Luspatercept (transfusion-dependent beta-thalassaemia)

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 of persons concerned was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

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

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ECOG	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
pRBC	packed red blood cells
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form-36 Health Survey Version 2
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TranQoL	Transfusion-dependent Quality of Life Questionnaire

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 15 May 2023.

Research question

The aim of this report is to assess the added benefit of luspatercept in comparison with the appropriate comparator therapy (ACT) in adult patients with anaemia associated with transfusion-dependent beta-thalassaemia.

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 anaemia associated with transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with packed red blood cells (pRBC) as needed in combination with chelation therapy in accordance with the approval, preferably as monotherapy
a. Presented is the ACT specified by the G-BA. b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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

Study pool and study design

The BELIEVE study is used for the benefit assessment. The BELIEVE study is a completed double-blind RCT comparing luspatercept with placebo in adult patients with transfusion-dependent beta-thalassaemia. To be included in the study, patients had to have beta-thalassaemia or haemoglobin E β-thalassaemia documented by means of genotyping. Moreover, patients had to have received 6 to 20 packed red blood cell (pRBC) units in the 24 weeks prior to randomization and had to have no transfusion-free period of > 35 days during this period. Overall, 336 patients were included and randomly allocated in a 2:1 ratio either

to treatment with luspatercept (n = 224) or to placebo (n = 112). Apart from the exceptions described below, treatment with luspatercept in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). The minimum dose of 0.45 mg/kg body weight, which was allowed in the study but did not comply with the SPC, was not used in the double-blind treatment phase of the BELIEVE study and therefore has no consequences for the present benefit assessment. According to the SPC, treatment with luspatercept should moreover be discontinued if patients do not notice a reduction in the transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.25 mg/kg). In the BELIEVE study, no such criterion for discontinuation of the study medication was defined. Data are available on how many patients received the maximum dose (103 of 223 [46%] vs. 72 of 109 [66%] in the intervention vs. the comparator arm; primary data cut-off). However, due to a lack of data, it is unclear how high the proportion of patients is who, after 9 weeks of treatment (3 doses) with the highest dose of the study medication, did not record a reduction in the transfusion burden and still received further treatment. At the data cut-off on 11 May 2018, 2 patients in the intervention arm and 8 patients in the comparator arm had discontinued treatment due to lack of efficacy. This has particular consequences for the luspatercept arm, as it cannot be ruled out that adverse events (AEs) occurring under treatment could have been avoided if treatment had been discontinued early. Overall, this leads to relevant uncertainties in the interpretability of the study results and to a limitation of the certainty of conclusions.

After the last patient included had completed 48 weeks of treatment or had discontinued treatment prematurely, the study was unblinded. Patients in both study arms were then able to receive luspatercept in an open treatment phase. At the investigator's discretion, transfusions of pRBCs were permitted for the treatment of low haemoglobin levels, anaemia-related symptoms or comorbidities in both treatment arms. Chelation therapies could be administered if needed.

Primary outcome of the BELIEVE study was the reduction in transfusion burden, operationalized as the proportion of patients with a reduction in the administered pRBC units by ≥ 33% and by ≥ 2 pRBC units in Week 13 to Week 24 compared to the 12-week interval before randomization.

Risk of bias

The risk of bias across outcomes was rated as low for the study. The risk of bias for the results on all outcomes was rated as low. The certainty of results for the outcome "discontinuation due to AEs" was limited despite a low risk of bias, however.

Summary assessment of the certainty of conclusions

For the BELIEVE study, there are uncertainties regarding the administration of luspatercept in compliance with the SPC. However, it is unclear how high the proportion of patients is who,

after 9 weeks of treatment (3 doses) with the highest dose of the study medication, did not record a reduction in the transfusion burden and still received further treatment. Therefore, based on the results of the BELIEVE study, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

Mortality

All-cause mortality

One death occurred in each of the 2 treatment arms. There was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

With regard to transfusion avoidance, no statistically significant difference between the treatment arms was shown for the proportion of patients who did not require transfusions for ≥ 24 weeks.

Overall, this resulted in no hint of an added benefit of luspatercept in comparison with the ACT for the outcome “transfusion avoidance”; an added benefit is therefore not proven.

Health-related quality of life

Short Form-36 Health Survey Version 2 (SF-36v2) and Transfusion-dependent Quality of Life Questionnaire (TranQoL)

There was no statistically significant difference between the treatment arms for either of the outcomes “SF-36v2” and “TranQoL”. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of luspatercept was shown between the treatment arms for the outcome “serious AEs (SAEs)”. There is a hint of greater harm from luspatercept in comparison with the ACT.

It cannot be ruled out that a relevant proportion of the SAEs that occurred in the luspatercept arm - particularly in the later course of treatment - could have been avoided if treatment had been discontinued early in accordance with the specifications of the SPC. The extent of the observed effect cannot be quantified for these outcomes due to the uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose.

Severe AEs

A statistically significant difference to the disadvantage of luspatercept was shown between the treatment arms for the outcome “severe AEs”. There is a hint of greater harm from luspatercept in comparison with the ACT.

It cannot be ruled out that a relevant proportion of the severe AEs that occurred that in the luspatercept arm - particularly in the later course of treatment - could have been avoided if treatment had been discontinued early in accordance with the specifications of the SPC. The extent of the observed effect cannot be quantified for these outcomes due to the uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome “discontinuation due to AEs”. There is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Bone pain

A statistically significant difference to the disadvantage of luspatercept was shown for the outcome "bone pain (PT, AEs)”. There is a hint of greater harm from luspatercept in comparison with the ACT.

Most of the events occurred early in the course of treatment. The described uncertainty in the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose - is therefore of no consequence for determining the extent of the observed effect for the outcome of bone pain (PT, AEs). The extent of the observed effect can be quantified for this outcome.

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 in comparison with the ACT is assessed as follows:

[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].

In the overall consideration, there were only negative effects for outcomes in the side effects category, in particular hints of non-quantifiable harm for severe and serious AEs of luspatercept versus the ACT. The extent of the observed effects cannot be quantified for these outcomes due to the described uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose. At the same time, it remains unclear in the present indication whether the observed statistically significant differences in the reduction of the transfusion burden, which was given as additional information, mean relevant advantages for luspatercept, even if in the BELIEVE study only individual patients were able to achieve longer-lasting complete transfusion avoidance. For example, 18% of patients in the intervention vs. 1% in the comparator arm achieved a halving of their transfusion burden over ≥ 24 weeks. Patients in the intervention arm achieved an average reduction of approx. 2 pRBC units/24 weeks in the period up to unblinding, while the transfusion burden in patients in the comparator arm remained almost unchanged.

In summary, in this data constellation, the added benefit of luspatercept over the ACT is not proven for adult patients with anaemia associated with transfusion-dependent beta-thalassaemia.

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 anaemia associated with transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with pRBC as needed in combination with chelation therapy in accordance with the approval, preferably as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2020, where the G-BA had determined a non-quantifiable added benefit of luspatercept. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of luspatercept in comparison with the ACT in adult patients with anaemia associated with transfusion-dependent beta-thalassaemia.

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 anaemia associated with transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with pRBC as needed in combination with chelation therapy in accordance with the approval, preferably as monotherapy

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum duration of 24 weeks are 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:

Sources of the company in the dossier:

- study list on luspatercept (status: 3 April 2023)
- bibliographical literature search on luspatercept (last search on 3 April 2023)
- search in trial registries/trial results databases for studies on luspatercept (last search on 4 April 2023)
- search on the G-BA website for luspatercept (last search on 4 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on luspatercept (last search on 24 May 2023); for search strategies, see Appendix I A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

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

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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ACE-536-B-THAL-001 (BELIEVE[c])	Yes	Yes	No	Yes [3-5]	Yes [6,7]	Yes [8]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The BELIEVE study is used for the benefit assessment. The study pool concurs with that of the company. The study is described in the following section.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: luspatercept vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BELIEVE	RCT, double-blind, parallel-group	Adults (> 18 years) with transfusion-dependent[b] beta-thalassaemia ▪ haemoglobin E (HbE)/beta thalassaemia was allowed[c] ▪ haemoglobin S (HbS)/beta-thalassaemia and alpha-thalassaemia was excluded ▪ ECOG PS 0 or 1	Luspatercept[d] (N = 224) placebo[d] (N = 112)	Screening: 12 weeks treatment: 48 weeks[e] follow-up observation: up to 156 days after the last dose of the study medication	65 study centres in Australia, Bulgaria, Canada, France, Greece, Israel, Italy, Lebanon, Malaysia, Taiwan, Thailand, Tunisia, Turkey, United Kingdom, USA 05/2016–01/2021 data cut-offs: ▪ 11 May 2018[g] (primary analysis) ▪ 05 January 2021[h] (final analysis)	Primary: proportion of participants with a reduction in packed red blood cell units by ≥ 33% and by ≥ 2 packed red blood cell units in Weeks 13-24 compared to the 12-week interval before randomization secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Defined as a transfusion requirement of 6-20 packed red blood cell units in the 24 weeks prior to randomization (12 weeks prior to screening [retrospectively] and 12 weeks during screening) and no transfusion-free period of > 35 days during this period.
c. Introduced with Amendment 1 (21 April 2017) to the protocol.
d. Patients could receive packed red blood cells and/or iron chelation therapy if needed.
e. Optional further treatment:

▫ Blinded further treatment with the respective study medication at the physician's discretion until the last patient had completed or discontinued the 48-week treatment phase or until the study was unblinded.

▫ Open-label extension phase: After completion of the 48-week treatment phase by the last patient, the study was unblinded. Thereafter, patients in both treatment arms could receive luspatercept until all patients originally randomized to luspatercept had been treated for a total of 5 years, discontinued treatment or switched to the ACE-536-LTFU-001 rollover study. The unblinded part of the study is not relevant for the present benefit assessment and is not presented below.

f. See Table 8 for outcome-specific information.
g. After (almost) all patients had completed or discontinued the 48-week treatment phase; last visit after 48 weeks of the last patient: 14 May 2018.
h. Date of the last visit of the last patient (end of study); the final analysis, whose analysis period is based on the entire observation period up to the end of the study (including the unblinded study phase), is not relevant for the present benefit assessment and is disregarded below.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Hb: haemoglobin; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: luspatercept versus placebo

Study	Intervention	Comparison
BELIEVE	Luspatercept 1 mg/kg body weight, SC every 3 weeks	Placebo SC every 3 weeks
	▪ Dose increase to a maximum of 1.25 mg/kg body weight in case of insufficient reduction of the transfusion load[a]; maximum total dose: 120 mg ▪ dose reduction by approx. 25% per administration; minimum dose: 0.45 mg/kg body weight if the Hb value increases by > 2.0 g/dL compared to the pre-dose value of the previous cycle, or in the case of treatment-related AEs grade ≥ 3 ▪ discontinuation in case of grade 3 leukocytosis, haematological malignancy, treatment-related AEs (SAEs, grade ≥ 3 AEs with treatment interruption ≥ 15 weeks, > 2 dose reductions due to AEs)	
	Pretreatment <u>allowed</u> ▪ iron chelation therapy if started at least 24 weeks before randomization <u>not allowed</u> ▪ luspatercept or Sotatercept ▪ chronic treatment with anticoagulants < 28 days before randomization ▪ erythropoiesis-stimulating substances and/or hydroxyurea ≤ 24 weeks before randomization ▪ cytotoxic drugs, immunosuppressants ≤ 28 days prior to randomization (antithymocyte globulin or ciclosporin) ▪ chronic treatment with systemic glucocorticoids < 12 weeks before randomization[b] ▪ major surgery ≤ 12 weeks before randomization **concomitant treatment** <u>allowed</u> ▪ transfusion therapy with packed red blood cells[c] and iron chelation therapy ▪ anticoagulants for prophylaxis, platelet aggregation inhibitors, acetylsalicylic acid and low molecular weight heparin ▪ supportive treatment with antibiotics, antimycotics, antivirals and/or supportive nutritional measures <u>not allowed</u> ▪ hydroxyurea ▪ anagrelide ▪ haematopoietic growth factors	

a. Reduction in transfusions compared to the start of the study over ≥ 2 dose cycles < 33%; at the investigator's discretion, a dose increase was also possible with a reduction in transfusions of ≥ 33 to ≤ 50%.
b. Physiological replacement therapy for adrenal insufficiency and individual days with glucocorticoid administration (e.g. to prevent transfusion reactions) were permitted.
c. The administration of packed red blood cells should be delayed by ≥ 7 days and/or the number of transfused packed red blood cells should be reduced by ≥ 1 unit if the pre-transfusion Hb value increases by ≥ 1 g/dl compared to the value in the 24 weeks prior to the 1st dose of the study medication. Overall, transfusions of packed red blood cells were permitted for the treatment of low Hb levels, anaemia-related symptoms or comorbidities at the investigator's discretion.

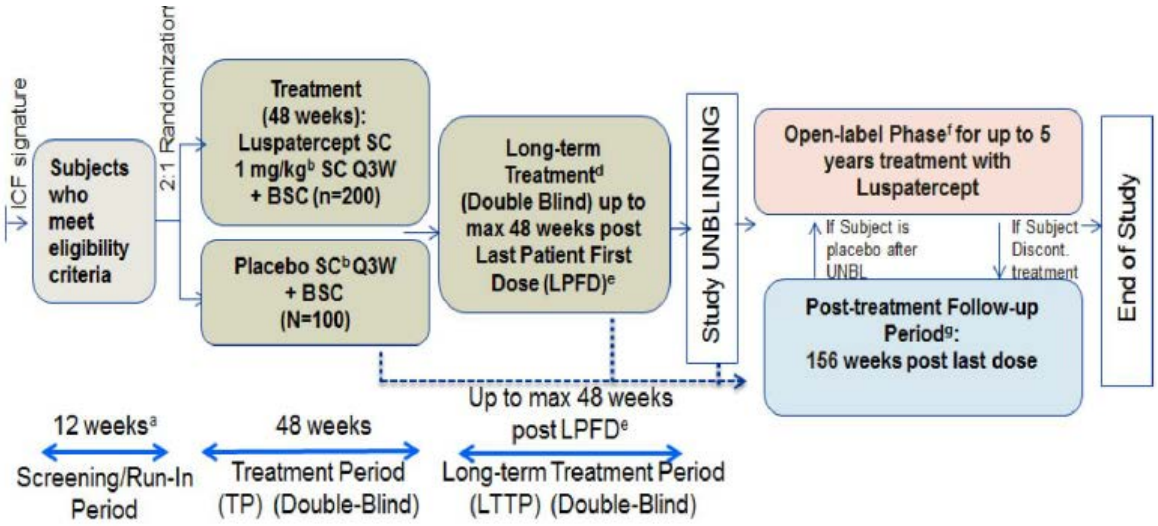
AE: adverse event; Hb: haemoglobin; RCT: randomized controlled trial; SAE: serious adverse event; SC: subcutaneous

The BELIEVE study is a completed double-blind RCT comparing luspatercept with placebo in adult patients with transfusion-dependent beta-thalassaemia.

To be included in the study, patients had to have beta-thalassaemia or haemoglobin E β-thalassaemia documented by means of genotyping. The presence of beta-thalassaemia with mutation and/or multiplication of the alpha-globin gene was allowed. Patients with haemoglobin S/beta-thalassaemia or alpha-thalassaemia (e.g. haemoglobin H disease) were excluded from the study. Moreover, patients had to have received 6 to 20 pRBC units in the 24 weeks prior to randomization and had to have no transfusion-free period of > 35 days during this period. Patients had to be in good general condition at study entry, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The inclusion criteria of the BELIEVE study for the representation of transfusion-dependent beta-thalassaemia are considered sufficient for the present benefit assessment.

Overall, 336 patients were included and randomly allocated in a 2:1 ratio either to treatment with luspatercept (n = 224) or to placebo (n = 112). Randomization was stratified by geographic region (North America and Europe vs. Middle East and North Africa vs. Asia-Pacific).

Figure 1 shows the study design.



[a] Angaben zur Transfusionsabhängigkeit in den 24 Wochen vor Randomisierung sollten verfügbar sein (transfundierte EK-Einheiten, Prätransfusions-Hb)
[b] Dosistitration bis maximal 1,25 mg/kg Körpergewicht
[c] Randomisierung im Verhältnis 2:1 in Luspatercept + BSC versus Placebo + BSC
[d] Patient:innen, die die 48 Wochen der doppelblinden primären Behandlungsphase abgeschlossen hatten, konnten nach ärztlichem Ermessen im Rahmen der doppelblinden Langzeit-Behandlungsphase (long-term treatment period, LTTP) weiter behandelt werden. Patient:innen, die nicht in der LTTP weiter behandelt wurden oder frühzeitig die Behandlung abgebrochen hatten, wurden in der *Posttreatment-Follow-up*-Phase nachbeobachtet.
[e] Maximale Dauer von 48 Wochen nach der ersten Dosis der Studienmedikation des oder der letzten eingeschlossenen Patient:in (last patient first dose, LPFD) bzw. bis zum Abschluss oder Abbruch der primären Behandlungsphase durch alle Patient:innen oder bis zur Entblindung durch das DMC.
[f] Offene Extensionsphase: Patient:innen, die innerhalb der ersten 48 Wochen nach Therapiebeginn keine Protokoll-verletzungen aufwiesen, durften in die offene Extensionsphase übergehen, sofern es keine relevanten Ausschlussgründe gab.
[g] Patient:innen, die die Behandlung abbrachen wurden für insgesamt 156 Wochen (= 3 Jahre) nach der lezten Dosis der Studienmedikation nachbeobachtet.

BSC: *Best Supportive Care* ; DMC: *Data Monitoring Committee*; EK: Erythrozytenkonzentrat; Hb: Hämoglobin; ICF: *Informed Consent Form*; LPFD: *Last Patient First Dose*; LTTP: *Long-term Treatment Period*; Q3W: alle 3 Wochen; s. c.: subkutan; UNBL: *Unblinding*

[a] Information on transfusion dependency in the 24 weeks prior to randomization should be available (transfused EC units, pre-transfusion Hb)
[b] Dose titration up to a maximum of 1.25 mg/kg body weight
[c] Randomization in a ratio of 2:1 in luspatercept + BSC versus placebo + BSC
[d] Patients who completed the 48 weeks of the double-blind primary treatment phase could, at the physician's discretion, continue treatment in the double-blind long-term treatment period (LTTP). Patients who were not treated in the LTTP or who discontinued treatment early were followed up in the *post-treatment follow-up phase*.
[e] Maximum duration of 48 weeks after the first dose of study medication of the last patient included (last patient first dose, LPFD) or until completion or discontinuation of the primary treatment phase by all patients or until unblinding by the DMC.
[f] Open extension phase: Patients who had no protocol violations within the first 48 weeks after the start of treatment were allowed to enter the open extension phase, provided there were no relevant reasons for exclusion.
[g] Patients who discontinued treatment were followed up for a total of 156 weeks (= 3 years) after the last dose of study medication.
BSC: *Best Supportive Care*; DMC: *Data Monitoring Committee*; pRBC: *packed red blood cells*; Hb: *haemoglobin*; ICF: *informed consent form*; LPFD: *last patient first dose*; LTTP: *long-term treatment period*; Q3W: *every 3 weeks*; SC: *subcutaneous*; UNBL: *unblinding*

Figure 1: Study design of the BELIEVE study (Figure of the company)

After the last patient included had completed 48 weeks of treatment or had discontinued treatment prematurely, the study was unblinded. Patients in both study arms were then able to receive luspatercept in an open treatment phase.

Primary outcome of the BELIEVE study was the reduction in transfusion burden, operationalized as the proportion of patients with a reduction in the administered pRBC units by ≥ 33% and by ≥ 2 pRBC units in Week 13 to Week 24 compared to the 12-week interval before randomization.

Uncertainties in the administration of luspatercept in the BELIEVE study

Apart from the exceptions described below, treatment with luspatercept in the intervention arm was in compliance with the specifications of the [9] SPC . The minimum dose of 0.45 mg/kg body weight, which was allowed in the study but did not comply with the SPC, was not used in the double-blind treatment phase of the BELIEVE study and therefore has no consequences for the present benefit assessment. According to the SPC, treatment with luspatercept should moreover be discontinued if patients do not notice a reduction in the transfusion burden after 9 weeks of treatment (3 doses) with the highest dose (1.25 mg/kg). Depending on the respective response, treatment with luspatercept should therefore be discontinued after 15 weeks at the earliest in accordance with the SPC. In the BELIEVE study, no such criterion for discontinuation of the study medication was defined. The company did not address this deviation in its dossier. Data are available on how many patients received the maximum dose (103 of 223 [46%] vs. 72 of 109 [66%] in the intervention vs. the comparator arm; data cut-off: 11 May 2018). However, by the data cut-off on 11 May 2018, the dose had only been reduced again in a few of these patients (5 vs. 1). However, due to a lack of data, it is unclear how high the proportion of patients is who, after 9 weeks of treatment (3 doses) with the highest dose of the study medication, did not record a reduction in the transfusion burden and still received further treatment. At the data cut-off on 11 May 2018, 2 patients in the intervention arm and 8 patients in the comparator arm had discontinued treatment due to lack of efficacy. This has particular consequences for the luspatercept arm, as it cannot be ruled out that AEs occurring under treatment (see Table 14) could have been avoided if treatment had been discontinued early. Overall, this leads to relevant uncertainties in the interpretability of the study results and to a limitation of the certainty of conclusions (see Section I 4.2).

Implementation of the ACT

The G-BA specified a need-based transfusion therapy with pRBC in combination with chelation therapy in accordance with the approval, preferably as monotherapy, as ACT.

According to the guidelines, the clinical situation of the patient and not just the measured haemoglobin value is decisive for determining the indication for transfusion of pRBCs [10,11].

According to the guidelines, iron chelation therapy is indicated if the liver iron concentration exceeds certain threshold values or, if liver iron measurement is not possible, on the basis of the serum ferritin value [10-12].

Patients in the control arm of the BELIEVE study received treatment with placebo. In both treatment arms, transfusions of pRBCs were permitted at the investigator's discretion to treat low haemoglobin levels (compared to the individual haemoglobin threshold [average pre-transfusion haemoglobin level in the 24 weeks prior to the start of treatment with the study medication]), anaemia-related symptoms or comorbidities. Chelation therapies could be administered if needed. 97% of the patients had already received iron chelation therapy before the start of the study, 99% of the patients received iron chelation therapy as concomitant medication as part of the study.

Overall, it is assumed that the implementation of the ACT in the control arm of the BELIEVE study was adequate.

Analyses used for the benefit assessment

A primary analysis of the outcomes on efficacy and side effects was planned for the study for the time when all patients had completed or discontinued the 48-week double-blind treatment phase. The data cut-off for this primary analysis took place on 11 May 2018, the last visit after 48 weeks of the last patient took place on 14 May 2018. The study was unblinded on 1 August 2018. The final data cut-off took place at the end of the study on 5 January 2021 (date of the last visit of the last patient) and thus includes all data between start and unblinding of the study.

In Module 4 A, the company presents analyses on the final data cut-off from 5 January 2021 for all patient-relevant outcomes of the outcome categories of mortality, morbidity, health-related quality of life and side effects, which refer to 2 different points in time:

- Time of analysis: at Week 48.
- Time of analysis: entire observation period until unblinding of the study (1 August 2018)

After 48 weeks of treatment, the patients remained blinded in the study and could continue treatment with the respective study medication at the physician's discretion until the last patient had completed the 48-week treatment phase. The outcomes were recorded beyond Week 48 until the last randomized participant had completed the planned treatment duration of 48 weeks or had discontinued treatment. This study design results in treatment and observation times that vary from patient to patient depending on the time of study entry (see also Figure 1 and Table 8). However, the treatment times are largely comparable between the treatment arms (see Table 10). It can also be assumed that the observation periods for the

individual outcomes are comparable between the study arms (for details, see the following text section on treatment and observation periods).

For the benefit assessment in this chronic disease, the longer observation period until unblinding of the study based on its final data cut-off is considered appropriate. For the patient-reported outcomes (PROs) on health-related quality of life, the company only presented analyses on the pre-specified analysis period at Week 48 in Module 4 A. At Week 48, 92% of patients in the intervention arm and 93% in the comparator arm were still being treated with the study medication; the response rates of the PROs were 82% in each case at this time. After Week 48, the response rates of the respective questionnaires declined (at Week 60: approx. 70% vs. 62%; at Week 72: approx. 54% vs. 41% in the intervention vs. comparison arm). The analyses for the analysis period at Week 48 are therefore used for the PROs.

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 versus placebo

Study **outcome category** **outcome**	**Planned follow-up observation**
BELIEVE	
Mortality	
All-cause mortality[a]	Until 9 weeks after the last dose of the study medication
Morbidity	
Transfusion avoidance	Until 9 weeks after the last dose of the study medication[b]
Health-related quality of life (Sf-36v2, TranQoL)	Until the end of the blinded treatment
Side effects	
All outcomes in the side effects category	Until 9 weeks after the last dose of the study medication

a. Deaths were recorded as AEs.

b. Patients who discontinued the study medication prematurely were followed up until 48 weeks after the first dose or 9 weeks after the last dose, whichever occurred later.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey version 2; TranQoL: Transfusion-dependent Quality of Life Questionnaire

Table 9 shows the patient characteristics of the included study.

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

Study characteristic category	**Luspatercept N[a] = 224**	**Placebo N[a] = 112**
BELIEVE		
Age [years], mean (SD)	32 (11)	32 (10)
Sex [f/m], %	59/41	56/44
Region, n (%)		
North America and Europe	100 (45)	51 (46)
Middle East and North Africa	52 (23)	26 (23)
Asia-Pacific	72 (32)	35 (31)
Beta-thalassaemia genotype, n (%)		
β^0/β^0	68 (30)	35 (31)
Non-β^0/β^0	155 (69)	77 (69)
β^0/β^+	84 (38)[b]	43 (38)[b]
β^+/β^+	64 (29)[b]	32 (29)[b]
β^0/β	4 (2)[b]	2 (2)[b]
β/β	1 (< 1)[b]	0 (0)[b]
Missing	1 (< 1)	0 (0)
Age at onset of transfusion dependency [years][c], median [Q1; Q3]	2 [1; 5]	2 [1; 5]
Transfused packed red blood cell units in the 24 weeks prior to start of treatment[d], mean (SD)	14.5 (3.6)	14.8 (3.5)
Transfused packed red blood cell units in the 24 weeks before the start of treatment, n (%)		
≤ 10 packed red blood cell units	33 (15)	14 (13)
> 10-≤ 15 packed red blood cell units	96 (43)	47 (42)
> 15 packed red blood cell units	95 (42)	41 (46)
Pre-transfusion Hb value in the 24 weeks before the start of the study[e] [g/dL], mean (SD)	9.1 (1.1)	9.1 (1.1)
Serum ferritin level[f] (µg/L), median [Q1; Q3]	1441.3 [759.0; 3118.6]	1301.5 [683.0; 2442.0]
Liver iron concentration at baseline [mg/g d. w.] (by MRI)[g], median [Q1; Q3]	6.1 [2.1; 17.3]	5.1 [2.5; 13.7]
Myocardial iron concentration at baseline [mg/g d. w.] (by MRI)[g], median [Q1; Q3]	0.6 [0.5; 0.8]	0.6 [0.5; 0.8]
Previous splenectomy, n (%)	129 (58)	65 (58)
Previous iron chelation therapy, n (%)	217 (97)	106 (97)
Treatment discontinuation before Week 48, n (%)[i]	22 (10)	16 (14)
Treatment discontinuation before unblinding, n (%)[j]	50 (22)	29 (26)
Study discontinuation, n (%)[k, l]	49 (22)	24 (21)

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

Study characteristic category	Luspatercept N[a] = 224	Placebo N[a] = 112

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. In relation to patients for whom information was available: intervention arm N = 169; comparator arm N = 85.
d. Based on data on transfused packed red blood cells in the 12 weeks prior to screening (retrospective recording) and in the 12 weeks during screening (Day 1 with the first dose with study mediation included).
e. Mean value from all documented Hb values before transfusions in the 24 weeks prior to the first dose of study medication.
f. Mean value from the serum ferritin levels in the 12 weeks before or on the day of the 1st dose of the study medication.
g. Based either on electronic patient report or the derived value from the T2*, R2* or R2 parameter, depending on the technique and software used to determine the liver iron concentration by MRI.
h. If information on [g/dl], MW (SD) was missing, this was derived from the existing myocardial T2* value: 45/(T2*)^1.22.
d. Common reasons for treatment discontinuation in the intervention vs. control arm were: patient decision (5% vs. 9%), AEs (3% vs. 1%).
d. Common reasons for treatment discontinuation in the intervention vs. control arm were: patient decision (13% vs. 13%), AEs (5% vs. 2%).
k. Institute's calculation based on patients who discontinued the study, excluding those who were counted as dropouts due to their switch to the rollover study.
l. The most common reason for study discontinuation in the intervention vs. control arm was: patient decision (17% vs. 14%).

AE: adverse event; d. w.: dry weight; F: female; Hb: haemoglobin; M: male; MRI: magnetic resonance imaging; n: number of patients in the category; N: number of randomized patients; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment arms. The mean age of the patients was 32 years, and most of them were female (59% and 56%). Almost half of the patients came from the regions North America and Europe, around one third from the Asia-Pacific region and around a quarter from the Middle East and North Africa. The median age of the patients at the start of transfusion dependency was 2 years, and around 30% of the patients had a β^0/β^0 genotype. 44% of the patients received > 15 pRBC units in the 24 weeks before the start of treatment. The mean Hb value was 9.1 g/dL. In 58 % of the patients, a splenectomy had been performed earlier in the course of their disease.

Treatment duration and observation period

Table 10 shows patients' mean and median treatment durations and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: luspatercept vs. placebo

Study **duration of the study phase** **outcome category**	**Luspatercept** **N = 224**	**Placebo** **N = 112**
BELIEVE		
Data cut-off 5 January 2021		
Treatment discontinuation, n (%)		
48 weeks of treatment completed, n (%)	202 (90.2)	96 (85.7)
Total blinded treatment phase[a] completed, n (%)	174 (77.7)	83 (74.1)
Treatment duration[b,c] [weeks]		
Median [min; max]	74.9 [2; 105]	73.0 [9; 101]
Mean (SD)	70.1 (19.8)	67.8 (20.0)
Treatment duration [weeks]		
Mortality	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects[d]	ND	ND

a. Further treatment with the respective study medication at the physician's discretion until the last patient had completed or discontinued the 48-week treatment phase or until the study was unblinded.
b. Time from the 1st dose to 20 days after the last dose or until study discontinuation or death.
c. Data refer to the safety population: 203 vs. 109 patients in the intervention arm vs. control arm.
d. AEs were observed from the day of the 1st dose until 9 weeks after the last dose.

AE: adverse event; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median and mean treatment duration is comparable between the study arms. Information on the observation periods of other outcomes is not available. The outcomes on health-related quality of life were recorded during the blinded treatment (no further survey was conducted after premature discontinuation of the study medication), it can therefore be assumed that the observation period is comparable between the study arms. Since the observation period for the outcomes of mortality, morbidity and side effects is linked to the treatment duration (up to 9 weeks after the last dose), it can be assumed that this - as well as the treatment duration - is comparable between the study arms.

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. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treating staff			
BELIEVE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

Based on the results of two multicentre surveys in Germany [13-15], analyses of the University of Ulm [16] and analyses of routine data of the statutory health insurance funds [17] commissioned by the company in the context of the dossier compilation, the company comes to the conclusion that the results of the BELIEVE study are transferable to the German healthcare context.

- The company states that beta-thalassaemia is a congenital disease that manifests itself symptomatically in severe courses as early as childhood and requires transfusion. Patients with severe symptoms, i.e. beta-thalassaemia major, must start transfusion therapy from the age of 1 to 2 years, while patients with severe beta-thalassaemia intermedia often start transfusion dependency at the age of 2 to 6 years; however, transfusion dependency can also occur later in life. The company states that the median age at the start of transfusion therapy in the BELIEVE study was 2 years. According to the company, the study thus reflects the patient population of transfusion-dependent beta thalassaemia patients.
- Due to the genetic cause, the company assumes that female and male patients are equally affected by beta-thalassaemia. Accordingly, women and men were included in the study in roughly equal proportions (42.0% men, 58.0% women). The slightly higher number of women was also reflected in the results of the health insurance data analysis (41.07% men, 58.93% women).
- The company states that the inclusion of patients in the USA, Asia, Africa and Europe meant that primarily white patients (54.2%), but also a significant proportion of Asian patients (34.8%) were included in the study. According to the company, patients with beta-thalassaemia in Germany often have foreign roots: In addition to patients who are

predominantly of white ethnicity, e.g. Italy, Turkey or Greece, many patients are of Asian origin (Middle East, South East Asia, India/Pakistan). The company thus assumes that the patient population in the BELIEVE study is an adequate reflection of the affected ethnic groups in Germany. Furthermore, many study centres in Western countries ensure a healthcare standard comparable to the one in Germany.

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
  - All-cause mortality
- Morbidity
  - Transfusion avoidance
- Health-related quality of life
  - Measured using the TranQoL
  - Measured using the SF-36v2
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Bone pain (PT, AEs)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4A).

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

Table 12: Matrix of outcomes – RCT, direct comparison: luspatercept versus placebo

Study	Outcomes							
	All-cause mortality[a]	Transfusion avoidance[b]	Health-related quality of life (SF-36v2, TranQoL)	SAEs[c]	Severe AEs[c, d]	Discontinuation due to AEs[c]	Bone pain (PT, AEs)[c]	Other specific AEs
BELIEVE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]

a. Deaths were surveyed under AEs.
b. Defined as the proportion of patients who did not require a red blood cell concentrate transfusion for ≥ 24 weeks until the study was unblinded.
c. Contains events of the underlying disease.
d. Severe AEs are operationalized as CTCAE grade ≥ 3. The severity of AEs for which no CTCAE criteria are 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 [see below]).
e. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey version 2; TranQoL: Transfusion-dependent Quality of Life Questionnaire

Notes on included outcomes

Transfusion avoidance

In its dossier, the company presents analyses on the reduction of the transfusion burden by ≥ 33% or ≥ 50% in any 24-week interval, on the cumulative duration of this reduction in the transfusion burden, on the change in the transfusion burden/24 weeks, and on transfusion avoidance over ≥ 6, ≥ 8, ≥ 12, ≥ 16 or ≥ 24 weeks. The company uses the analysis date at Week 48 to derive the added benefit. In the dossier, it presents the results for the analysis date until unblinding of the study as supplementary information.

In the present therapeutic indication, the required transfusions are the essential cause of late complications due to secondary iron overload, such as cardiac complications, liver fibrosis or cirrhosis and multiple endocrine abnormalities [11], which can occur despite iron elimination therapy. Avoiding transfusions is therefore considered relevant for patients. The following operationalization is used for the patient-relevant outcome "transfusion avoidance" in the present benefit assessment:

- Proportion of patients who did not require a pRBC transfusion for ≥ 24 weeks until the study was unblinded.

Regarding the transfusion burden, the change in transfusion burden (average transfused pRBC units/24 weeks) in the period up to unblinding of the study and the proportion of patients with a reduction in transfused pRBC units over ≥ 24 weeks by ≥ 50% compared to baseline in the period up to unblinding of the study are presented as supplementary information. Overall, however, it is unclear - particularly in view of the fact that no symptoms were recorded in the BELIEVE study - what kind of change or reduction in the transfusion burden represents a relevant and noticeable improvement for the patients. The company also provides no information on how a partial reduction of the transfusion burden affects an improvement in symptoms and the avoidance of late complications of transfusion therapy or whether threshold values can be derived for this. This is taken into account in the present benefit assessment when interpreting the results on the change or reduction of the transfusion burden.

Patient-reported outcomes on health-related quality of life

TranQoL

The TranQoL is a validated questionnaire developed for patients with transfusion-dependent thalassaemia [18-20], which measures disease-specific health-related quality of life. The adult version of the questionnaire used in the BELIEVE study contains 36 items categorized into 5 domains: physical health (questions 1 to 10), emotional health (questions 11 to 24), sexual activity (question 25), family situation (questions 26 to 30) as well as school and work (questions 31 to 36). The reference period of the questionnaire is one week. There are 5 answer categories per question, which are specified by the patient: never, almost never, sometimes, often, always. In the BELIEVE study, the questionnaire was considered evaluable if at least 27 of the 36 questions (≥ 75%) were answered. Scores per domain and an overall score are calculated based on the information provided by the patient. The scores are each transformed to a range of 0 to 100. In its dossier, the company presented responder analyses with an improvement by 15 points (corresponds to 15 % of the scale range) at Week 48 for the overall score and the individual domains of the TranQoL. As explained in the General Methods of the Institute [1,21], for a response criterion to reflect a patient-noticeable change with sufficient certainty, it should correspond to at least 15% of the scale range of an instrument, in post-hoc analyses to exactly 15% of the scale range. The response criterion presented by the company thus meet the requirements.

Analyses on patient-reported outcomes presented by the company

For the patient-reported outcomes on health-related quality of life (SF-36v2, TranQoL), the company presented responder analyses at Week 48 for both improvement and deterioration. In the present therapeutic indication, the aim of treatment is to improve symptoms and health-related quality of life, which is why the analyses of the proportion of patients with improvement at Week 48 are used (see also Section I 3.2). Since the response rates of the respective questionnaires have declined after Week 48 (see text section "Analyses used for

the benefit assessment"), the analyses presented by the company for the analysis date at Week 48 were used for the PROs.

Side effects

In the BELIEVE 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: significant 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 [22], this approach has no consequences for the benefit assessment.

The analyses of the outcomes of SAEs, severe AEs and discontinuations due to AEs include events such as the System Organ Class (SOC) “infections and infestations” and/or the PTs “bone pain” and “hypertension”, which may either represent side effects or reflect the symptoms or late complications of the underlying disease. It cannot be conclusively clarified to what extent the events can be assigned to the outcome category of morbidity or side effects. This remains of no consequence for the present benefit assessment.

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 versus placebo

Study	Study level	Outcomes							
		All-cause mortality[a]	Transfusion avoidance[b]	Health-related quality of life (SF-36v2, TranQoL)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Bone pain (PT, AEs)	Other specific AEs
BELIEVE	Low	Low	Low	Low	Low	Low	Low[d]	Low	–

a. Deaths were surveyed under AEs.
b. Defined as the proportion of patients who did not require a red blood cell concentrate transfusion for ≥ 24 weeks until the study was unblinded
c. Severe AEs are operationalized as CTCAE grade ≥ 3. The severity of AEs for which no CTCAE criteria are 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 reasons, see Section I 4.1, side effects]).
d. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey version 2; TranQoL: Transfusion-dependent Quality of Life Questionnaire

The risk of bias for the results on all outcomes was rated as low. For the outcomes on health-related quality of life (SF-36v2, TranQoL), there was a high proportion of patients who were not considered in the analysis (between 17% and 19%). However, the company presented supplementary sensitivity analyses in the dossier, in which missing values were imputed as non-responders (see Table 14). As the results of the sensitivity analysis are comparable with those of the main analysis, the overall certainty of results for the outcomes on health-related quality of life is considered to be high.

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after discontinuation for other reasons, AEs that would have led to discontinuation may have occurred, but the criterion of discontinuation could no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

As described in Section I 3.2, there are uncertainties regarding the administration of luspatercept in compliance with the SPC for the BELIEVE study. However, it is unclear how high the proportion of patients is who, after 9 weeks of treatment (3 doses) with the highest

dose of the study medication, did not record a reduction in the transfusion burden and still received further treatment. Therefore, based on the results of the BELIEVE study, at most hints, e.g. of an added benefit, can be derived for all outcomes.

I 4.3 Results

Table 14 summarizes the results on the comparison of luspatercept with placebo in adult patients with anaemia associated with transfusion-dependent beta-thalassaemia. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on overall hospitalization are presented as supplementary information in I Appendix D of the full dossier assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix C.

Table 14: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study outcome category (time point) outcome	Luspatercept N	Luspatercept patients with event n (%)	Placebo N	Placebo patients with event n (%)	Luspatercept vs. placebo RR [95% CI]; p-value[a]
BELIEVE					
Mortality (until unblinding)					
All-cause mortality[b]	224	1 (0.4)	112	1 (0.9)	0.50 [0.03; 7.92]; 0.736[c]
Morbidity (until unblinding)					
Transfusion avoidance ≥ 24 weeks[d]	224	5 (2.2)	112	0 (0)	5.52 [0.31; 99.03]; 0.120[c]
Reduction of the transfusion burden[e] (presented as supplementary information)	*224*	*40 (17.9)*	*112*	*1 (0.9)*	*20.02 [2.78; 144.31]; 0.003*
Health-related quality of life (proportion of patients with improvement; at Week 48)					
SF-36v2					
Physical Component Summary (PCS)[f, g,h]	183	12 (6.6)	91	5 (5.5)	1.21 [0.44; 3.34]; 0.714
Mental Component Summary (MCS)[g, h, i]	183	17 (9.3)	91	7 (7.7)	1.20 [0.52; 2.77]; 0.674
TranQoL					
Total score[j, k]	186	20 (10.8)	91	7 (7.7)	1.38 [0.61; 3.13]; 0.436
Physical health	186	34 (18.3)	91	11 (12.1)	1.52 [0.81; 2.85]
Emotional health	186	33 (17.7)	91	10 (11.0)	1.60 [0.83; 3.10]
Sexual activity				No usable data[l]	
Family situation	186	35 (18.8)	91	12 (13.2)	1.43 [0.78; 2.61]
School and work	186	39 (21.0)	90	21 (23.3)	0.90 [0.56; 1.45]
Side effects (until unblinding[m])					
AEs[n] (supplementary information)	223	216 (96.9)	109	102 (93.6)	–
SAEs[n]	223	37 (16.6)	109	8 (7.3)	2.26 [1.09: 4.69]; 0.029[o]
Severe AEs[n p]	223	70 (31.4)	109	19 (17.4)	1.80 [1.15; 2.83]; 0.011[o]
Discontinuation due to AE[n]	223	15 (6.7)	109	2 (1.8)	3.67 [0.85; 15.77]; 0.080[o]
Bone pain[n] (PT, AEs)	223	44 (19.7)	109	9 (8.3)	2.39 [1.23; 4.67]; 0.011[o]

Table 14: Results (mortality, morbidity, health-related quality of life, dichotomous) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study	Luspatercept		Placebo		Luspatercept vs. placebo
outcome category (time point) outcome	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]

a. Unless designated otherwise: Mantel-Haenszel method adjusted for geographic region; CIs and p-value were calculated using normal approximation.
b. Deaths were recorded under AEs.
c. Institute's calculation; RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]).
d. Defined as the proportion of patients who did not require packed red blood cell transfusion for ≥ 24 weeks until the study was unblinded.
e. Defined as the proportion of patients with a reduction in transfused packed red blood cells over ≥ 24 weeks by ≥ 50 % compared to the start of the study (based on the 24 weeks before the start of therapy) in the period up to unblinding of the study.
f. Percentage of patients with PCS score increase by ≥ 9.4 points from baseline at week 48, given a scale range of 7 to 63. Higher (increasing) values indicate an improvement of health status/health-related quality of life.
g. No data are available on the SF-36v2 subscales.
h. Supplementary sensitivity analyses of the company with imputation of missing values as non-responders (RR [95% CI], p-value[a]): PCS: 1.20 [0.43; 3.32], p = 0.731; MCS: 1.19 [0.51; 2.76], p = 0.691.
i. Percentage of patients with MCS score increase by ≥ 9.6 points from baseline at week 48, given a scale range of 6 to 64. Higher (increasing) values indicate an improvement of health-related quality of life.
j. Proportion of patients with a total score increase by ≥ 15 points from baseline at week 48, given a scale range of 0 to 100. Higher (increasing) values indicate an improvement of health-related quality of life.
k. Supplementary sensitivity analyses of the company with imputation of missing values as non-responders (RR [95% CI], p-value[a]): total score 1.39 [0.61; 3.17], p = 0.431.
l. Only 31% vs. 33% of randomized patients in the intervention vs. comparator arm are included in the analysis, the data are therefore not usable.
m. Events that occurred from the day of the 1st dose of study medication until 9 weeks after the last dose.
n. Includes events of the underlying disease.
o. Stratified by geographical region.
p. 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 reasons, see Section I 4.1, side effects]).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NC: not calculable; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; TranQoL: Transfusion-dependent Quality of Life Questionnaire

Table 15: Results (morbidity, continuous, supplementary presentation) – RCT, direct comparison: luspatercept vs. placebo

Study outcome category outcome	Luspatercept			Placebo			Luspatercept vs. placebo
	N[a]	values at baseline[b] mean (SD)	change on unblinding mean (95% CI)	N[a]	values at baseline[b] mean (SD)	change on unblinding mean (95% CI)	MD [95% CI]; p-value
BELIEVE							
Morbidity (until unblinding)							
Transfusion burden/24 weeks	*223*	*14.5 (3.6)*	*−2.35 [−2.75; −1.96]*	*111*	*14.8 (3.5)*	*0.43 [−0.12; 0.99]*	*−2.79 [−3.46; −2.12]; < 0.001[c]*

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Transfused packed red blood cells within 24 weeks based on the 24-week interval before or on the day of the 1st dose of study medication.
c. ANCOVA model adjusted by geographical region and baseline value.

CI: confidence interval; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (for reasons, see Section I 4.2).

Mortality

All-cause mortality

One death occurred in each of the 2 treatment arms. There was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Transfusion avoidance

With regard to transfusion avoidance, no statistically significant difference between the treatment arms was shown for the proportion of patients who did not require transfusions for ≥ 24 weeks.

Overall, this resulted in no hint of an added benefit of luspatercept in comparison with the ACT for the outcome “transfusion avoidance”; an added benefit is therefore not proven.

Health-related quality of life

SF-36v2 and TranQoL

There was no statistically significant difference between the treatment arms for either of the outcomes “SF-36v2” and “TranQoL”. In each case, there was no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of luspatercept was shown between the treatment arms for the outcome “serious AEs (SAEs)”. There is a hint of greater harm from luspatercept in comparison with the ACT.

It cannot be ruled out that a relevant proportion of the SAEs that occurred in the luspatercept arm (see Kaplan-Meier curves in Figure 2 in I Appendix B) - particularly in the later course of treatment - could have been avoided if treatment had been discontinued early in accordance with the specifications of the SPC (see Section I 3.2). The extent of the observed effect cannot be quantified for these outcomes due to the uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose.

Severe AEs

A statistically significant difference to the disadvantage of luspatercept was shown between the treatment arms for the outcome “severe AEs”. There is a hint of greater harm from luspatercept in comparison with the ACT.

It cannot be ruled out that a relevant proportion of the severe AEs that occurred in the luspatercept arm (see Kaplan-Meier curves in Figure 3 in I Appendix B) - particularly in the later course of treatment - could have been avoided if treatment had been discontinued early in accordance with the specifications of the SPC (see Section I 3.2). The extent of the observed effect cannot be quantified for these outcomes due to the uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome “discontinuation due to AEs”. There is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Bone pain

A statistically significant difference to the disadvantage of luspatercept was shown for the outcome "bone pain (PT, AEs)”. There is a hint of greater harm from luspatercept in comparison with the ACT.

Most events occurred early in the course of treatment (see Kaplan-Meier curves in Figure 4 in I Appendix B). The described uncertainty in the use of luspatercept in the BELIEVE study (see Section I 3.2) - potential continuation of treatment despite the lack of reduction in the

transfusion burden with the highest luspatercept dose - is therefore of no consequence for determining the extent of the observed effect for the outcome of bone pain (PT, AEs). The extent of the observed effect can be quantified for this outcome.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present benefit assessment:

- age (≤ 32 versus > 32 years)
- Sex (female versus male)
- Beta-thalassaemia genotype (β^0/β^0 vs. non-β^0/β^0)
- previous splenectomy (yes vs. no)

Interaction tests are conducted when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

The company presented subgroup analyses only for the prespecified analysis at the analysis date at Week 48, but not for the analysis date up to unblinding of the study presented by the company as supplementary information, which is considered useful as a longer observation period for the benefit assessment in this chronic disease. However, the subgroup analyses on all-cause mortality, reduction in transfusion burden, SF-36v2, TranQoL and side effects presented by the company in the dossier at the analysis date at Week 48 did not result in any effect modifications using the methodology described above. However, no subgroup analyses on the change in transfusion burden and transfusion avoidance are available for the subgroup characteristics under consideration for any of the analysis dates. For a complete assessment of potential effect modifications, however, subgroup analyses would be required for all patient-relevant outcomes used in the present benefit assessment for the time of analysis until unblinding of the study.

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 Section I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category outcome	**Luspatercept vs. placebo proportion of events (%) or mean effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
Mortality (until unblinding)		
All-cause mortality	0.4% vs. 0.9% RR: 0.50 [0.03; 7.92] p = 0.736	Lesser/added benefit not proven
Morbidity (until unblinding)		
Transfusion avoidance ≥ 24 weeks	2.2% vs. 0% RR: 5.52 [0.31; 99.03] p = 0.120	Lesser/added benefit not proven
Health-related quality of life (at Week 48)		
SF-36v2		
PCS (improvement by ≥ 9.4 points)	6.6% vs. 5.5% RR: 1.21 [0.44; 3.34] p = 0.714	Lesser/added benefit not proven
MCS (improvement by ≥ 9.6 points)	9.3% vs. 7.7% RR: 1.20 [0.52; 2.77] p = 0.674	Lesser/added benefit not proven
TranQoL		
Total score (improvement by ≥ 15 points)	10.8% vs. 7.7% RR: 1.38 [0.61; 3.13] p = 0.436	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: luspatercept versus ACT (multipage table)

Outcome category **outcome**	**Luspatercept vs. placebo** **proportion of events (%) or mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects (until unblinding)		
SAEs	16.6% vs. 7.3% RR: 2.26 [1.09: 4.69] RR: 0.44 [0.21; 0.92][c] p = 0.029 Probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "non-quantifiable[d]
Severe AEs	31.4 % vs. 17.4 % RR: 1.80 [1.15; 2.83] RR: 0.56 [0.35; 0.87][c] p = 0.011 Probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "non-quantifiable[d]
Discontinuation due to AEs	6.7% vs. 1.8% RR: 3.67 [0.85; 15.77] p = 0.080	Greater/lesser harm not proven
Bone pain (AEs)	19.7 % vs. 8.3 % RR: 2.39 [1.23; 4.67] RR: 0.42 [0.21; 0.81][c] p = 0.011 probability: “hint”	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: “minor”

a. Probability provided there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made 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. See Section I 4.3, Side Effects, for reasons.

AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; MD: mean difference; NC: not calculable; PCS: Physical Component Summary; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; TranQol: Transfusion-dependent Quality of Life Questionnaire

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of luspatercept in comparison with the ACT

Positive effects	Negative effects
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: non-quantifiable ▪ severe AEs: hint of greater harm – extent: “non-quantifiable”
–	Non-serious/non-severe side effects ▪ bone pain (AEs): hint of greater harm – extent: “minor”
AE: adverse event; SAE: serious adverse event	

In the overall consideration, there were only negative effects for outcomes in the side effects category, in particular hints of non-quantifiable harm for severe and SAEs of luspatercept versus the ACT. The extent of the observed effects cannot be quantified for these outcomes due to the described uncertainties associated with the use of luspatercept in the BELIEVE study - potential continuation of treatment despite the lack of reduction in the transfusion burden with the highest luspatercept dose. At the same time, it remains unclear in the present indication whether the observed statistically significant differences in the reduction of the transfusion burden, which was given as additional information, mean relevant advantages for luspatercept, even if in the BELIEVE study only individual patients were able to achieve longer-lasting complete transfusion avoidance. For example, 18% of patients in the intervention vs. 1% in the comparator arm achieved a halving of their transfusion burden over ≥ 24 weeks. Patients in the intervention arm achieved an average reduction of approx. 2 pRBC units/24 weeks in the period up to unblinding, while the transfusion burden in patients in the comparator arm remained almost unchanged.

In summary, in this data constellation, the added benefit of luspatercept over the ACT is not proven for adult patients with anaemia associated with transfusion-dependent beta-thalassaemia.

Table 18 summarizes the result of the assessment of the added benefit of luspatercept in comparison with the ACT.

Table 18: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with anaemia associated with transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with pRBC as needed in combination with chelation therapy in accordance with the approval, preferably as monotherapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients are in need of treatment and that an allogeneic stem cell transplantation is not an option for them at the time of treatment with luspatercept.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of non-quantifiable added benefit of luspatercept versus the ACT.

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.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2020, where the G-BA had determined a non-quantifiable added benefit of luspatercept. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

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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