate) taking into account the erythropoietin serum level, cytogenetics and prior therapy
a. Presented is the ACT specified by the G-BA. b. Patients with hypocellular MDS are not taken into account in the determination of the ACT by the G-BA. c. According to the G-BA, patients with MDS with del(5q) mutation are included in the therapeutic indication. d. According to the G-BA, it is assumed that patients with very low, low or intermediate risk (up to 3.5 points) according to IPSS-R are included in the therapeutic indication. e. It is assumed that the patients are in need of treatment and are not eligible for an allogeneic stem cell transplant at the time of therapy. f. It should be possible to adapt the study medication/concomitant medication to the patient's individual needs in both study arms. A therapy adjustment can include both dosage adjustments and therapy changes if existing symptoms worsen. g. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. del(5q): deletion of the q-arm of chromosome 5; G-BA: Federal Joint Committee; IPSS-R: International Prognostic Scoring System-Revised; MDS: myelodysplastic syndromes	

The company departed from the ACT specified by the G-BA. On the one hand, it did not consider lenalidomide to be part of the ACT and, on the other hand, named erythropoiesis-stimulating agents as a treatment option for patients with a serum erythropoietin (sEPO) level < 500 U/L.

With reference to section 5.1 of the Summary of Product Characteristics (SPC), the company justified the deviation with regard to lenalidomide by stating that the use of luspatercept in patients with del(5q) MDS was off-label. It assumed that luspatercept was generally not suitable for this particular patient group. The company did not appropriately justify its deviation from the ACT specified by the G-BA. Patients with del(5q) MDS are included in the present therapeutic indication, which, in accordance with the approval of luspatercept, is aimed at the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk MDS.

The company justified the deviation with regard to the suitability of the erythropoiesis-stimulating agents with the fact that epoetin alfa and epoetin zeta are recommended by

national and international guidelines for the treatment of patients with low-risk MDS with sEPO levels < 500 U/L. In its reasoning, the company also pointed out that a response to epoetin alfa or epoetin zeta is generally possible in patients with sEPO levels < 500 U/L according to the Nordic Score. The company did not appropriately justify its deviation from the ACT specified by the G-BA. In the present therapeutic indication, epoetin alfa and epoetin zeta are only approved for the treatment of patients with an epoetin serum level < 200 U/L. The German Society for Haematology and Medical Oncology (DGHO) guideline on myelodysplastic neoplasms recommends therapy with erythropoiesis-stimulating agents for patients with sEPO levels < 200 U/L. According to the guideline, a response is possible in sEPO levels of up to 500 U/L. In the present benefit assessment, the use of erythropoiesis-stimulating agents is therefore considered adequate in patients with sEPO levels < 200 U/L as determined by the G-BA.

As explained above, the company's justification for deviating from the G-BA's ACT is overall not plausible. The present assessment was conducted in accordance with the research question and in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The COMMANDS study is used for the benefit assessment. The COMMANDS study is an ongoing, open-label RCT comparing luspatercept versus epoetin alfa. The study included adult patients with MDS according to World Health Organization (WHO) 2016 classification and with very low, low or intermediate risk according to the International Prognostic Scoring System-Revised (IPSS-R) for MDS. In addition, they had to have < 5% blasts in bone marrow. Patients with MDS del(5q) (deletion of the q-arm of chromosome 5), MDS unclassifiable (MDS-U) or secondary MDS were excluded from participation in the study. To be eligible for study inclusion, patients had to have transfusion-dependent anaemia due to MDS and sEPO levels < 500 U/L.

A total of 363 patients were included in the COMMANDS study and randomly allocated in a 1:1 ratio either to treatment with luspatercept (N = 182) or to epoetin alfa (N = 181).

Luspatercept treatment in the intervention arm was largely in compliance with the specifications of the SPC. According to the SPC, treatment with luspatercept should be discontinued if there is no reduction in transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.75 mg/kg). Since the assessment of the clinical benefit in the COMMANDS study took place during the visit on Day 169 (Week 25), it is possible that, in

accordance with the SPC, patients in the luspatercept arm received 2 luspatercept doses with the initial dose of 1.0 mg/kg (6 weeks), 2 consecutive doses of 1.33 mg/kg (6 weeks) and, in deviation, 4 instead of 3 consecutive doses of 1.75 mg/kg (12 weeks) up to and including Week 24. Apart from the exceptions described below, treatment with epoetin alfa in the comparator arm was in compliance with the specifications of the SPC. According to the SPC, appropriate dose adjustments should be made to maintain haemoglobin (Hb) concentrations within the target range of 10 g/dL to 12 g/dL. It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. According to the planning of the COMMANDS study, a dose increase was already possible at the Week 7 Day 1 dose visit. The median time to the first dose escalation in the patients in the total study population was approx. 6 weeks (minimum: approx. 5 weeks; data on the relevant subpopulation are not available).

In both study arms, red blood cell transfusions were permitted at the investigator's discretion in the event of low Hb levels (compared with the individual Hb threshold value [average pre-transfusion Hb value in the 8 weeks before the first dose of study medication]), anaemia-related symptoms or concomitant diseases. According to the study protocol, iron chelation therapy could be given at the investigator's discretion in accordance with the approval.

After randomization, the COMMANDS study was divided into a treatment phase (comprising a primary treatment phase and a continued treatment phase) and a (long-term) follow-up phase. The planned duration of the primary treatment phase was 24 weeks. After Day 169 (Week 25), treatment in the continued treatment phase was only continued in patients with evidence of clinical benefit – defined as a transfusion reduction of ≥ 2 packed red blood cell units per 8 weeks compared with baseline (for any 8-week period within the 12 weeks preceding Day 169) – and absence of disease progression (per International Working Group [IWG] criteria 2006) (Day 169 assessment). Patients with treatment discontinuation in the primary treatment phase or in the continued treatment phase transitioned to the (long-term) follow-up phase, which was planned to last up to 3 years after the last dose or 5 years after the first dose of study medication (whichever was last). At no time during the treatment period of the study was a switch from erythropoietin alfa to luspatercept permitted.

The primary outcome of the COMMANDS study is transfusion independence for 12 weeks during Weeks 1 to 24, with a concurrent mean Hb increase of ≥ 1.5 g/dL from baseline. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Relevant subpopulation of the COMMANDS study

When determining the ACT, the G-BA stipulated that erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta) as an option of individualized therapy only represent the ACT for patients with sEPO levels of < 200 U/L.

The COMMANDS study included patients with sEPO levels < 500 U/L, who received therapy with erythropoiesis-stimulating agents in the comparator arm of the study. In Module 4 D, the company additionally presented analyses of a subpopulation of the COMMANDS study, which only includes patients with sEPO levels < 200 U/L (79.6% of the total study population). The subpopulation formed by the company is used for the present benefit assessment.

Data cut-offs and analysis periods

In Module 4 D of the dossier, the company considered different analysis periods for the ongoing COMMANDS study (including Weeks 1 to 24) and data cut-offs (3rd data cut-off from 31 March 2023 and 4th data cut-off from 22 September 2023), depending on the outcome. Since the median treatment duration up to the 4th data cut-off on 22 September 2023 in the relevant subpopulation was longer in the intervention arm (81.1 weeks) than in the comparator arm (63.5 weeks), it is assumed for the outcomes whose observation periods were linked to the end of treatment (concerns the outcome categories of morbidity, health-related quality of life and side effects) that the observation period also differed between the study arms. In addition, the response rates for the patient-reported outcomes on symptoms and health-related quality of life at the dose visits already fell below 70% in Weeks 1 to 24. The present benefit assessment uses analyses over the period of the primary treatment phase (Weeks 1 to 24) with comparable follow-up observation periods for all outcomes in the categories of morbidity, health-related quality of life, and side effects. When using the analyses over the period from Week 1 to Week 24, it is not relevant whether the 3rd data cut-off on 31 March 2023 or the 4th data cut-off on 22 September 2023 is considered, as all patients had already completed or prematurely discontinued the primary treatment phase by the 3rd data cut-off on 31 March 2023. The 3rd data cut-off from 31 March 2023 presented by the company was used for the outcomes on symptoms, health-related quality of life, and side effects. For the outcome of transfusion independence, the 4th data cut-off from 22 September 2023 presented by the company was used. For the outcome category of mortality, overall survival on the basis of a time-to-event analysis at the 4th data cut-off (22 September 2023) was used. This corresponds to the data cut-offs presented by the company for the respective outcomes.

Risk of bias

The risk of bias across outcomes for the COMMANDS study is rated as low. The risk of bias of the results for the outcomes of overall survival, serious adverse events (SAEs), severe adverse events (AEs), and thromboembolic events is rated as low. For the outcomes of transfusion

independence, discontinuation due to AEs and eye disorders (SOC, AEs), the risk of bias is rated as high due to the lack of blinding in subjective recording of outcomes or subjective decision to discontinue. There is also a high risk of bias of the results for the outcomes of symptoms (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) and health-related quality of life (recorded using the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy-Anaemia [FACT-An]). The main reasons for this are the lack of blinding in subjective recording of outcomes and the decreasing response rates, which in some cases differ between the arms.

Results

Mortality

Overall survival

For the outcome of overall survival, there was no statistically significant difference between treatment groups up to the data cut-off on 22 September 2023. There is no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion independence

Over the primary treatment phase (Weeks 1 to 24), a statistically significant difference was found in favour of luspatercept in comparison with the ACT for the outcome of transfusion independence. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Symptoms (recorded with the EORTC QLQ-C30)

No statistically significant difference between treatment groups was shown for any of the following outcomes during the primary treatment phase (Weeks 1 to 24): fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, and diarrhoea (recorded using EORTC QLQ-C30). There is no hint of an added benefit of luspatercept in comparison with the ACT for any of them; an added benefit for these outcomes is therefore not proven.

Health-related quality of life (recorded with EORTC-QLQ-C30, FACT-An)

For health-related quality of life, no statistically significant difference between treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning (recorded using the EORTC QLQ-C30) and for the FACT-An over the primary treatment phase (Weeks 1 to 24). There is no hint of an added benefit of luspatercept in

comparison with the ACT for any of them; an added benefit for these outcomes is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs for the primary treatment phase (Weeks 1 to 24). For each of them, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm for these outcomes is therefore not proven.

Thromboembolic events (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of thromboembolic events (severe AEs) for the primary treatment phase (Weeks 1 to 24). There is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Eye disorders (AEs)

Over the primary treatment phase (Weeks 1 to 24), a statistically significant difference was found to the disadvantage of luspatercept in comparison with the ACT for the outcome of eye disorders (AEs). There is a hint of greater harm from luspatercept in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug luspatercept compared with the ACT is assessed as follows:

Overall, there is a negative effect in the category of non-serious/non-severe side effects for the outcome of eye disorders (AEs) with the extent “considerable” and the probability of a “hint”. This negative effect of luspatercept in an outcome in the category of non-serious/non-severe side effects is not considered sufficient to derive lesser benefit of luspatercept compared with the ACT. In summary, the added benefit of luspatercept in comparison with the ACT is not proven for adult patients with transfusion-dependent anaemia due to very low,

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

low and intermediate-risk MDS who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy.

The company presented no data in Module 4 E for adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS, without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy. The added benefit of luspatercept in comparison with the ACT is not proven for these patients either.

Table 3 presents a summary of the probability and extent of added benefit of luspatercept.

Table 3: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk[d] MDS[b, c] ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy[e]	Individualized treatment[f, g] selected from ▪ erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L[h]) ▪ transfusion therapy with packed red blood cells as needed in combination with chelation therapy ▪ lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate) taking into account the erythropoietin serum level, cytogenetics and prior therapy	Patients ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e]: added benefit not proven[i] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy[e]: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Patients with hypocellular MDS are not taken into account in the determination of the ACT by the G-BA.
c. According to the G-BA, patients with MDS with del(5q) mutation are included in the therapeutic indication.
d. According to the G-BA, it is assumed that patients with very low, low or intermediate risk (up to 3.5 points) according to IPSS-R are included in the therapeutic indication.
e. It is assumed that the patients are in need of treatment and are not eligible for an allogeneic stem cell transplant at the time of therapy.
f. It should be possible to adapt the study medication/concomitant medication to the patient's individual needs in both study arms. A therapy adjustment can include both dosage adjustments and therapy changes if existing symptoms worsen.
g. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
h. According to the G-BA, and in compliance with the approval, erythropoiesis-stimulating agents are determined as ACT only for patients with a serum epoetin level of < 200 U/L as part of individualized therapy.
i. No patients with MDS del(5q), MDS unclassifiable (MDS-U) or secondary MDS were included in the COMMANDS study. It remains unclear whether the observed effects are transferable to patients with MDS del(5q), MDS unclassifiable (MDS-U) or secondary MDS. In addition, it remains unclear whether the observed effects of the subpopulation of the COMMANDS study relevant for the benefit assessment with sEPO levels < 200 U/L can be transferred to patients with sEPO levels ≥ 200 U/L in the present therapeutic indication.

del(5q): deletion of the q-arm of chromosome 5; G-BA: Federal Joint Committee; IPSS-R: International Prognostic Scoring System-Revised; MDS: myelodysplastic syndromes; MDS-U: MDS unclassifiable; sEPO: serum erythropoietin

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of luspatercept in comparison with the ACT in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS who either have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy, or without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of luspatercept

Therapeutic indication	**ACT[a]**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk[d] MDS[b, c] ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy[e]	Individualized treatment[f, g] selected from ▪ erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L) ▪ transfusion therapy with packed red blood cells as needed in combination with chelation therapy ▪ lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate) taking into account the erythropoietin serum level, cytogenetics and prior therapy
a. Presented is the ACT specified by the G-BA. b. Patients with hypocellular MDS are not taken into account in the determination of the ACT by the G-BA. c. According to the G-BA, patients with MDS with del(5q) mutation are included in the therapeutic indication. d. According to the G-BA, it is assumed that patients with very low, low or intermediate risk (up to 3.5 points) according to IPSS-R are included in the therapeutic indication. e. It is assumed that the patients are in need of treatment and are not eligible for an allogeneic stem cell transplant at the time of therapy. f. It should be possible to adapt the study medication/concomitant medication to the patient's individual needs in both study arms. A therapy adjustment can include both dosage adjustments and therapy changes if existing symptoms worsen. g. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. del(5q): deletion of the q-arm of chromosome 5; G-BA: Federal Joint Committee; IPSS-R: International Prognostic Scoring System-Revised; MDS: myelodysplastic syndromes	

The company subdivided the patient population of adults with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS in its dossier and presented 2 separate modules:

- Module 3 D and Module 4 D: patients who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy
- Module 3 E and Module 4 E: patients without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy

Together, the populations cited by the company correspond to the patient population covered by the G-BA's research question. The company deviated from the G-BA's specification of the ACT, however. This is explained below.

According to the G-BA, lenalidomide is a therapeutic option only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate. However, in contrast to the G-BA, the company did not consider lenalidomide to be part of the ACT for either of the above-mentioned populations. With reference to section 5.1 of the SPC [3], the company justified this by stating that the use of luspatercept in patients with del(5q) MDS was off-label. It assumed that luspatercept was generally not suitable for this particular patient group. The company did not appropriately justify its deviation from the ACT specified by the G-BA. Patients with del(5q) MDS are included in the present therapeutic indication, which, in accordance with the approval of luspatercept [3], is aimed at the treatment of transfusion-dependent anaemia due to very low, low and intermediate-risk MDS.

According to the G-BA, and in compliance with the approval, erythropoiesis-stimulating agents are a treatment option only for patients with a sEPO level of < 200 U/L. However, in deviation from G-BA, the company cited erythropoiesis-stimulating agents as a treatment option for patients who have not received and who are eligible for erythropoiesis-stimulating agent-based therapy if their sEPO level is < 500 U/L. According to the company, epoetin alfa and epoetin zeta are recommended by national and international guidelines for the treatment of patients with low-risk MDS with sEPO levels < 500 U/L [4-7]. In its reasoning, the company also pointed out that a response to epoetin alfa or epoetin zeta is generally possible in patients with sEPO levels < 500 U/L according to the Nordic Score [8]. The company did not appropriately justify its deviation from the ACT specified by the G-BA. In the present therapeutic indication, epoetin alfa and epoetin zeta are only approved for the treatment of patients with an epoetin serum level < 200 U/L [6,7]. The DGHO guideline [4] recommends therapy with erythropoiesis-stimulating agents for patients with sEPO levels < 200 U/L. According to the guideline, a response is possible in sEPO levels of up to 500 U/L [4]. In the present benefit assessment, the use of erythropoiesis-stimulating agents is therefore considered adequate in patients with sEPO levels < 200 U/L as determined by the G-BA.

As explained above, the company's justification for deviating from the G-BA's ACT is overall not plausible. The present assessment was conducted in accordance with the research question and in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Company sources in the dossier (identical for Module 4 D and Module 4 E):

- study list on luspatercept (status: 4 March 2024)
- bibliographical literature search on luspatercept (last search on 4 March 2024)
- search in trial registries/trial results databases for studies on luspatercept (last search on 4 March 2024)
- search on the G-BA website for luspatercept (last search on 4 March 2024)

To check the completeness of the study pool:

- search in trial registries for studies on luspatercept (last search on 17 May 2024); for search strategies, see I Appendix A of the full dossier assessment

As described in Chapter I 2, the company subdivided the patient population of the therapeutic indication of luspatercept to be assessed (Module 4 D and Module 4 E), deviating from the G-BA's specification of the ACT. On this basis, the company identified the RCT COMMANDS for patients who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy, and used this study in Module 4 D of the dossier. For patients without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy, the company did not identify any relevant study and did not present any data in Module 4 E of the dossier.

The check of the completeness of the company's study pool – based on the research question and ACT according to the G-BA – did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: luspatercept vs. epoetin alfa

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study ACE-536-MDS-002 (COMMANDS[c])	Yes	Yes	No	Yes [9-11]	Yes [12,13]	Yes [14]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The study pool is consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMMANDS	RCT, open-label, parallel	Adults with transfusion-dependent anaemia[b] due to MDS[c]: ▪ with very low, low or intermediate risk[d] ▪ with sEPO levels < 500 U/L ▪ treatment-naive to erythropoietin-based therapies[e] ▪ ECOG PS ≤ 2	Luspatercept[f] (N = 182) epoetin alfa[f] (N = 181) Relevant subpopulation thereof[g]: luspatercept[f] (N = 145) epoetin alfa[f] (N = 144)	Screening: ≤ 35 days Treatment: ▪ Primary treatment phase: 24 weeks[h] ▪ Continued treatment phase[h]: after Week 25 until loss of clinical benefit, disease progression, death, unacceptable toxicity, physician or patient decision, or withdrawal of consent Observation[i]: outcome-specific, at most until death, withdrawal of consent, lost to follow-up, or end of study[j]	144 study centres[k] in Australia, Austria, Belgium, Canada, Czech Republic, Germany, France, Greece, Hungary, Israel, Italy, Japan, Lithuania, Netherlands, Poland, Portugal, Russia[l], South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine[l], United Kingdom, United States 1/2019–ongoing Data cut-offs: ▪ 16 September 2020 (interim analysis for futility[m]) ▪ 31 August 2022 (interim analysis for superiority[n]) ▪ 31 March 2023 (primary analysis[o]) ▪ 22 September 2023 (follow-up analysis[p])	Primary: transfusion independence for 12 weeks with mean Hb increase of ≥ 1.5 g/dL (Weeks 1–24)[q] Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The following criteria of packed red blood cell-transfusion dependence had to be met:
- transfusion requirement of 2–6 packed red blood cell units per 8 weeks confirmed for a minimum of 8 weeks immediately before randomization
- Hb value of ≤ 9.0 g/dL at the time of red blood cell transfusion or within 7 days before a red blood cell transfusion in the presence of symptoms of anaemia (without symptoms of anaemia Hb value of ≤ 7 g/dL)
- Hb value of < 11.0 g/dL after the last red blood cell transfusion before randomization

Table 6: Characteristics of the included study – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

c. Patients with MDS del(5q), MDS unclassifiable (MDS-U) according to WHO 2016 classification [15], or secondary MDS were excluded from participation in the study.
d. According to the IPSS-R for MDS [16].
e. As of amendment 1.0 to the study protocol (26 February 2019), patients who had received ≤ 2 doses of epoetin alfa (previous treatment with darbepoetin was not permitted) could be included at the discretion of the investigator. The last dose of epoetin alfa had to be given ≥ 8 weeks before randomization.
f. If needed, patients could receive packed red blood cell transfusions and iron chelation therapy (at a stable dosage).
g. Patients with sEPO levels < 200 U/L at baseline.
h. In both study arms, treatment after Day 169 (Week 25) was only continued in those patients who fulfilled the following criteria:
- evidence of clinical benefit, defined as a transfusion reduction of ≥ 2 packed red blood cell units per 8 weeks compared with baseline (for any 8-week period within the 12 weeks preceding Day 169)
- absence of disease progression per IWG criteria 2006 [17] In the further course, the assessment of the clinical benefit and disease status had to be repeated and confirmed every 24 weeks.

i. Outcome-specific information is provided in Table 8.
j. The study will be terminated after all remaining patients have completed a follow-up phase of 5 years after the first dose of study medication or of 3 years after the last dose of study medication (whichever occurs later).
k. Module 4 D, Appendix 4-E of Module 4 D and the CSR provide slightly different information on the primary analysis (31 March 2023) (only affects individual study centres).
l. By the end of May 2022, the dispensing of drug was stopped at all 7 sites in Russia. All 9 patients from Russia discontinued the study by 17 June 2022. No further patients were enrolled at the 4 sites in Ukraine as of March 2022.
m. Prespecified interim analysis for futility after approx. 105 patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely.
n. Interim analysis for superiority after approx. 300 patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely (implemented with amendment 4.0 to the study protocol [31 March 2022]).
o. Prespecified primary analysis after all patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely.
p. Prespecified follow-up analysis after all patients had completed the first 48 weeks of study treatment or had discontinued treatment prematurely.
q. Prior to amendment 1.0 to the study protocol (26 February 2019), the primary outcome was defined as transfusion independence of 24 weeks (Weeks 1–24).

AE: adverse event; CSR: clinical study report; del(5q): deletion of the q-arm of chromosome 5; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Hb: haemoglobin; IPSS-R: International Prognostic Scoring System-Revised; IWG: International Working Group; MDS: myelodysplastic syndromes; MDS-U: MDS unclassifiable; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; sEPO: serum erythropoietin

Table 7: Characteristics of the intervention – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study	Intervention	Comparison
COMMANDS	Luspatercept 1.0 mg/kg body weight, SC every 3 weeks (Day 1 of a 21-day cycle)	Epoetin alfa 450 IU/kg body weight SC once a week (Day 1 of a 7-day cycle)
	Dose adjustments ▪ In patients whose Hb level was not 10–12 g/dL, the dose should be increased by one dose level to 1.33 mg/kg and 1.75 mg/kg (from Day 1 of the 3rd cycle)[a] ▪ Dose delays or dose reductions – by one dose level (minimum: 0.45 mg/kg) – were allowed in case of AEs or increased Hb level.	▪ In patients whose Hb level was not 10–12 g/dL, the dose should be increased by one dose level to a maximum of 1050 IU/kg (from Day 1 of the 7th cycle; at most every 4 weeks) ▪ Dose delays or dose reductions – by one dose level (minimum: 337.5 IU/kg) – were allowed in case of AEs or increased Hb level
	Pretreatment ▪ transfusion of 2–6 packed red blood cell units per 8 weeks confirmed for a minimum of 8 weeks immediately before randomization **Disallowed pretreatment** ▪ erythropoiesis-stimulating agents[b] ▪ disease-modifying substances (e.g. immunomodulators such as lenalidomide)[c] ▪ HMA[d] ▪ luspatercept or sotatercept ▪ immunosuppressive therapy for the treatment of MDS ▪ haematopoietic stem cell transplantation ▪ the following substances/therapies ≤ 8 weeks before randomization: ▫ G-CSF/GM-CSF[e] ▫ cytotoxic chemotherapy ▫ corticosteroids[f] ▫ iron chelation therapy (unless on a stable/decreasing dose for ≥ 8 weeks before randomization) ▫ other haematopoietic growth factors (e.g. interleukin-3) ▫ androgens[g] ▫ hydroxyurea ▫ oral retinoids (except topical retinoids) ▫ arsenic trioxide ▫ interferons and interleukins ▫ major surgery (full recovery after any surgery before randomization) ▪ live COVID-19 vaccine ≤ 4 weeks before randomization **Allowed concomitant treatment** ▪ red blood cell transfusions at the investigator's discretion in case of low Hb level[h], symptoms of anaemia (e.g. shortness of breath, fatigue) or concomitant diseases ▪ iron chelation therapy – according to approval – at the investigator's discretion ▪ corticosteroids[f] ▪ live vaccines (e.g. influenza vaccine) at the investigator's discretion ▪ phlebotomy[i] ▪ supportive treatment with antibiotics, virostatics, antimycotics and/or supportive nutritional measures	

Table 7: Characteristics of the intervention – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study	Intervention	Comparison
	Disallowed concomitant treatment ▪ cytotoxic, chemotherapeutic or targeted substances/therapies ▪ erythropoiesis-stimulating agents (except study medication) and other haematopoietic growth factors (e.g. interleukin-3) ▪ granulocyte colony-stimulating factors (z. B. G-CSF, GM-CSF)[e] ▪ azacitidine, decitabine or other HMA ▪ lenalidomide, thalidomide or other IMiD ▪ hydroxyurea ▪ androgens[g] ▪ oral retinoids (except topical retinoids) ▪ arsenic trioxide ▪ interferon and interleukins ▪ live COVID-19 vaccine	

a. The following criteria had to be met for a dose increase:
- Hb value < 10–12 g/dL; if an Hb value of 10–12 g/dL had been achieved due to a red blood cell transfusion, the dose could still be adjusted
- increase in Hb value by ≤ 1 g/dL compared with the Hb value before the last luspatercept dose administered; in the event of an increase in Hb value by > 1 g/dL, the dose could also be adjusted if the increase was due to a red blood cell transfusion
- The 2 most recent luspatercept injections were given at the same dose, and the criteria for a dose delay/reduction according to the study protocol were not met for the respective administration.

b. When using ≤ 2 doses of epoetin alfa, study inclusion was possible at the investigator's discretion. The last dose of epoetin alfa had to be given ≥ 8 weeks before randomization. Prior darbepoetin treatment was disallowed.
c. A ≤ 1-week treatment up to ≥ 8 weeks before randomization was allowed.
d. Patients could be included at the investigator's discretion if they had been treated with ≤ 2 doses of HMA until ≥ 8 weeks before randomization.
e. Administration of G-CSF/GM-CSF was allowed as concomitant treatment for febrile neutropenia.
f. Corticosteroids for the treatment of medical conditions other than MDS were allowed on a stable/decreasing dose for ≥ 1 week before randomization. The use of topical corticosteroids and the occasional administration before a transfusion to prevent allergic reactions were allowed.
g. Except for the treatment of hypogonadism.
h. The patient's individual transfusion burden before the start of the study is documented (number of transfused packed red blood cell units in the 8-week period before the first dose of study medication) and the Hb value at which red blood cell transfusions were administered before the start of the study (Hb threshold value; mean value of all documented Hb values of a patient before packed red blood cell transfusion in the 8 weeks before the first dose of study medication). Furthermore, (pre-transfusion) Hb values were determined regularly and also at the time of the expected transfusion. If there was an increase in pre-transfusion Hb value by ≥ 1 g/dL during the study compared with the Hb threshold value, the transfusion should be delayed by ≥ 7 days. In addition, a red blood cell transfusion was possible at the discretion of the investigator in the event of symptoms of anaemia or for other reasons (e.g. infection).
i. Emergency measure for excessively high Hb levels.

AE: adverse event; COVID-19: coronavirus disease 2019; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; Hb: haemoglobin; HMA: hypomethylating agent; IMiD: immunomodulatory drug; IU: international units; MDS: myelodysplastic syndromes; RCT: randomized controlled trial; SC: subcutaneous

Study design

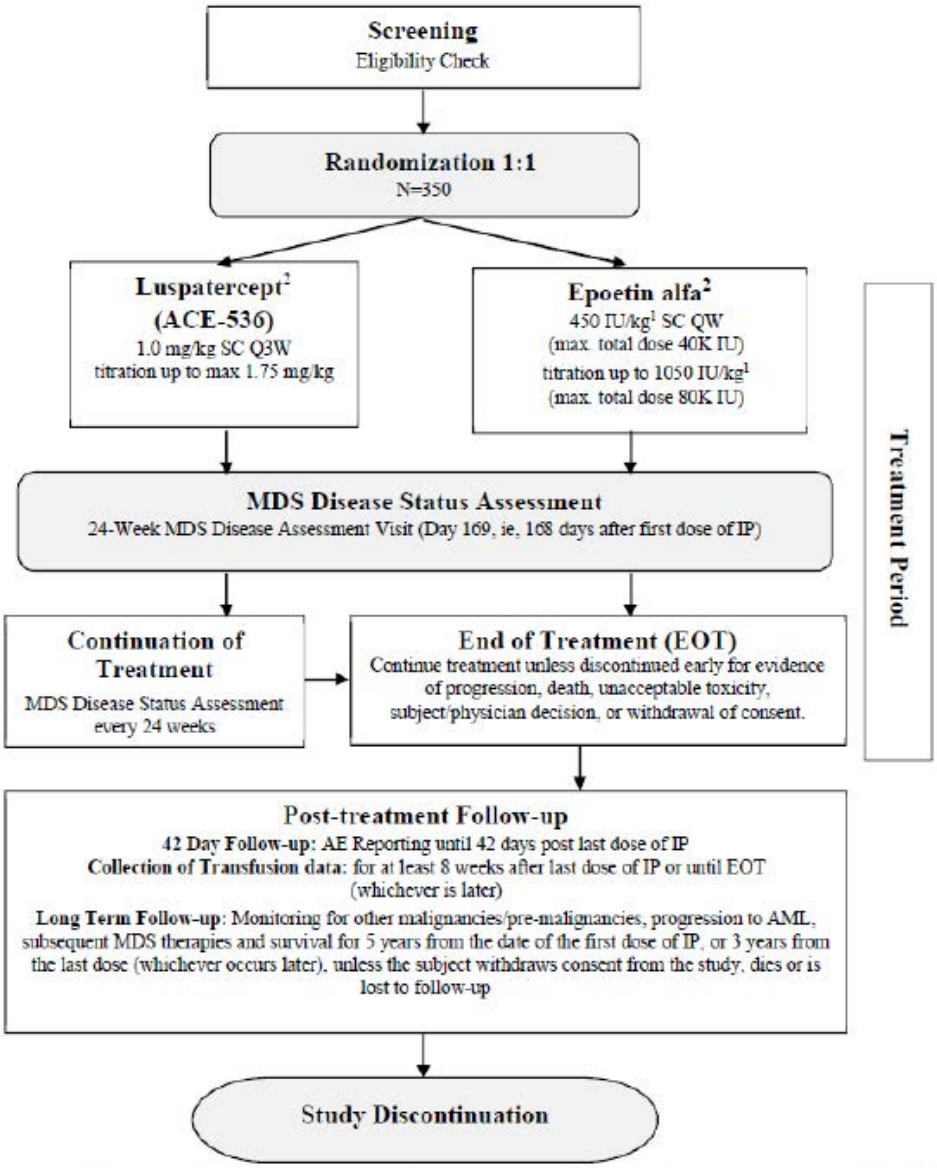
The COMMANDS study is an ongoing, open-label RCT comparing luspatercept versus epoetin alfa. The study included adult patients with MDS according to WHO 2016 classification [15] that meets IPSS-R classification [16] of very low, low, or intermediate risk disease. In addition, they had to have < 5% blasts in bone marrow. Patients with MDS del(5q), MDS-U or secondary MDS were excluded from participation in the study. To be eligible for study inclusion, patients had to have transfusion-dependent anaemia due to MDS. Transfusion dependence was defined as a requirement of 2 to 6 packed red blood cell units per 8 weeks confirmed for a minimum of 8 weeks immediately before randomization. Hb levels at the time of or within 7 days prior to administration of a red blood cell transfusion had to be ≤ 9.0 g/dL (with symptoms of anaemia) or ≤ 7 g/dL (without symptoms of anaemia). Hb levels after the last red blood cell transfusion prior to randomization had to be < 11.0 g/dL. Moreover, patients had to have sEPO levels of ≤ 500 U/L. Patients were not allowed to have received any previous treatment with erythropoiesis-stimulating agents. However, patients who had received ≤ 2 doses of epoetin alfa (previous treatment with darbepoetin was not permitted) could be included at the discretion of the investigator. The last dose of epoetin alfa had to be given ≥ 8 weeks before randomization. In addition, the patients were not allowed to have received any previous haematopoetic cell transplant.

A total of 363 patients were included in the COMMANDS study and randomly allocated in a 1:1 ratio either to treatment with luspatercept (N = 182) or to epoetin alfa (N = 181). Randomization was stratified according to transfusion burden at baseline (< 4 packed red blood cell units per 8 weeks versus ≥ 4 packed red blood cell units per 8 weeks [based on the 8-week period prior to the first dose of study medication]), ring sideroblast status at baseline (with ring sideroblasts [+] [defined as ring sideroblasts ≥ 15% of erythroid precursors in bone marrow, or ≥ 5% if a SF3B1 mutation is present] versus no ring sideroblasts [−]), and sEPO level at baseline (≤ 200 U/L versus > 200 U/L).

After randomization, the COMMANDS study was divided into a treatment phase (comprising a primary treatment phase and a continued treatment phase) and a (long-term) follow-up phase. The planned duration of the primary treatment phase was 24 weeks. After Day 169 (Week 25), treatment in the continued treatment phase was only continued in patients with evidence of clinical benefit – defined as a transfusion reduction of ≥ 2 packed red blood cell units per 8 weeks compared with baseline (for any 8-week period within the 12 weeks preceding Day 169) – and absence of disease progression (per IWG criteria 2006) (Day 169 assessment). In the further course, the assessment had to be repeated and confirmed by the investigator every 24 weeks in order to continue treatment with the study medication. Patients with treatment discontinuation in the primary treatment phase or in the continued treatment phase were included in the (long-term) follow-up phase. The long-term follow-up phase was planned for up to 3 years after the last dose or 5 years after the first dose of study

medication (whichever occurred later). At no time during the treatment period of the study was a switch from erythropoietin alfa to luspatercept permitted.

Figure 1 below shows the design of the study.



AE: Adverse Event (Unerwünschtes Ereignis); IP: Investigational Product (Prüfpräparat); Q3W: alle 3 Wochen; QW: wöchentlich; SC: subcutaneous (subkutan)

Figure 1: Design of the COMMANDS study (Figure of the company from Module 4 D of the dossier)

The primary outcome of the COMMANDS study is transfusion independence for 12 weeks during Weeks 1 to 24, with a concurrent mean Hb increase of ≥ 1.5 g/dL from baseline. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Uncertainties in the administration of study treatments in the COMMANDS study

Treatment with luspatercept in the intervention arm was largely in compliance with the specifications of the SPC [3]. According to the SPC, treatment with luspatercept should be discontinued if there is no reduction in transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.75 mg/kg). Since the assessment of the clinical benefit in the COMMANDS study took place during the visit on Day 169 (Week 25), it is possible that, in accordance with the SPC, patients in the luspatercept arm, who were not free from red blood cell transfusions during their treatment and thus were to increase their dosage, received 2 luspatercept doses with the initial dose of 1.0 mg/kg (6 weeks), 2 consecutive doses of 1.33 mg/kg (6 weeks) and, in deviation, 4 instead of 3 consecutive doses of 1.75 mg/kg (12 weeks) up to and including Week 24. The company did not present any information on the proportion of patients treated with 4 consecutive doses (12 weeks) of the highest dose (1.75 mg/kg) up to the assessment of clinical benefit. Nevertheless, it is assumed that the possibility of a 12-week instead of a 9-week luspatercept administration at the highest dose until potential treatment discontinuation does not lead to relevant uncertainties in the interpretability of the study results.

The COMMANDS study used epoetin alfa in the comparator arm. Apart from the exceptions described below, treatment with epoetin alfa was in compliance with the specifications of the SPC [6]. According to the SPC, appropriate dose adjustments should be made to maintain Hb concentrations within the target range of 10 g/dL to 12 g/dL. It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. According to the planning of the COMMANDS study, a dose increase was already possible at the Week 7 Day 1 dose visit. Until the 3rd data cut-off on 31 March 2023, the median time to the first dose escalation in the patients in the total study population was approx. 6 weeks (minimum: approx. 5 weeks; data on the relevant subpopulation are not available). A large proportion of patients therefore had a premature dose increase. Nevertheless, it is assumed that this does not lead to relevant uncertainties in the interpretability of the study results.

Concomitant therapies

The concomitant therapies permitted in the COMMANDS study were adequate. In both study arms, red blood cell transfusions were permitted at the investigator's discretion in the event of low Hb levels (compared with the individual Hb threshold value [average pre-transfusion Hb value in the 8 weeks before the first dose of study medication]), anaemia-related symptoms or concomitant diseases. According to guidelines, the therapeutic indication for red blood cell transfusion is based on an assessment of the patient's overall clinical picture and should not be determined solely on the basis of laboratory parameters (e.g. Hb level) [4,18,19]. When deciding on the administration of packed red blood cells, the anaemia-related symptoms and impairment of quality of life must be taken into account [18]. More specific

criteria for the administration of red blood cell transfusions cannot be inferred from the guidelines. The procedure in the study is considered appropriate.

According to the study protocol, iron chelation therapy could be given at the investigator's discretion in accordance with the approval. According to guidelines, chelation therapy can be considered in patients after transfusion of ≥ 20 packed red blood cell units or with a serum ferritin level of > 1000 µg/L to prevent dangerous iron overload of the organism [4,19].

Overall, it is assumed that in the COMMANDS study, transfusion therapy with packed red blood cells in combination with chelation therapy was carried out as needed in the sense of the ACT. However, the investigator's subjective assessment regarding the administration of red blood cell transfusions in an open-label study design is taken into account in the assessment of the outcome-specific risk of bias of the results of the outcome of transfusion independence (see Section I 4.2).

Relevant subpopulation of the COMMANDS study

When determining the ACT, the G-BA stipulated that erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta) as an option of individualized therapy only represent the ACT for patients with sEPO levels of < 200 U/L (see Table 4).

The COMMANDS study included patients with sEPO levels < 500 U/L, who received therapy with erythropoiesis-stimulating agents in the comparator arm of the study. In Module 4 D, the company additionally presented analyses of a subpopulation of the COMMANDS study, which only includes patients with sEPO levels < 200 U/L (79.6% of the total study population). The subpopulation formed by the company is used for the present benefit assessment.

Deviations of the population from the present research question

Luspatercept is approved for patients with very low, low or intermediate risk [3]. Patients with very low, low or intermediate risk according to IPSS-R for MDS were included in the COMMANDS study, which was the pivotal study for the approval [20] (see Table 6). According to the IPSS-R [16], a score > 3 to 4.5 points indicates intermediate risk. The international guidelines of the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the British Society for Haematology (BSH) [5,19,21] distinguish between patients with ≤ 3.5 points according to IPSS-R (low-risk MDS) and those with > 3.5 points according to IPSS-R (high-risk MDS) with regard to the respective treatment algorithm. The treatment algorithm provides for treatment of anaemia only in low-risk MDS. Against this background, patients with intermediate risk > 3.5 points according to IPSS-R are not comprised by the research question of the G-BA for the present benefit assessment (see Table 4 in Chapter I 2). In the relevant subpopulation (N = 289) with patients with sEPO levels < 200 U/L, 27 (18.6%) patients in the intervention and 20 (13.9%) patients in the comparator arm had an intermediate risk at baseline. However, the company's dossier does

not provide any information on the score of the patients with intermediate risk. It is therefore unclear how many patients had a score of > 3.5 according to IPSS-R and are therefore not comprised by the G-BA's research question. In addition, the international guidelines of the NCCN, the ESMO and the BSH [5,19,21] do not recommend treatment with epoetin alfa, as was used in the comparator arm of the COMMANDS study, for patients with intermediate risk > 3.5 points. In contrast, azacitidine or, if suitable for the patient, an allogeneic stem cell transplant is recommended, for example. However, since the COMMANDS study only included patients with < 5% blasts in bone marrow, for whom a low risk can be assumed according to the DGHO guideline [4], taking into account the WHO classification, it is assumed that potential undertreatment affected at most only a few patients in the COMMANDS study. Overall, this does not lead to uncertainties in the interpretability of the results of the COMMANDS study.

Data cut-offs

To date, 4 data cut-offs have been performed for the ongoing COMMANDS study:

- 1st data cut-off on 16 September 2020: prespecified interim analysis for futility after approx. 105 patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely
- 2nd data cut-off on 31 August 2022: interim analysis for superiority after approx. 300 patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely (implemented with amendment 4.0 to the study protocol [31 March 2022])
- 3rd data cut-off on 31 March 2023: prespecified primary analysis after all patients had completed the first 24 weeks of study treatment or had discontinued treatment prematurely
- 4th data cut-off on 22 September 2023: prespecified follow-up analysis after all patients had completed the first 48 weeks of study treatment or had discontinued treatment prematurely

According to the planning of the study, the end of the COMMANDS study is planned when the last patient has completed follow-up or has discontinued the study, or when the last data of the last patient required for the prespecified primary, secondary and/or exploratory analyses have been recorded, whichever occurs later. According to the information provided by the company in Module 4 D of the dossier, the end of the study is expected in the 4th quarter of 2027.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: luspatercept vs. epoetin alfa

Study Outcome category Outcome	Planned follow-up observation
COMMANDS	
Mortality	
Overall survival	Up to 3 years after the last dose or 5 years after the first dose of study medication (whichever occurred later), withdrawal of consent, death, or lost to follow-up
Morbidity	
Transfusion independence	Up to 8 weeks after the last dose of study medication or until the EOT visit[a] (whichever occurred later)[b]
Symptoms (EORTC QLQ-C30)	Until the EOT visit[a]
Health-related quality of life	
(EORTC QLQ-C30, FACT-An)	Until the EOT visit[a]
Side effects	
All outcomes in the side effects category	Up to 42 days after the last dose of study medication[c]

a. The EOT visit should be carried out as soon as possible after the decision to discontinue treatment has been made. If treatment was discontinued at a regular study visit, all measurements scheduled at the end of treatment should have been completed at this time. The EOT visit could also take place as part of the 42-day follow-up visit, provided that the patient completed treatment at the 42-day follow-up visit (± 7 days).
b. With amendment 5.0 to the study protocol (24 August 2023), the duration of the follow-up observation of transfusions was extended to 24 months after the last dose of study medication or until the end of the first subsequent therapy, whichever occurred first. This protocol change was only made after the data cut-off for the primary analysis (31 March 2023).
c. SAEs that occurred at a later time point and were suspected to be causally related to the study medication were recorded beyond this period.

EORTC: European Organisation for Research and Treatment of Cancer; EOT: end of treatment;
QLQ-C30: Quality of Life Questionnaire-Core 30; FACT-An: Functional Assessment of Cancer Therapy-Anaemia;
RCT: randomized controlled trial; SAE: serious adverse event

The observation periods for the outcomes of morbidity, health-related quality of life and side effects are systematically shortened because they were recorded only for the period of treatment with the study medication (plus 42 days for side effects and 8 weeks for transfusion independence). However, drawing a reliable conclusion on the total study period would require obtaining data regarding these outcomes throughout the entire period, as was done for survival.

Data cut-offs used by the company and analysis periods presented

In Module 4 D of the dossier, the company presented results from the COMMANDS study based on the 3rd data cut-off of the primary analysis (31 March 2023) or on the 4th data cut-off of the prespecified follow-up analysis (22 September 2023), depending on the outcome. For the outcomes of overall survival and transfusion independence, the company presented results based on the data cut-off of 22 September 2023. For the outcomes on symptoms, health-related quality of life, and side effects, the company presented results based on the data cut-off of 31 March 2023. For the outcomes in the side effects category – with the exception of AEs of special interest – the company also presented descriptive results based on the data cut-off of 22 September 2023.

In Module 4 D of the dossier, the company considered different analysis periods for the ongoing COMMANDS study, depending on the outcome:

- Analysis period of the primary treatment phase (Weeks 1 to 24): for the outcomes of transfusion independence and on symptoms, health-related quality of life, and side effects
- Analysis periods of the treatment phase from Week 1 to Week 36 or Week 1 to Week 48 (i.e. including continued treatment after Week 25 in the case of evidence of clinical benefit and absence of disease progression): for the outcome of transfusion independence
- Analysis period of the entire treatment phase (i.e. including continued treatment after Week 25 with evidence of clinical benefit and absence of disease progression): for the outcomes of transfusion independence, as well as on symptoms, health-related quality of life (descriptive), and side effects (with the exception of AEs of special interest; descriptive)
- Analysis over the entire course of the study until the latest data cut-off: for the outcome of overall survival

In Module 4 D, the company used analyses on the basis of Weeks 1 to 24 to derive the added benefit for the outcomes in the categories of morbidity, health-related quality of life and side effects, irrespective of the underlying data cut-off. This approach used by the company is appropriate. This is explained below.

After Week 25 – after completion of the primary treatment phase – treatment with the study medication was continued during the continued treatment phase in patients with evidence of clinical benefit and absence of disease progression. As the observation period in the COMMANDS study was linked to the end of treatment for all outcomes in the categories of morbidity, health-related quality of life and side effects (see Table 8), these outcomes were

recorded after Week 25 – with the exception of the planned follow-up observation after the end of treatment – only in patients with evidence of clinical benefit and absence of MDS progression on Day 169 (Week 25) and then every 24 weeks. No information is available on how many patients met the criteria for continued treatment at the Day 169 (Week 25) visit or continued treatment with the study medication after Week 25. However, the available data on treatment duration until the data cut-off on 22 September 2023 show that the median treatment duration in the relevant subpopulation was longer in the intervention arm (81.1 weeks) than in the comparator arm (63.5 weeks). Since the observation period for the outcomes in the categories of morbidity, health-related quality of life and side effects was linked to the treatment duration in each case, it is assumed that the observation periods also differ between the study arms (for details, see the following text section with information on the course of the study). This assumption is supported by the data available for the total study population on the observation periods in the intervention versus comparator arm until the data cut-off on 22 September 2023 (see Table 10). In addition, the response rates for the patient-reported outcomes on symptoms and health-related quality of life at the dose visits already fell below 70% in Weeks 1 to 24. Corresponding to the company's approach, the present benefit assessment uses analyses over the period of the primary treatment phase (Weeks 1 to 24) with comparable follow-up observation periods for all outcomes in the categories of morbidity, health-related quality of life, and side effects.

When using the analyses over the period from Week 1 to Week 24, it is not relevant whether the 3rd data cut from 31 March 2023 or the 4th data cut from 22 September 2023 is considered. This is due to the fact that by the time of the 3rd data cut-off on 31 March 2023, all patients had completed or prematurely discontinued the primary treatment phase (Weeks 1 to 24), so that when looking at the later 4th data cut-off on 22 September 2023, there were no further recordings for the period of Weeks 1 to 24. The 3rd data cut-off from 31 March 2023 presented by the company was used for the outcomes on symptoms, health-related quality of life, and side effects. For the outcome of transfusion independence, the 4th data cut-off from 22 September 2023 presented by the company was used. This corresponds to the data cut-offs presented by the company for the respective outcomes.

Deaths were recorded independently of the end of treatment. Therefore, overall survival on the basis of a time-to-event analysis at the 4th data cut-off on 22 September 2023 was used as outcome in the category of mortality for the present benefit assessment.

Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics in the subpopulation of the COMMANDS study with sEPO levels < 200 U/L, which is the relevant subpopulation for the benefit assessment.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study **Characteristic** **Category**	**Luspatercept** **N = 145**	**Epoetin alfa** **N = 144**
COMMANDS		
Age [years], mean (SD)	74 (9)	74 (10)
Sex [F/M], %	42/58	49/51
Region, n (%)		
North America	8 (6)	8 (6)
Europe	90 (62)	89 (62)
Asia	15 (10)	20 (14)
Rest of the world	32 (22)	27 (19)
Disease duration: time between first diagnosis and randomization [months], median [Q1; Q3]	6.5 [2.0; 29.6]	4.2 [1.2; 16.6]
Risk group according to IPSS-R, n (%)		
Very low	13 (9)	15 (10)
Low	103 (71)	107 (74)
Intermediate	27 (19)	20 (14)
High	1 (< 1)	0 (0)
Missing	1 (< 1)	2 (1)
Ring sideroblast status[a], n (%)		
With ring sideroblasts (+)	106 (73)	101 (70)
Without ring sideroblasts (-)	39 (27)	42 (29)
Missing	0 (0)	1 (< 1)
SF3B1 mutation, n (%)		
Yes	94 (65)	80 (56)
No	50 (34)	58 (40)
Missing	1 (< 1)	6 (4)
Serum ferritin [µg/L], median [Q1; Q3]	ND[b]	ND[b]
Haemoglobin[c] [g/dL], mean (SD)	7.7 (0.8)	7.7 (0.9)
Transfusion burden, n (%)		
Packed red blood cell units per 8 weeks[d]		
Mean (SD)	3.1 (1.5)	3.0 (1.4)
≥ 4 units	47 (32)	48 (33)
< 4 units	98 (68)	96 (67)
Pretreatment with iron chelators, n (%)	ND[e]	ND[e]
Treatment discontinuation, n (%)[f]		
In Weeks 1–24[g]	15 (10)	24 (17)
Study period until data cut-off 22 Sep 2023[h]	86 (59)	114 (80)

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study Characteristic Category	Luspatercept N = 145	Epoetin alfa N = 144
Study discontinuation, n (%)		
In Weeks 1–24[i]	5 (3)	13 (9)
Study period until data cut-off 22 Sep 2023[j]	60 (41)	69 (48)

a. Definition of patients with ring sideroblasts (+) according to WHO criteria 2016 [15]: ring sideroblasts ≥ 15% of erythroid precursors in bone marrow, or ≥ 5% if a SF3B1 mutation is present.
b. Data on serum ferritin [µg/L] for the total study population in the intervention vs. comparator arm (182 vs. 181), median [Q1; Q3]: 623.0 [12.4; 3170.0] vs. 650.0 [39.4; 6960.5].
c. Defined as the lowest Hb level within 56 days prior to the first dose of study medication based on measurements from the central laboratory, local laboratory or documented pre-transfusion Hb levels.
d. Number of transfused packed red blood cell units in the 8-week period prior to the first dose of study medication.
e. Information on prior therapy with iron chelators for the total study population in the intervention vs. comparator arm (182 vs. 179), drug n (%): deferasirox 11 (6) vs. 8 (4), deferoxamine 1 (< 1) vs. 0 (0).
f. Number (%) of patients who completed 24 weeks of treatment in the intervention vs. comparator arm: 130 (90) vs. 118 (83). Number (%) of patients still under treatment in the intervention vs. comparator arm at the time of the data cut-off on 22 September 2023: 59 (41) vs. 29 (20).
g. Common reasons for treatment discontinuation in the intervention arm vs. comparator arm in Weeks 1 to 24 were the following (percentages based on randomized patients): withdrawal of consent (3% vs. 3%), lack of efficacy (2% vs. 3%), death (1% vs. 3%).
h. Common reasons for treatment discontinuation in the intervention arm vs. comparator arm until the data cut-off on 22 September 2023 were the following (percentages based on randomized patients): lack of efficacy (19% vs. 38%), withdrawal of consent (9% vs. 13%), death (9% vs. 9%).
i. Common reasons for study discontinuation in the intervention arm vs. comparator arm in Weeks 1 to 24 were the following (percentages based on randomized patients with sEPO levels < 200 U/L at baseline): death (2% vs. 4%), withdrawal of consent (1% vs. 3%).
j. Common reasons for study discontinuation in the intervention arm vs. comparator arm until the data cut-off on 22 September 2023 were the following (percentages based on randomized patients with sEPO levels < 200 U/L at baseline): death (23% vs. 23%), withdrawal of consent (10% vs. 17%), discontinuation by sponsor (4% vs. 2%).

F: female; IPSS-R: International Prognostic Scoring System-Revised; M: male; n: number of patients in the category; N: number of randomized patients with sEPO levels < 200 U/L at baseline; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; sEPO: serum erythropoietin; SF3B1: splicing factor 3b subunit 1; WHO: World Health Organization

The patient characteristics of the relevant subpopulation are largely balanced between the 2 treatment arms. The mean age of the patients was 74 years; 42% of the patient population in the intervention arm and 49% in the comparator arm were female. The majority (62%) of patients came from Europe. The majority of patients had a low risk according to IPSS-R (71% and 74%) and ring sideroblasts according to WHO 2016 criteria (73% and 70%). The average Hb value at baseline was 7.7 g/dL. The average packed red blood cell transfusion burden at baseline was ≥ 4 units per 8 weeks in 33% of patients and < 4 units per 8 weeks in 67%.

At the last available data cut-off on 22 September 2023, 59% of patients in the relevant subpopulation in the intervention and 80% in the comparator arm had discontinued treatment with the study medication. The most common reason for treatment discontinuation in both study arms was lack of efficacy.

Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients. The company did not provide any information on the median or mean observation periods for individual outcomes for the relevant subpopulation in the dossier (Module 4 D). Information on the median and mean observation periods for individual outcomes for the total study population – if available – is provided as supplementary information in Table 10 (see corresponding footnotes).

Table 10: Information on the course of the study – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study **Duration of the study phase** **Outcome category**	**Luspatercept** **N[a] = 145**	**Epoetin alfa** **N[a] = 143**
COMMANDS		
Treatment discontinuation (until data cut-off on 22 September 2023), n (%)	86 (59.3)	114 (79.7)
≥ 24 weeks completed	130 (89.7)	118 (82.5)
≥ 48 weeks completed	ND[b]	ND[b]
Treatment duration (primary treatment phase; Weeks 1–24) [weeks]		
Median [Q1; Q3]	24.0 [24.0; 24.0]	24.0 [24.0; 24.0]
Mean (SD)	22.8 (3.9)	21.9 (5.5)
Treatment duration (until data cut-off on 22 September 2023) [weeks]		
Median [Q1; Q3]	64.0 [39.0; 117.7]	48.9 [25.0; 89.9]
Mean (SD)	81.1 (52.6)	63.5 (50.4)
Observation period [weeks]		
Overall survival	ND[c]	ND[c]
Morbidity (transfusion independence, symptoms [EORTC QLQ-C30])	ND[d]	ND[d]
Health-related quality of life (EORTC QLQ-C30, FACT-An)	ND	ND
Side effects	ND[e]	ND[e]

Table 10: Information on the course of the study – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study	**Luspatercept**	**Epoetin alfa**
Duration of the study phase	**N[a] = 145**	**N[a] = 143**
Outcome category		

a. Data are based on all randomized patients who received at least one dose of study medication.
b. Data on the proportion of patients who completed ≥ 48 weeks of treatment until the data cut-off for the primary analysis (31 March 2023), for the total study population in the intervention vs. comparator arm (182 vs. 179), n (%): 101 (55.5) vs. 76 (42.5).
c. Data on the observation period of the overall survival outcome for the total study population in the intervention vs. comparator arm (182 vs. 181) until the data cut-off on 22 September 2023, median [min; max]; mean (SD): 93.1 [5; 220] vs. 88.4 [0; 226]; 100.3 (53.2) vs. 94.8 (52.7); time from randomization to death or last patient contact.
d. Data on the observation period of the outcome of transfusion independence for the total study population in the intervention vs. comparator arm (182 vs. 181), median [min; max]; mean (SD): Weeks 1–24 (data cut-off: 31 March 2023) 24.1 [4; 24] vs. 24.1 [0; 24]; 23.2 (3.3) vs. 21.7 (5.8); until the cut-off on 22 September 2023 62.8 [4; 201] vs. 46.0 [0; 227]; time from the day after the first dose of study medication to the end of treatment visit, start of subsequent MDS therapy or study discontinuation/death, whichever occurred first.
e. Data on the observation period of the side effect outcomes for the total study population (all randomized patients who received at least one dose of study medication) in the intervention vs. comparator arm (182 vs. 179), median [min; max]; mean (SD): Weeks 1–24 (data cut-off: 31 March 2023) 24.0 [4; 24] vs. 24.0 [3; 24]; 23.0 (3.4) vs. 22.0 (5.1); until the cut-off on 22 September 2023 63.1 [4; 220] vs. 45.4 [3; 226]; 76,5 (50,4) vs. 59.3 (46.9); time from the day after the first dose of study medication to the end of treatment visit, start of subsequent MDS therapy or study discontinuation/death, whichever occurred first; the company did not provide any separate data on SAEs, although, in contrast to AEs, the follow-up observation for SAEs was planned for 42 days after the last dose of study medication if they were suspected of being causally related to the study medication; see Table 8.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FACT-An: Functional Assessment of Cancer Therapy-Anaemia; max: maximum; MDS: myelodysplastic syndromes; min: minimum; n: number of patients in the category; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event, SD: standard deviation

In the COMMANDS study, the median and mean treatment duration until the data cut-off on 22 September 2023 was longer in the intervention arm (64.0 weeks and 81.1 weeks) than in the comparator arm (48.9 weeks and 63.5 weeks). Treatment with the study medication after Week 25 was only continued in patients with evidence of clinical benefit and absence of disease progression (see Section I 3.1). However, due to the lack of information, it is unclear how many patients met the criteria for continued treatment at the Day 169 (Week 25) visit or continued treatment with the study medication after Week 25 (see Section I 3.1). The company also did not provide any information for the relevant subpopulation on how many patients completed 48 weeks of study treatment. For the total study population (182 versus 179), this was the case in 101 (55.5%) versus 76 (42.5%) in the intervention versus comparator arm. In the dossier, the company also did not provide any information for the relevant subpopulation on the median or mean observation periods for the individual outcomes. As

the observation periods for the outcomes in the categories of morbidity, health-related quality of life and side effects was linked to the end of treatment (see Table 8), the observation periods differed between the study arms and were shortened compared with the observation period for overall survival, which was recorded over the entire period. When considering the primary treatment phase (Weeks 1 to 24) as the analysis period (see previous text section on analysis periods presented by the company), no relevant difference in observation periods between the study arms is expected, taking into account the treatment discontinuations in Weeks 1 to 24.

Information on subsequent therapies

After discontinuation of the study medication, there were no restrictions regarding subsequent therapies. For the relevant subpopulation with sEPO levels < 200 U/L, the company did not provide any information on the subsequent therapies used in the dossier. The data available for the total study population (see Table 20 in I Appendix B of the full dossier assessment) shows that in both study arms, some of the drugs used as subsequent therapy were not used in compliance with the approval. The use of these drugs appears to be fundamentally justifiable due to the lack of treatment alternatives for patients with MDS. Furthermore, in the total study population, 6 patients in the intervention arm and 20 patients in the comparator arm received subsequent therapy with luspatercept. For patients with ring sideroblasts who had unsatisfactory response to the erythropoietin-based therapy in the comparator arm (patient population of benefit assessment A23-44), luspatercept is an adequate guideline-compliant subsequent therapy [4]. For patients without ring sideroblasts, however, who had unsatisfactory response to the erythropoietin-based therapy in the comparator arm, the administration of luspatercept as a subsequent therapy means treatment switching. Taking into account the proportion of patients who discontinued treatment with the study medication in the Week 1 to 24 period considered here (intervention versus comparator arm: 11% versus 20% of the total study population [182 versus 181]; 10% versus 17% of the relevant subpopulation [145 versus 144]), this has no consequences for the present benefit assessment.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: luspatercept vs. epoetin alfa

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
COMMANDS	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the COMMANDS study is rated as low.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described that, overall, the study results of the COMMANDS study can be assumed to be readily transferable to the German health care context. A total of 60.3% of the included patients came from Europe, which is why the company assumed a sufficiently similar standard of care. It added that the baseline characteristics of the patients included in the COMMANDS study were sufficiently comparable to the characteristics of the patients in the German MDS registry. For example, the median age of the study participants at baseline was 74 years, and slightly more men (55.4%) than women (44.6%) were included in the study, and the median age of patients in the MDS registry was 68 years at first diagnosis, and MDS was also slightly more common in men than in women (58% versus 42%) [22]. In summary, the company presumed sufficient transferability of study results to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - transfusion independence
  - symptoms recorded using the EORTC QLQ-C30
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
  - recorded using the FACT-An
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - thromboembolic events (severe AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 D).

Table 12 shows the outcomes for which data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: luspatercept vs. epoetin alfa

Study	Outcomes								
	Overall survival	Transfusion independence[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30, FACT-An)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Thromboembolic events[c] (severe AEs[b])	Eye disorders (SOC, AEs)
COMMANDS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Defined as proportion of patients without red blood cell transfusion in Weeks 1–24.
b. Operationalized as CTCAE grade ≥ 3; the severity of AEs for which no CTCAE criteria were defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [for explanation, see text section below, side effects]).
c. The AE of interest recorded by the company in the study is considered; for explanations, see following text.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-An: Functional Assessment of Cancer Therapy-Anaemia; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Notes on included outcomes

Transfusion independence

Patient relevance

In Module 4 D of the dossier, the company presented analyses for the outcome of transfusion independence at different transfusion-free periods (≥ 24 weeks, ≥ 48 weeks) and analysis periods (Weeks 1 to 24, Weeks 1 to 36, Weeks 1 to 48, Week 1 until the end of treatment with the study medication).

For patients in the present therapeutic indication, long-term or sustainable independence of transfusions while maintaining a defined minimum Hb level is a primary treatment goal, with the aim of controlling anaemia and anaemia-related symptoms while at the same time avoiding transfusions. The company justified the patient relevance of the outcome in Module 4 D of the dossier with the following 3 aspects in particular:

- Every packed red blood cell transfusion is associated with the risk of acute and delayed side effects, such as allergic reactions and late complications [23,24]. Long-term packed red blood cell transfusions may also lead to secondary iron overload (secondary haemosiderosis) and toxic deposits in various organs, resulting in organ damage or failure and even death, according to the company, and iron overload leads to restrictions

in the patient's health status and quality of life and is also associated with a deterioration in survival prognosis.

- It added that transfusion therapy with packed red blood cells is not able to achieve a sustained, stable correction of Hb levels and therefore no lasting relief of anaemia symptoms, and that
- transfusion therapy is associated with major psychosocial and time-related burdens for patients and is only an inadequate therapeutic measure.

It should be noted that, in general, the aspects of (anaemia-related) symptoms (e.g. fatigue) and quality of life, as well as psychosocial aspects, can and should be represented directly via patient-reported outcomes in clinical trials. The company's argument that late complications (not usually recorded within the scope of the usual study duration) can be prevented by avoiding transfusions is comprehensible per se and avoiding transfusions is considered patient relevant.

Relevant analysis period

When considering the period including the continued treatment phase after Week 25 or the entire course of the study until the latest data cut-off, the treatment durations and the resulting observation periods are different (see Table 10). As a result, a valid interpretation of the results presented by the company on the outcome of transfusion independence is not possible for analysis periods beyond the primary treatment phase (Weeks 1 to 24) (see Section I 3.2, data cut-offs used by the company and analysis periods presented). Transfusion independence of 24 weeks (until the end of the primary treatment phase [Weeks 1 to 24]) is therefore used as the relevant period for the present assessment. Transfusion independence of 24 weeks is generally considered sufficient to be able to presume long-term transfusion independence (transfusion freedom). However, it remains uncertain whether the patients were actually free from red blood cell transfusions beyond the primary treatment phase in all cases and whether secondary complications (organ complications due to secondary haemosiderosis) could actually be avoided to a relevant extent in the patient population concerned here. If there is an added benefit/lesser benefit for this outcome, this must be taken into account when determining the extent.

In addition to the operationalizations described above, in Module 4 D the company also presented results on the primary outcome of the study, transfusion independence for 12 weeks with a concurrent mean Hb increase of ≥ 1.5 g/dL, for the analysis periods of Weeks 1 to 24 (prespecified) and Week 1 to the end of treatment with the study medication (post hoc). However, the 2 components – transfusion independence and Hb increase – are of different importance for patients in this therapeutic indication. As already explained in more detail, transfusion independence is rated as patient relevant. The increase in Hb value, on the

other hand, is not rated as patient relevant, as this is based on a laboratory parameter whose change is not immediately noticeable to the patient. The guidelines also describe that the therapeutic indication for red blood cell transfusion should be based on an assessment of the patient's overall clinical picture and not solely on laboratory parameters (e.g. Hb level) [4,18,19]. The primary outcome of the study is therefore unsuitable for the present benefit assessment. Furthermore, the company presented a post hoc analysis of an operationalization it described as "longest period of transfusion independence of ≥ 24 weeks" in Week 1 until the end of treatment with the study medication. Not all randomized patients were included in this analysis, but only those who achieved transfusion independence of ≥ 24 weeks. Since achieving transfusion independence is a progression parameter, it cannot be assumed that the structural equality between the intervention and comparator arm achieved at the start of the study through randomization will continue to exist in the patients included in the analysis. A randomized comparison is therefore no longer feasible.

Symptoms (EORTC QLQ-C30) and health-related quality of life (EORTC QLQ-C30, FACT-An)

The company's dossier (Module 4 D) contains analyses of symptoms recorded using the EORTC QLQ-C30 and of health-related quality of life recorded using the EORTC QLQ-C30 and FACT-An.

The EORTC QLQ-C30 is a generic instrument that has been validated for the recording of symptoms and health-related quality of life in patients with cancer and can be supplemented by numerous additional modules. In addition, the EORTC QLQ-C30 is the most frequently used instrument in studies in the therapeutic indication of MDS [25]. Since the main symptoms of MDS (e.g. fatigue and [exertional] dyspnoea) are queried via the EORTC QLQ-C30, this instrument is used for the benefit assessment in the present situation.

The EORTC QLQ-C30 (version 3.0) was recorded in the screening phase (35 days before randomization), on the day of the first dose of study medication (Week 1) and then every 6 weeks during the dose visits (Week 7, Week 13, Week 19, etc.), during the visit to decide on further treatment with the study medication on Day 169 (Week 25) and on Day 337 (Week 49), and during the visit at the end of treatment with the study medication.

The FACT-An is a validated instrument for recording health-related quality of life in cancer patients suffering from anaemia and fatigue [26,27]. Content validity is also presumed to be given in the present therapeutic indication [28,29]. The FACT-An consists of the 4 FACT-G subscales (physical, social/family, emotional, and functional wellbeing) as well as an anaemia-specific subscale with 20 items on anaemia (7 items) and fatigue (13 items). A FACT-An total score is formed by adding up the scores of the 5 subscales. The FACT-An total score ranges from 0 to 188, with higher values indicating better quality of life. The FACT-An (version 4.0) was recorded in the screening phase (35 days before randomization), on the day of the first dose of study medication (Week 1), in Week 2 and Week 3, and then every 3 weeks during the

dose visits (Week 4, Week 7, Week 10, etc.), during the visit to decide on further treatment with the study medication on Day 169 (Week 25) and on Day 337 (Week 49), and during the visit at the end of treatment with the study medication.

Analyses presented by the company on the change in the course of the study

In Module 4 D of the dossier, the company presented analyses of the change in the course of the study (Weeks 1 to 24) using a mixed-effects model with repeated measures (MMRM) for symptoms recorded using the EORTC QLQ-C30 and for health-related quality of life recorded using the EORTC QLQ-C30 and FACT-An. These analyses included all recordings from the dose visits up to and including Week 25 Day 1 (4 [EORTC] or 10 [FACT-An] planned time points of recording after the start of the study). These analyses presented by the company are suitable for the present benefit assessment.

Responder and time-to-event analyses prespecified in the planning of the study

According to the planning of the study, in addition to analyses of the change in the course of the study, responder analyses (occurrence of an improvement or deterioration) and time-to-event analyses (time to sustained improvement or confirmed deterioration) were planned for the data cut-off of the interim analysis for superiority (31 August 2022). The company did not present results of these prespecified responder and time-to-event analyses for the relevant data cut-offs of 31 March 2023 and 22 September 2023 in the dossier.

It should be noted that there is a high proportion of missing values (30%) for the EORTC QLQ-C30 on Day 169 (Week 25). It would therefore be necessary to use suitable imputation methods when carrying out responder analyses. The use of suitable imputation methods would also make sense for the FACT-An with 25% missing values on Day 169 (Week 25). Irrespective of this, the predefined response criterion of 7 points for the FACT-An total score in the COMMANDS study corresponds to only 3.7% of the scale range and thus does not meet the specifications of the Institute's *General Methods* [1]. Therefore, responder and time-to-event analyses based on this response criterion would not be suitable for the present benefit assessment. For the time-to-event analyses (time to sustained improvement or confirmed deterioration), it should be noted that the criteria of improvement or deterioration linked to transfusion requirement or discontinuation of study medication are not appropriate in the present therapeutic indication.

Side effects

Severe AEs

In the COMMANDS study, the severity of AEs was classified according to CTCAE, version 4.03. AEs whose severity is not defined according to CTCAE were assessed by the investigator using a 5-point scale as follows:

- Grade 1 – mild: temporary or mild discomfort; no restriction of activity; no medical intervention/therapy required
- Grade 2 – moderate: mild to moderate limitation of activity, some support may be required; no or minimal medical intervention/therapy required
- Grade 3 – severe: notable limitation of activity, usually some support is required; medical intervention/therapy required, hospitalization is possible
- Grade 4 – life-threatening: extreme limitation of activity, major support required; major medical intervention/therapy required, hospitalization or hospice care likely
- Grade 5 – fatal: the event is fatal

Due to a sufficient similarity between the 5 criteria selected by the company and the 5 generic CTCAE criteria [30], this approach has no consequences for the benefit assessment.

With the dossier (Module 4 D), the company presented analyses for the overall rate of SAEs, severe AEs and discontinuations due to AEs that do not take into account events attributable to the underlying disease. The company excluded all events with the Preferred Term (PT) myelodysplastic syndrome. The company's approach is appropriate. According to the company, no further PTs were identified for which it can be assumed with sufficient certainty that they were attributable to the underlying disease. However, 5.5% of patients in the comparator arm and 7.7% in the intervention arm of the COMMANDS study, had the PT anaemia as AE, which can be presumed to be attributable to the underlying disease (see Table 21 of the full dossier assessment).

Thromboembolic events

Thromboembolic events are relevant AEs in the present therapeutic indication. The dossier contains analyses of thromboembolic events in the context of AEs of interest, which were in principle planned to be recorded in the COMMANDS study. However, the operationalization of the respective AEs of interest was not prespecified. In such a situation, it is generally appropriate to use established constructs such as Standardized Medical Dictionary for Regulatory Activities Queries (SMQs) if they adequately reflect the content of the AE of interest. In Module 4 D, the company based its analyses of thromboembolic events on a combination of the narrow scope of the SMQ embolic and thrombotic events and the broad scope of the SMQ thrombophlebitis. The company excluded all device-associated PTs as well as the PTs transient ischaemic attack and transient blindness. The company did not provide a rationale for its approach. The consideration of a post hoc defined combination of individual SMQs and exclusion of PTs is not appropriate, as selective reporting cannot be ruled out. For the present benefit assessment, the analyses on severe (CTCAE grade ≥ 3) thromboembolic events presented in Module 4 D can nevertheless be used. This is explained below.

In principle, the sole consideration of the SMQ embolic and thrombotic events would be a sufficiently comprehensive operationalization of thromboembolic events. However, the clinical study report (CSR) (total study population) shows that the only 2 occurred PTs (thrombosis and deep vein thrombosis) from the SMQ thrombophlebitis, which were included in the analyses of the company on the AE of interest, are also part of the SMQ embolic and thrombotic events. The exclusion of all device-associated PTs appears meaningful in terms of content. Each of the PTs transient ischaemic attack and transient blindness, which were also excluded by the company, only occurred in a maximum of one patient (total study population).

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: luspatercept vs. epoetin alfa

Study	Study level	Outcomes								
		Overall survival	Transfusion independence[a]	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30, FACT-An)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Thromboembolic events[c] (severe AEs[b])	Eye disorders (SOC, AEs)
COMMANDS	L	L	H[d]	H[e]	H[e]	L	L	H[d]	L	H[d]

a. Defined as proportion of patients without red blood cell transfusion in Weeks 1–24.
b. Operationalized as CTCAE grade ≥ 3; the severity of AEs for which no CTCAE criteria were defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [for explanation, see Section I 4.1, side effects]).
c. The AE of interest recorded by the company in the study is considered; for explanations, see Section I 4.1.
d. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue.
e. Lack of blinding in subjective recording of outcomes, decreasing response rates, which in some cases differ between the arms, as well as unclear handling of late recordings in the analysis; see following text section.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-An: Functional Assessment of Cancer Therapy-Anaemia; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias of the results for the outcomes of overall survival, SAEs, severe AEs, and thromboembolic events is rated as low.

For the outcomes of transfusion independence, discontinuation due to AEs and eye disorders (SOC, AEs), the risk of bias is rated as high due to the lack of blinding in subjective recording of outcomes or subjective decision to discontinue.

There is also a high risk of bias of the results for the outcomes of symptoms (recorded using the EORTC QLQ-C30) and health-related quality of life (recorded using the EORTC QLQ-C30 and the FACT-An). The reasons for this are the lack of blinding in subjective recording of outcomes and the decreasing response rates, which in some cases differ between the arms. In addition, the company did not provide any specific information on how the recordings during the dose visits were assigned in terms of time in the event of dose delays. Based on the available information, it is assumed that the delayed recordings were assigned to the actually planned time point of the visit. However, there is no information available on how often this was the case in the relevant subpopulation and how long the delays were. Recording could have been assigned to a notably different point in time, which can cause bias.

I 4.3 Results

Table 14, Table 15 and Table 16 summarize the results of the comparison of luspatercept versus epoetin alfa in adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs, severe AEs and discontinuations due to AEs at SOC and PT level are presented in I Appendix D of the full dossier assessment. I Appendix E of the full dossier assessment contains a supplementary presentation of results for the outcome of overall hospitalization.

Table 14: Results (mortality) – RCT, direct comparison: luspatercept vs. epoetin alfa

Study Outcome category (data cut-off) Outcome	Luspatercept		Epoetin alfa		Luspatercept vs. epoetin alfa
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
COMMANDS					
Mortality (data cut-off 22 September 2023)					
Overall survival	145	NA [37.2; NC] 34 (23.4)	144[b]	46.7 [42.4; NC] 33 (22.9)[b]	0.97 [0.60; 1.59]; 0.907

a. HR and CI: Cox proportional hazards model, p-value: log rank test; each stratified by average transfusion burden (< 4 packed red blood cell units per 8 weeks vs. ≥ 4 packed red blood cell units per 8 weeks) and ring sideroblast status (with ring sideroblasts [+] vs. without ring sideroblasts [-]).

b. According to the company, the analysis was conducted under exclusion of one patient in the comparator arm due to a missing ring sideroblast status. The company took the information on N and n (%) from Module 4 D. However, the number of patients included in the analysis and the number of patients with event based on this population may differ (possibly reduced by the patient with missing ring sideroblast status).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Table 15: Results (morbidity, side effects, dichotomous) – RCT, direct comparison: luspatercept vs. epoetin alfa

Study	Luspatercept		Epoetin alfa		Luspatercept vs. epoetin alfa
Outcome category (analysis period; data cut-off) **Outcome**	**N**	**Patients with event n (%)**	**N[a]**	**Patients with event n (%)[a]**	**RR [95% CI]; p-value[b]**
COMMANDS					
Morbidity (Weeks 1–24[c]; data cut-off 22 September 2023)					
Transfusion independence	145	79 (54.5)	144	55 (38.2)	1.41 [1.10; 1.80]; 0.007
Side effects (Weeks 1–24[c]; data cut-off 31 March 2023)					
AEs (supplementary information)	145	131 (90.3)	143	117 (81.8)	-
SAEs	145	29 (20.0)	143	32 (22.4)	0.94 [0.60; 1.46]; 0.770
Severe AEs[d]	145	56 (38.6)	143	50 (35.0)	1.13 [0.84; 1.53]; 0.415
Discontinuation due to AEs	145	4 (2.8)	143	5 (3.5)	0.84 [0.23; 3.03]; 0.785
Thromboembolic events (severe AEs)	145	1 (0.7)	143	1 (0.7)	0.96 [0.06; 15.01]; 0.976
Eye disorders (SOC, AEs)	145	23 (15.9)	143	3 (2.1)	7.70 [2.31; 25.69]; < 0.001

a. According to the company, the analysis was conducted under exclusion of one patient in the comparator arm due to a missing ring sideroblast status. The company took the information on N and n (%) from Module 4 D. However, the number of patients included in the analysis and the number of patients with event based on this population may differ (possibly reduced by the patient with missing ring sideroblast status).
b. RR, CI, and p-value: CMH method; stratified by average transfusion burden (< 4 packed red blood cell units per 8 weeks vs. ≥ 4 packed red blood cell units per 8 weeks) and ring sideroblast status (with ring sideroblasts [+] vs. without ring sideroblasts [-]).
c. From the day after the first dose of study medication up to and including Day 169 (transfusion independence) or from the day of the first dose of study medication up to and including Day 168 (side effect outcomes)
d. Operationalized as CTCAE grade ≥ 3; the severity of AEs for which no CTCAE criteria were defined was classified by the investigator using a 5-point scale (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening; grade 5: fatal [for explanation, see Section I 4.1, side effects]).

AE: adverse event; CMH: Cochran-Mantel-Haenszel; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study Outcome category (analysis period; data cut-off) Outcome	Luspatercept			Epoetin alfa			Luspatercept vs. epoetin alfa
	N[a]	Values at baseline mean (SD)	Change in the course of the study Weeks 1–24 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change in the course of the study Weeks 1–24 mean[b] (SE)	MD [95% CI]; p-value[b]
COMMANDS							
Morbidity (Weeks 1–24; data cut-off 31 March 2023)							
Symptoms (EORTC QLQ-C30)[c]							
Fatigue	128	41.1 (23.9)	−4.0 (1.7)	115	46.7 (25.4)	−7.5 (1.8)	3.55 [−0.89; 7.98]; 0.116
Nausea and vomiting	128	3.9 (9.2)	1.3 (0.9)	115	4.7 (12.3)	−0.6 (0.9)	1.94 [−0.30; 4.18]; 0.089
Pain	128	21.4 (24.4)	−2.0 (1.6)	115	20.9 (23.9)	−3.7 (1.7)	1.62 [−2.57; 5.80]; 0.447
Dyspnoea	128	27.1 (28.3)	−3.4 (2.0)	115	31.9 (27.8)	−6.1 (2.1)	2.77 [−2.29; 7.83]; 0.282
Insomnia	128	30.7 (28.9)	−2.9 (2.1)	115	29.2 (29.5)	−4.0 (2.2)	1.16 [−4.22; 6.54]; 0.672
Appetite loss	128	17.7 (26.1)	−2.6 (1.7)	115	18.4 (24.3)	−0.4 (1.8)	−2.24 [−6.56; 2.09]; 0.310
Constipation	128	13.5 (23.5)	−4.1 (1.5)	115	16.1 (25.2)	−2.9 (1.6)	−1.22 [−5.20; 2.76]; 0.547
Diarrhoea	128	5.5 (15.0)	2.5 (1.2)	115	5.0 (13.5)	0.6 (1.3)	1.83 [−1.39; 5.06]; 0.263
Health-related quality of life (Weeks 1–24; data cut-off 31 March 2023)							
EORTC QLQ-C30[d]							
Global health status	128	60.4 (18.0)	2.0 (1.4)	115	59.3 (20.4)	2.1 (1.5)	−0.12 [−3.71; 3.46]; 0.946
Physical functioning	128	68.6 (20.5)	1.7 (1.4)	115	63.1 (21.7)	3.3 (1.5)	−1.61 [−5.19; 1.97]; 0.376
Role functioning	128	72.4 (25.3)	2.3 (1.8)	115	72.2 (25.4)	0.4 (1.9)	1.94 [−2.78; 6.65]; 0.420
Emotional functioning	128	77.3 (19.2)	3.5 (1.4)	115	73.0 (20.8)	4.5 (1.4)	−1.08 [−4.62; 2.47]; 0.550
Cognitive functioning	128	79.6 (22.4)	2.8 (1.3)	115	79.1 (22.3)	1.2 (1.4)	1.56 [−1.84; 4.97]; 0.366
Social functioning	128	82.7 (20.2)	−1.2 (1.6)	115	79.5 (22.2)	0.4 (1.7)	−1.61 [−5.86; 2.65]; 0.458

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: luspatercept vs. epoetin alfa (multipage table)

Study Outcome category (analysis period; data cut-off) Outcome	Luspatercept			Epoetin alfa			Luspatercept vs. epoetin alfa
	N[a]	Values at baseline mean (SD)	Change in the course of the study Weeks 1–24 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change in the course of the study Weeks 1–24 mean[b] (SE)	MD [95% CI]; p-value[b]
FACT-An[e]							
Total score	134	128.8 (25.3)	3.8 (1.1)	131	122.4 (27.3)	3.8 (1.1)	−0.01 [−2.93; 2.91]; 0.995
Physical wellbeing	134	22.1 (4.3)	0.3 (0.2)	131	21.4 (4.9)	0.5 (0.2)	−0.22 [−0.78; 0.33]
Social/family wellbeing	134	19.7 (5.2)	0.3 (0.3)	131	18.9 (5.5)	−0.4 (0.3)	0.68 [−0.00; 1.36]
Emotional wellbeing	134	17.4 (4.3)	1.1 (0.2)	131	17.1 (4.3)	0.5 (0.2)	0.52 [0.03; 1.00]
Functional wellbeing	134	16.3 (5.5)	0 (0.3)	131	14.9 (5.4)	−0.1 (0.3)	0.08 [−0.56; 0.72]
Anaemia-specific subscale	134	53.3 (13.4)	2.2 (0.6)	131	50.1 (15.2)	3.0 (0.6)	−0.73 [−2.26; 0.79]

a. Number of patients taken into account in the effect estimation; baseline values may rest on different patient numbers.
b. Mean and SE (per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for mean transfusion burden (< 4 packed red blood cell units per 8 weeks vs. ≥ 4 packed red blood cell units per 8 weeks) and ring sideroblast status (with ring sideroblasts [+] vs. without ring sideroblasts [-]); based on all recordings from the dose visits up to and including Week 25 Day 1. The effect represents the difference in the changes (from baseline) averaged over the course of the study Weeks 1–24 between the treatment groups.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range: 0 to 100).
d. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
e. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 188).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT-An: Functional Assessment of Cancer Therapy-Anaemia; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Based on the available information, at most indications of an added benefit can be determined for the outcomes of overall survival, SAEs, severe AEs, and thromboembolic events (severe AEs). Due to the high risk of bias (see Section I 4.2), at most hints, e.g. of added benefit, can be determined for the outcomes of transfusion independence, discontinuation due to AEs, eye disorders (SOC, AEs) and the outcomes on symptoms (recorded using the EORTC QLQ-C30) and health-related quality of life (recorded using the EORTC QLQ-C30 and FACT-An).

Mortality

Overall survival

For the outcome of overall survival, there was no statistically significant difference between treatment groups up to the 4th data cut-off on 22 September 2023. There is no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion independence

Over the primary treatment phase (Weeks 1 to 24), a statistically significant difference was found in favour of luspatercept in comparison with the ACT for the outcome of transfusion independence. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. There is no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Symptoms (recorded with the EORTC QLQ-C30)

No statistically significant difference between treatment groups was shown for any of the following outcomes during the primary treatment phase (Weeks 1 to 24): fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, and diarrhoea (recorded using EORTC QLQ-C30). There is no hint of an added benefit of luspatercept in comparison with the ACT for any of them; an added benefit for these outcomes is therefore not proven.

Health-related quality of life (recorded with EORTC-QLQ-C30, FACT-An)

For health-related quality of life, no statistically significant difference between treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning (recorded using the EORTC QLQ-C30) and for the FACT-An over the primary treatment phase (Weeks 1 to 24). There is no hint of an added benefit of luspatercept in comparison with the ACT for any of them; an added benefit for these outcomes is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs for the primary treatment phase (Weeks 1 to 24). For each of them, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm for these outcomes is therefore not proven.

Thromboembolic events (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of thromboembolic events (severe AEs) for the primary treatment phase (Weeks 1 to 24). There is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Eye disorders (AEs)

Over the primary treatment phase (Weeks 1 to 24), a statistically significant difference was found to the disadvantage of luspatercept in comparison with the ACT for the outcome of eye disorders (AEs). There is a hint of greater harm from luspatercept in comparison with the ACT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (≤ 64 years versus 65 to 74 years versus ≥ 75 years)
- sex (female versus male)
- transfusion burden at baseline (number of packed red blood cell transfusions/8-week period before the first dose of study medication) (< 4 units vs. ≥ 4 units)
- ring sideroblast status (with ring sideroblasts [+] versus without ring sideroblasts [-])

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results in the dossier do not reveal any effect modifications. In the dossier, the company did not present any subgroup analyses for the patient-relevant outcome of thromboembolic events (severe AEs), for which, however, overall (at least) one event occurred in only 2 patients of the relevant subpopulation, and the outcome of hospitalization, presented as supplementary information in the present benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Determination of outcome category for the outcome of transfusion independence

It cannot be inferred from the dossier whether the following morbidity outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Transfusion independence

Information on the assignment to the severity category is insufficient for the outcome of transfusion independence. The outcome of transfusion independence was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: luspatercept vs. epoetin alfa (multipage table)

Outcome category **Outcome**	**Luspatercept vs. epoetin alfa** **Median time to event (months) or proportion of events (%) or mean change in the course of the study** **Weeks 1–24** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. 46.7 months HR: 0.97 [0.60; 1.59]; p = 0.907	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Transfusion independence	54.5% vs. 38.2% RR: 1.41 [1.10; 1.80] RR: 0.71 [0.56; 0.91][c]; p = 0.007	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Symptoms (EORTC QLQ-C30)		
Fatigue	−4.0 vs. −7.5 MD: 3.55 [−0.89; 7.98]; p = 0.116	Lesser/added benefit not proven
Nausea and vomiting	1.3 vs. −0.6 MD: 1.94 [−0.30; 4.18]; p = 0.089	Lesser/added benefit not proven
Pain	−2.0 vs. −3.7 MD: 1.62 [−2.57; 5.80]; p = 0.447	Lesser/added benefit not proven
Dyspnoea	−3.4 vs. −6.1 MD: 2.77 [−2.29; 7.83]; p = 0.282	Lesser/added benefit not proven
Insomnia	−2.9 vs. −4.0 MD: 1.16 [−4.22; 6.54]; p = 0.672	Lesser/added benefit not proven
Appetite loss	−2.6 vs. −0.4 MD: −2.24 [−6.56; 2.09]; p = 0.310	Lesser/added benefit not proven
Constipation	−4.1 vs. −2.9 MD: −1.22 [−5.20; 2.76]; p = 0.547	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: luspatercept vs. epoetin alfa (multipage table)

Outcome category **Outcome**	**Luspatercept vs. epoetin alfa** **Median time to event (months) or proportion of events (%) or mean change in the course of the study** **Weeks 1–24** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Diarrhoea	2.5 vs. 0.6 MD: 1.83 [−1.39; 5.06]; p = 0.263	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Global health status	2.0 vs. 2.1 MD: −0.12 [−3.71; 3.46]; p = 0.946	Lesser/added benefit not proven
Physical functioning	1.7 vs. 3.3 MD: −1.61 [−5.19; 1.97]; p = 0.376	Lesser/added benefit not proven
Role functioning	2.3 vs. 0.4 MD: 1.94 [−2.78; 6.65]; p = 0.420	Lesser/added benefit not proven
Emotional functioning	3.5 vs. 4.5 MD: −1.08 [−4.62; 2.47]; p = 0.550	Lesser/added benefit not proven
Cognitive functioning	2.8 vs. 1.2 MD: 1.56 [−1.84; 4.97]; p = 0.366	Lesser/added benefit not proven
Social functioning	−1.2 vs. 0.4 MD: −1.61 [−5.86; 2.65]; p = 0.458	Lesser/added benefit not proven
FACT-An	3.8 vs. 3.8 MD: −0.01 [−2.93; 2.91]; p = 0.995	Lesser/added benefit not proven
Side effects		
SAEs	20.0% vs. 22.4% RR: 0.94 [0.60; 1.46]; p = 0.770	Greater/lesser harm not proven
Severe AEs	38.6% vs. 35.0% RR: 1.13 [0.84; 1.53]; p = 0.415	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: luspatercept vs. epoetin alfa (multipage table)

Outcome category **Outcome**	**Luspatercept vs. epoetin alfa** **Median time to event (months) or proportion of events (%) or mean change in the course of the study** **Weeks 1–24** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	2.8% vs. 3.5% RR: 0.84 [0.23; 3.03]; p = 0.785	Greater/lesser harm not proven
Thromboembolic events (severe AEs)	0.7% vs. 0.7% RR: 0.96 [0.06; 15.01]; p = 0.976	Greater/lesser harm not proven
Eye disorders (AEs)	15.9% vs. 2.1% RR: 7.70 [2.31; 25.69] RR: 0.13 [0.04; 0.43][c]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: “considerable”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_L: lower limit of the confidence interval; CI_U: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT-An: Functional Assessment of Cancer Therapy-Anaemia; HR: hazard ratio; MD: mean difference; NA: not achieved; QLQC-30: Quality of Life Questionnaire-Core 30; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of luspatercept in comparison with the ACT

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
–	Non-serious/non-severe side effects ▪ Eye disorders (AEs): hint of greater harm – extent: “considerable”
AE: adverse event	

Overall, there is a negative effect in the category of non-serious/non-severe side effects for the outcome of eye disorders (AEs) with the extent “considerable” and the probability of a “hint”. This negative effect of luspatercept in an outcome in the category of non-serious/non-severe side effects is not considered sufficient to derive lesser benefit of luspatercept compared with the ACT. In summary, the added benefit of luspatercept in comparison with the ACT is not proven for adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy.

The company presented no data in Module 4 E for adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk MDS, without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy. The added benefit of luspatercept in comparison with the ACT is not proven for these patients either.

Table 19 summarizes the result of the assessment of the added benefit of luspatercept in comparison with the ACT.

Table 19: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with transfusion-dependent anaemia due to very low, low and intermediate-risk[d] MDS[b, c] ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy[e]	Individualized treatment[f, g] selected from ▪ erythropoiesis-stimulating agents (erythropoietin alfa/erythropoietin zeta; only in patients with an erythropoietin serum level of < 200 U/L[h]) ▪ transfusion therapy with packed red blood cells as needed in combination with chelation therapy ▪ lenalidomide (only for patients with an isolated 5q deletion if other treatment options are insufficient or inappropriate) taking into account the erythropoietin serum level, cytogenetics and prior therapy	Patients ▪ who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy[e]: added benefit not proven[i] ▪ without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapye: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Patients with hypocellular MDS are not taken into account in the determination of the ACT by the G-BA.
c. According to the G-BA, patients with MDS with del(5q) mutation are included in the therapeutic indication.
d. According to the G-BA, it is assumed that patients with very low, low or intermediate risk (up to 3.5 points) according to IPSS-R are included in the therapeutic indication.
e. It is assumed that the patients are in need of treatment and are not eligible for an allogeneic stem cell transplant at the time of therapy.
f. It should be possible to adapt the study medication/concomitant medication to the patient's individual needs in both study arms. A therapy adjustment can include both dosage adjustments and therapy changes if existing symptoms worsen.
g. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
h. According to the G-BA, and in compliance with the approval, erythropoiesis-stimulating agents are determined as ACT only for patients with a serum epoetin level of < 200 U/L as part of individualized therapy.
i. No patients with MDS del(5q), MDS unclassifiable (MDS-U) or secondary MDS were included in the COMMANDS study. It remains unclear whether the observed effects are transferable to patients with MDS del(5q), MDS unclassifiable (MDS-U) or secondary MDS. In addition, it remains unclear whether the observed effects of the subpopulation of the COMMANDS study relevant for the benefit assessment with sEPO levels < 200 U/L can be transferred to patients with sEPO levels ≥ 200 U/L in the present therapeutic indication.

del(5q): deletion of the q-arm of chromosome 5; G-BA: Federal Joint Committee; IPSS-R: International Prognostic Scoring System-Revised; MDS: myelodysplastic syndromes; MDS-U: MDS unclassifiable; sEPO: serum erythropoietin

The assessment described above deviates from that of the company, which in its dossier (Module 4 D) used the entire study population of the COMMANDS study. The company derived a hint of considerable added benefit of luspatercept compared with the ACT for

patients with ring sideroblasts who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy. According to the company's assessment, the added benefit is not proven for patients without ring sideroblasts who have not yet received and who are eligible for erythropoiesis-stimulating agent-based therapy.

For patients without ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy, the assessment of the added benefit described above concurs with that of the company, which presented no data in Module 4 E.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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