Luspatercept (non-transfusion-dependent beta-thalassaemia)

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

EXTRACT

Project: A23-20 Version: 1.0 Status: 29 June 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Luspatercept (nicht transfusionsabhängige Beta-Thalassämie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Luspatercept (non-transfusion-dependent beta-thalassaemia) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

27 March 2023

Internal Project No.

A23-20

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Helmut Ostermann, LMU Hospital, Munich, Germany

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.

IQWiG employees involved in the dossier assessment

- Sebastian Meller
- Merlin Bittlinger
- Moritz Felsch
- Mandy Kromp
- Ulrike Lampert
- Katrin Nink
- Dominik Schierbaum
- Ulrike Seay

Keywords

Luspatercept, Anemia, beta-Thalassemia, Benefit Assessment, NCT03342404

Part I: Benefit assessment

I Table of contents

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
CTCAE	Common Terminology Criteria for Adverse Events
FACIT	Functional Assessment of Chronic Illness Therapy—Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NTD	non-transfusion-dependent
NTDT-PRO	Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RBC	red blood cell
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

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 27 March 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 non-transfusion-dependent (NTD) beta-thalassaemia.

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

Table 2: Research question for the benefit assessment of luspatercept

Therapeutic indication	**ACT**[a]
Adults with anaemia associated with non-transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with packed red blood cells as needed in combination with chelation therapy as per approval, preferably as monotherapy[c]
a. Presented is the ACT specified by the G-BA. b. 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. c. RBC transfusions and chelation therapy, if indicated, are presumed to be performed in both arms of the study. The criteria are to be documented. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RBC: red blood cell	

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 were used for deriving any added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The BEYOND study was used for the benefit assessment. The BEYOND study is a double-blind RCT comparing luspatercept versus placebo in adult patients with NTD beta-thalassaemia. To be included in the study, patients had to have beta-thalassaemia or haemoglobin E / beta-thalassaemia documented by genotyping. Overall, 145 patients were enrolled and randomly allocated in a 2:1 ratio to either treatment with luspatercept (N = 96) or placebo (N = 49). Treatment with luspatercept in the intervention arm was in compliance with the Summary of

Product Characteristics (SPC). In both treatment arms, transfusions of a red blood cell (RBC) concentrate were allowed at the investigator's discretion for the treatment of low Hb levels, anaemia-related symptoms, or comorbidities. Chelation therapies were allowed to be administered if needed.

After the last enrolled patient completed 48 weeks of treatment or discontinued therapy prematurely, the study was unblinded. The primary outcome of the BEYOND study was an increase in haemoglobin concentration, operationalized as the proportion of patients with an increase in mean haemoglobin concentration of ≥ 1.0 g/dL from baseline over a continuous 12-week interval between Weeks 13 and 24 in the absence of transfusions. In addition, patient-relevant outcomes on morbidity, health-related quality of life, and side effects were surveyed.

The 14 September 2020 data cutoff submitted by the company had been pre-specified and was implemented at the time when all patients completed the 48-week double-blind study phase.

Risk of bias

The risk of bias is deemed high for the results of all outcomes except all-cause mortality and discontinuation due to adverse events (AEs).

Results

Mortality

All-cause mortality

No deaths occurred in either of the 2 treatment arms. This results in no evidence of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (Non-Transfusion-Dependent Thalassemia—Patient Reported Outcomes [NTDT-PRO])

A statistically significant difference between treatment arms in favour of luspatercept was shown for the outcomes of tiredness/weakness as well as shortness of breath, surveyed with the NTDT-PRO. However, the extent of the effect is no more than marginal in both cases. This results in no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Beta-thalassaemia-related symptoms (Patient Global Impression of Severity [PGIS], Patient Global Impression of Change [PGIC])

A statistically significant difference between treatment arms in favour of luspatercept was shown for both of the outcomes of PGIS and PGIC. For each of them, this results in a hint of added benefit of luspatercept in comparison with the ACT.

Transfusion avoidance

No suitable data are available for the outcome of transfusion avoidance. This results in no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Short Form-36 Health Survey version 2 (SF-36v2)

For the outcomes of FACIT-F or SF-36v2, there was no statistically significant difference between treatment arms. This results in no hint of an added benefit of luspatercept in comparison with the ACT for either of them; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, a statistically significant difference between the treatment arms was found in favour of luspatercept. However, there is an effect modification by the characteristic of prior splenectomy (yes versus no). For patients who have undergone splenectomy, this results in a hint of lesser harm from luspatercept compared to the ACT. For patients without splenectomy, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven for this patient group.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of severe AEs or discontinuation due to AEs. For each of them, this results in no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Bone pain

For the outcome of bone pain (Preferred Term [PT], AEs), there is a statistically significant difference to the disadvantage of luspatercept. This results in 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, both favourable and unfavourable effects were found, each with the probability of hint, but of different extents. In the outcome category of morbidity, the 2 outcomes on beta-thalassaemia-related symptoms (PGIC, PGIS) each show a hint of added benefit, of minor and considerable extent, respectively. The overall interpretation, however, must take into account that some of the patients were only slightly symptomatic at baseline and potentially unable to achieve any measurable improvement in symptoms. Furthermore, only patients with prior splenectomy exhibit a hint of lesser harm of major extent for SAEs. It cannot be ruled out that the SAEs also include events which are due to the symptoms or secondary complications of the underlying disease. On the other hand, there is a hint of greater harm of considerable extent for the AE of bone pain. However, this unfavourable effect did not completely call into question the favourable effects.

In summary, there is a hint of minor added benefit of luspatercept in comparison with the ACT for patients with anaemia associated with NTD beta-thalassaemia.

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

[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].

Table 3: Luspatercept – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with anaemia associated with non-transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with packed red blood cells as needed in combination with chelation therapy as per approval, preferably as monotherapy[c]	Hint of minor added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. 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.
c. RBC transfusions and chelation therapy, if indicated, are presumed to be performed in both arms of the study. The reasons are to be documented.
d. The BEYOND study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RBC: red blood cell

The approach for deriving 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 this report is to assess the added benefit of luspatercept in comparison with the ACT in adult patients with anaemia associated with NTD beta-thalassaemia.

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

Table 4: Research question for the benefit assessment of luspatercept

Therapeutic indication	**ACT**[a]
Adults with anaemia associated with non-transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with packed red blood cells as needed in combination with chelation therapy as per approval, preferably as monotherapy[c]
a. Presented is the ACT specified by the G-BA. b. 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. c. RBC transfusions and chelation therapy, if indicated, are presumed to be performed in both arms of the study. The criteria are to be documented. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RBC: red blood cell	

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 were used for deriving 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: 21 February 2023)
- bibliographical literature search on luspatercept (last search on 2 February 2023)
- search in trial registries / trial results databases for studies on luspatercept (last search on 2 February 2023)
- search on the G-BA website for luspatercept (last search on 6 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on luspatercept (last search on 5 April 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

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 versus 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-002 (BEYOND[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

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. Hereinafter, the study is referred to by this designation.
RCT: randomized controlled trial

The BEYOND study was 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 included study – RCT, direct comparison: luspatercept versus placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BEYOND	RCT, double-blind, parallel-group	Adults (> 18 years) with anaemia due to NTD beta-thalassaemia ▪ Haemoglobin-E (HbE) / beta thalassaemia was allowed ▪ Haemoglobin S (HbS) / beta-thalassaemia and alpha-thalassaemia were excluded ▪ ECOG PS ≤ 1	Luspatercept[b] (N = 96) Placebo[b] (N = 49)	Screening: ≤ 4 weeks Treatment: ≥ 48 weeks[c] or until the occurrence of unacceptable toxicity or discontinuation of therapy as decided by the investigator or the patient[f] Observation: 9 weeks after the last dose of the study medication[d]	12 study centres in Greece, Italy, Lebanon, Thailand, United Kingdom, United States 02/2018–11/2022 Data cut-off: ▪ 14/09/2020 (primary analysis)	Primary: proportion of participants with an increase in mean haemoglobin concentration ≥ 1.0 g/dL from baseline over a continuous 12-week interval (Week 13 to Week 24) in the absence of transfusions Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients were allowed to receive packed red blood cells and/or iron chelation therapy if needed.
c. The study was unblinded upon the completion of the 48-week treatment phase by the last patient. After unblinding, patients were allowed to receive luspatercept in both treatment arms for up to 24 months in an open-label treatment phase and then switch to the ACE-536-LTFU-001 roll-over study for long-term follow-up observation[e]. This unblinded part of the study is not relevant for the present benefit assessment and is not shown in the following tables.
d. For patients who discontinued the study medication early, the effectiveness outcomes were collected up to Week 48 or 9 weeks after the last dose, whichever occurred later. Side effects were recorded in these patients for up to 9 weeks after the last dose.
e. Long-term follow-up ended 5 years after the first dose or 3 years after the last dose of the study medication, whichever occurred later.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; Hb: haemoglobin; N: number of randomized patients; RBC: red blood cell; RCT: randomized controlled trial

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

Study	Intervention	Comparison
BEYOND	Luspatercept ▪ Luspatercept 1.0 mg/kg body weight subcutaneously, every 3 weeks ▪ Dose increase: maximum 1.25 mg/kg body weight and maximum 120 mg[a] ▪ Dose reduction by about 25% per administration (minimum 0.45 mg/kg body weight)	Placebo ▪ Volume equivalent to luspatercept subcutaneously every 3 weeks
	Prior treatment <u>Allowed</u> ▪ Iron chelation therapy if started at least 24 weeks before randomization <u>Disallowed</u> ▪ Luspatercept or sotatercept ▪ Chronic treatment with anticoagulants < 28 days before randomization ▪ Treatment with haematopoietic growth factors and / or hydroxyurea ≤ 24 weeks before randomization ▪ Gene therapy ▪ Immunosuppressants ≤ 28 days before randomization ▪ 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 and iron chelation therapy ▪ Required treatment of other diseases <u>Disallowed</u> ▪ Anticoagulants for the therapy of treatment-related AEs which would lead to a dose delay ▪ Hydroxyurea ▪ Haematopoietic growth factors ▪ Anagrelide	

a. The maximum total dose was stated in the first 2 protocol versions (dated 12/05/2017 and 21/12/2018, respectively). Within the scope of Amendment 2 dated 12/06/2020, the specification of a total dose as per marketing authorisation was deleted. This change has no consequences for the present benefit assessment.
b. Physiological substitution therapy for adrenal insufficiency as well as individual days with glucocorticoid administration were allowed.

AE: adverse event; RBC: red blood cell; RCT: randomized controlled trial

The BEYOND study is a double-blind RCT comparing luspatercept versus placebo in adult patients with NTD beta-thalassaemia.

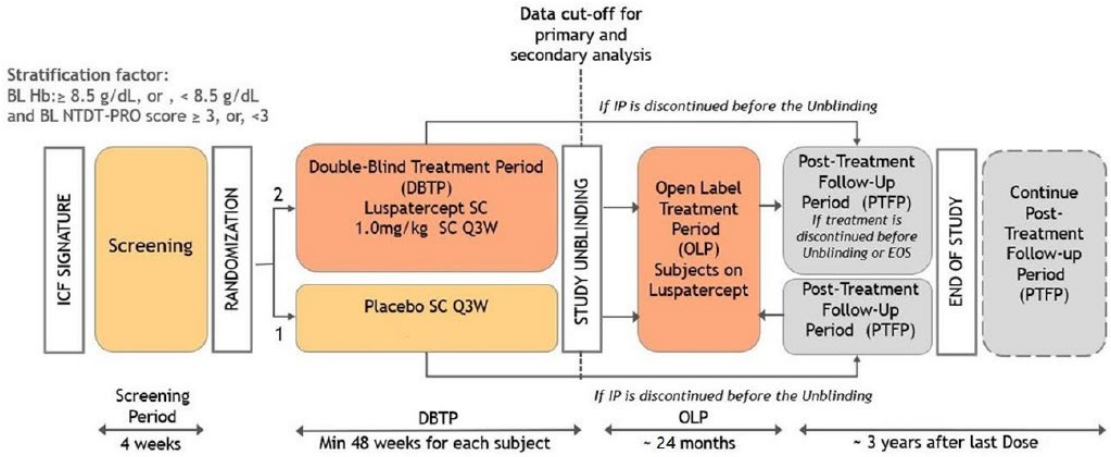
For inclusion in the study, patients had to have beta-thalassaemia or haemoglobin E / beta-thalassaemia documented by genotyping. Patients with beta-thalassaemia with mutation and/or multiplication of the alpha-globin gene were eligible for study inclusion. Patients with haemoglobin S / beta thalassaemia or alpha thalassaemia (e.g. haemoglobin H disease) were excluded from the study. The mean haemoglobin (Hb) value had to be below 10 g/dL for the

4 weeks prior to randomization. In addition, patients were allowed a maximum of 5 RBC concentrate units 24 weeks before randomization and no RBC concentrate transfusion 8 weeks before randomization. Patients had to be in good general health at study enrolment, corresponding to an ECOG-PS of 0 or 1. For the present benefit assessment, the inclusion criteria of the BEYOND study are deemed sufficient for representing NTD beta-thalassaemia.

Overall, 145 patients were enrolled and randomly allocated in a 2:1 ratio to either treatment with luspatercept (N = 96) or to placebo (N = 49). Randomization was stratified by Hb concentration (≥ 8.5 g/dL versus < 8.5 g/dL) and the Non-Transfusion-Dependent Thalassemia—Patient Reported Outcomes (NTDT-PRO) total score in the tiredness/weakness domain at baseline (< 3 points versus ≥ 3 points; scale range from 0 to 10 corresponding to no symptoms to extremely/very severe symptoms).

Treatment with luspatercept in the intervention arm was in compliance with the SPC [7]. The minimum dose of 0.45 mg/kg body weight, which was allowed in the study but diverted from the SPC, was not administered in the BEYOND study and therefore has no consequences for the present benefit assessment.

Figure 1 below shows the design of the study.



ICF: informed consent form; IP: investigational product; Q3W: every 3 weeks; SC: subcutaneous

Figure 1: BEYOND study design

The study was unblinded after the last enrolled patient completed 48 weeks of treatment or discontinued therapy prematurely. Afterwards, patients in both study arms were allowed to receive luspatercept in an open-label treatment phase.

The primary outcome of the BEYOND study was the increase in haemoglobin concentration, operationalized as the proportion of patients with an increase in mean haemoglobin concentration of ≥ 1.0 g/dL from baseline over a continuous 12-week interval between

Weeks 13 and 24 in the absence of transfusions. In addition, patient-relevant outcomes on morbidity, health-related quality of life, and side effects were surveyed.

The 14 September 2020 data cutoff submitted by the company had been pre-specified and was implemented at the time when all patients completed the 48-week double-blind study phase.

Implementation of the ACT

As the ACT, the G-BA specified transfusion therapy with packed red blood cells as needed in combination with chelation therapy as per approval, preferably as monotherapy. It is assumed that RBC transfusions and chelation therapy, if indicated, are performed in both arms of the study. The criteria are to be documented.

In the BEYOND study, control arm participants received placebo. In both treatment arms, transfusions of an RBC concentrate were allowed at the investigator's discretion for the treatment of low Hb levels, anaemia-related symptoms, or comorbidities. Chelation therapies were allowed to be administered if needed.

According to the guidelines, the decisive criterion for establishing the therapeutic indication for transfusion of an RBC concentrate is not only the measured Hb value, but also the patient's clinical situation [8,9]. As per the guidelines, a therapeutic indication for iron chelation therapy is established when certain limits of the liver iron concentration are exceeded or, if liver iron measurement is not possible, based on the serum ferritin value [8-10]. The most common reason for transfusion of an RBC concentrate during the course of the study was anaemia. Iron chelation therapy was administered to about 40% of the patients in both study arms.

Overall, the control arm of the BEYOND study presumably adequately implemented the ACT.

Analysis time points provided by the company

BEYOND is a completed study. For all patient-relevant outcomes from the categories of morbidity and health-related quality of life, the company presents analyses from the primary data cutoff dated 14 September 2020, referring to 3 different time points:

- Analysis time point: at Week 24
- Analysis time point: at Week 48
- Analysis time point: total observation duration up to the 14 September 2020 data cutoff (corresponds to the entire observation duration of the double-blind part of the BEYOND study)

For side effects, the company submitted only analyses including the entire observation period until 14 September 2020.

The primary analysis of the effectiveness outcomes had been planned to be conducted at the time when all patients had finished their 48-week treatment, and it was implemented for all patients based on the data between baseline and Week 48.

After reaching 48 weeks, patients remained blinded in the study and continued to receive treatment. The outcomes continued to be surveyed after Week 48 until the last randomized participant had completed the intended treatment duration of 48 weeks or had discontinued therapy. This study design leads to varying treatment and follow-up durations between individual participants based on their enrolment time point (see Figure 1).

For the purposes of the benefit assessment, the longer follow-up period surveyed at the 14 September 2020 data cutoff is deemed useful for this chronic disease. However, the return rates of the respective questionnaires strongly declined after Week 48. Thus, the number of patients, especially in the control arm, decreases continuously after Week 48 (see also Table 8 and Table 9). For patient-reported outcomes (PROs), the benefit assessment therefore uses the analyses at the Week 24 or Week 48 analyses time points (depending on the response rate of the respective questionnaires, see also Section I 4.1).

The company has additionally submitted responder analyses of PROs for the time to first improvement and deterioration. These have been disregarded because, while many events had occurred early on, it cannot be ruled out that patients' health may have worsened or improved again after an initial improvement/deterioration within the observation period. These analyses are therefore unsuitable for representing the treatment goal of a lasting improvement of symptoms and health-related quality of life and are disregarded in the present situation.

Table 8 shows the characteristics of the patients in the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: luspatercept versus placebo

Study **Characteristic** **Category**	**Luspatercept** **N = 96**	**Placebo** **N = 49**
BEYOND		
Age [years], mean (SD)	39 (13)	41 (12)
Sex [f/m], %	58/42	53/47
Region, n (%)		
North America and Europe	60 (63)	30 (61)
Middle East	9 (9)	8 (16)
Asia/Pacific	27 (28)	11 (22)
Beta thalassaemia genotype, n (%)		
β0/β0, β+/β+, β+/β0 without alpha thalassaemia[a]	69 (72)	33 (67)
β0/β0, β+/β+, β+/β0 with alpha thalassaemia[a]	6 (6)	4 (8)
β0/β, β+/β with alpha gene duplication[a]	21 (22)	12 (24)
Hb-value [g/dL], mean (SD)[b]	8.2 (1.2)	8.1 (1.3)
Liver iron concentration [mg/g d.w.] (by means of MRI), mean (SD)	6.1 (6.2)	5.9 (5.8)
Serum ferritin value [µg/L][c], mean (SD)	567.8 (523.2)	528.8 (444.9)
NTDT-PRO score domain tiredness/weakness at baseline[d]		
≥ 3 points	66 (68.8)	35 (71.4)
< 3 points	30 (31.3)	14 (28.6)
Prior splenectomy, n (%)		
Yes	34 (35)	26 (53)
No	62 (65)	23 (47)
Iron chelation therapy before study entry (within 24 weeks before study entry), n (%)		
Yes	28 (29)	16 (33)
No	68 (71)	33 (67)
Treatment discontinuation, n (%)[e, f]	15 (16)	31 (63)
Study discontinuation, n (%)	4 (4)	1 (2)

a. A more detailed breakdown by genotypes was not available.
b. Mean Hb value calculated from at least 2 documented Hb values during the screening phase.
c. Mean serum ferritin level within 24 weeks before the first dose.
d. Mean NTDT-PRO score based on the 7 days before the first dose.
e. Full completion of 24-week treatment period in intervention vs. control arm: 92 (96%) vs. 44 (90%); full completion of 48-week treatment period in intervention vs. control arm: 89 (93%) vs. 35 (71%).
f. Common reasons for treatment discontinuation in the intervention vs. control arm: discontinuation at the patient's request (9 vs. 10), lack of efficacy (1 vs. 17).

d.w.: dry weight; f: female; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; Hb: haemoglobin; m: male; MRI: magnetic resonance imaging; n: number of patients in category; N: number of randomized patients; NTDT-PRO: Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment arms. The mean patient age was 40 years; most patients were female (58% and 53%), and most were from North America or Europe. The mean Hb value was about 8 mg/dL. Imbalances between the study arms were found in patients with prior splenectomy. A total of 35% of patients in the intervention arm had a splenectomy at baseline, compared to 53% in the control arm. The baseline NTDT-PRO score for the domain of tiredness/weakness was under 3 (scale range from 0 to 10 corresponding to no to extreme/very severe symptoms) in about 1/3 of the patients. This means that these patients showed only minor or no symptoms in terms of tiredness/weakness.

The proportion of patients with treatment discontinuation by the present data cutoff was markedly higher in the control arm at 63% than in the intervention arm at 16%. The proportion of patients with treatment discontinuation by Week 48 was also notably higher in the control arm at 29% than in the intervention arm (7%). The most frequent reasons for discontinuing therapy were discontinuation at the patient's request in the intervention arm and lack of effectiveness in the control arm.

Treatment duration and observation period

Table 9 shows the patients' mean and median treatment duration and the mean and median observation period for individual outcomes.

Table 9: Information on the course of the study – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study **Duration of the study phase** **Outcome category** **Outcome**	**Luspatercept** **N = 96**	**Placebo** **N = 49**
BEYOND		
Treatment discontinuation, n (%)	15 (15.6)	31 (63.3)
≥ 24 weeks completed, n (%)	92 (95.8)	44 (89.8)
≥ 48 weeks completed, n (%)	89 (92.7)	35 (71.4)
Treatment duration [weeks][a]		
Median [min; max]	99.7 (15.0; 132.1)	61.1 (3.0; 121.9)
Mean (SD)	94.0 (29.8)	66.0 (35.0)

Table 9: Information on the course of the study – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study **Duration of the study phase** **Outcome category** **Outcome**	**Luspatercept** **N = 96**	**Placebo** **N = 49**
Follow-up observation duration [weeks][b]		
Morbidity		
NTDT-PRO		
Median [min; max]	79.4 (0; 130.3)	48.9 (3.0; 116.0)
Mean (SD)	73.3 (35.3)	59.8 (31.7)
PGIS		
Median [min; max]	79.4 (0; 130.3)	48.9 (3.0; 116.0)
Mean (SD)	73.3 (35.26)	59.8 (31.69)
PGIC		
Median [min; max]	95.9 (12.4; 130.4)	60.6 (19.4; 120.1)
Mean (SD)	89.9 (30.3)	70.1 (28.3)
Transfusion avoidance		
Median [min; max]	99.7 (15.0; 132.0)	61.1 (3.0; 122.0)
Mean (SD)	94.0 (29.8)	66.0 (35.0)
Health-related quality of life		
FACIT-F		
Median [min; max]	95.2 (0.1; 130.4)	59.1 (0.1; 120.1)
Mean (SD)	88.4 (32.2)	69.0 (29.3)
SF-36v2		
Median [min; max]	95.2 (0.1; 130.4)	59.1 (0.1; 120.1)
Mean (SD)	88.4 (32.1)	69.0 (29.3)
Side effects[c]	ND	ND

a. Time from first dose to last dose + 20 days or until prior death.
b. Outcomes in the morbidity and health-related quality of life outcome categories were collected for patients who discontinued the study medication early, up to Week 48 or 9 weeks after the last dose, whichever was later.
c. AEs were observed from the day of the first dose until 9 weeks after the last dose.

AE: adverse event; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; max: maximum; min: minimum; N: number of patients; ND: no data; NTDT-PRO: Non-Transfusion-Dependent Thalassemia -- Patient Reported Outcomes; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration is markedly longer in the intervention arm at 99.7 weeks than in the control arm at 61.1 weeks. Additionally, marked differences were found in the observation durations of the individual outcomes from the categories of morbidity and health-related quality of life. For side effects, data on the observation period are not available. However, as the observation period for side effects is linked to the treatment duration (until

9 weeks after the last dose), it can be safely assumed that these also differ markedly between the treatment arms.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: luspatercept versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
BEYOND	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

The company states that, due to the enrolment of patients from Greece, Italy, Lebanon, Thailand, the United Kingdom, and the United States, the study included mainly White patients (60.0%), but also a large proportion of Asian patients (30.3%). According to the company, German patients with beta-thalassaemia typically have foreign roots: in addition to patients who are predominantly of white ethnicity, e.g. those from Italy or Greece, many patients have Asian family origins (Middle East, Southeast Asia). The company thus assumes that the patient population in the BEYOND study is an adequate reflection of the affected ethnicities in Germany. Furthermore, given the large number of study centres in Western countries, a standard of health care comparable to Germany is reportedly ensured.

Due to the disease's 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 numbers. The slightly higher number of women is reportedly also found in the analyses of routine data of the statutory health insurance funds commissioned in the context of the preparation of the dossier. Based on the available patient characteristics and the multicentric study design, the company assumes that the study results are transferable 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
  - all-cause mortality
- Morbidity
  - symptoms recorded using the NTDT-PRO
  - beta-thalassaemia-related symptoms measured by PGIS and PGIC
  - transfusion avoidance
- Health-related quality of life
  - measured using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)
  - measured using the Short Form (SF)-36v2
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - further specific AEs, if any

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

Table 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: luspatercept versus placebo

Study	Outcomes								
	All-cause mortality[a]	Symptoms (NTDT-PRO)	Beta-thalassaemia-related symptoms (PGIS, PGIC)	Transfusion avoidance[b]	Health-related quality of life (FACIT-F, SF-36v2)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Bone pain (PT, AEs)
BEYOND	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes

a. Deaths were recorded as AEs.
b. Defined as the proportion of patients who did not require an RBC concentrate transfusion by Week 48.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. No suitable data available; see body of text below for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; NTDT-PRO: Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: preferred term; RBC: red blood cell; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2

Analyses of patient-reported outcomes submitted by the company

The company presents responder analyses for the patient-reported outcomes (NTDT-PRO, PGIS, PGIC, FACIT-F, SF-36v2) at Week 24 and Week 48 for both improvement and deterioration. Furthermore, it presents time-to-event analyses operationalized as time to first improvement/deterioration. In the present therapeutic indication, the treatment goal is an improvement in symptoms and health-related quality of life; therefore, the analyses of the proportion of patients with improvement, if possible at Week 48, are used in each case (see also Section I 3.2).

Notes on analyses of the morbidity outcome category

The majority of patients included in the BEYOND study were symptomatic at baseline and showed an improvement in patient-reported outcomes from baseline values (see Table 8). This is also reflected in the higher proportion of patients with an improvement at Week 24 and Week 48 compared to the proportion of patients with a deterioration by Week 24 and Week 48 in the respective outcomes. However, a relevant proportion of the included patients exhibited rather mild symptoms at baseline. For example, in about 1/3 of patients, the NTDT-PRO score for the domain tiredness/weakness was below 3 at baseline (scale range from 0 to 10 corresponding to no to extremely/very severe symptoms; see also Sections I 3.2 and I 5.1). The median baseline PGIS score, which indicates the severity of symptoms on a scale from 0 "no symptoms" to 10 "very severe symptoms", was approximately 4 (see also

Section I 5.1). The fact that some of the included patients thus showed no or only a minor potential for improvement in the corresponding outcomes is taken into account in the interpretation of the results.

NTDT-PRO

The NTDT-PRO is a validated questionnaire [11,12] developed for patients with NTD beta-thalassaemia to assess the anaemia-related symptoms of tiredness/weakness and shortness of breath. The questionnaire comprises a total of 6 items, each of which is used to assess the severity of symptoms on a numerical rating scale from 0 "none" to 10 "extremely/very severe". The results are summarised in the domains tiredness/weakness (4 items) and shortness of breath (2 items), each with a scale range of 0 to 10. In its dossier, the company presents responder analyses with an improvement of 1.5 points at Week 24 and Week 48 for the 2 cited domains. As explained in the Institute's General Methods [1,13], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The response criterion submitted by the company thus meets the requirements. Because the response rates of the NTDT-PRO at Week 48 were significantly below 70% in both treatment arms (50% versus 55%), the results on the proportion of patients with an improvement by 1.5 points at Week 24 were used for the benefit assessment.

PGIS

The PGIS consists of a single question asking the patient to rate his/her beta-thalassaemia-related symptoms on a 10-point scale (from 0 = "no symptoms" to 10 = "very severe symptoms"). In its dossier, the company presents responder analyses with an improvement by 1.5 points (corresponds to 15% of the scale range) at Week 24 and Week 48. As described above, the response criterion submitted by the company thus meets the requirements. However, for the PGIS, the response rates at Week 48 are significantly below 70% in both treatment arms (50% versus 55%). Therefore, the present benefit assessment uses results on the proportion of patients with an improvement by 1.5 points by Week 24.

PGIC

The PGIC consists of a single question asking patients to rate on a 7-point scale (from "very much better" to "very much worse") the overall change in their beta-thalassaemia-related symptoms since the start of the study. In its dossier, the company presents responder analyses in which the 2 best ratings of change ("much better" and "very much better") are deemed a relevant improvement. The benefit assessment used the results on the proportion of patients who rated their beta-thalassaemia-related symptoms as very much better or much better compared to baseline by Week 48.

Six-minute walk test

The 6-minute walk test is an established tool for determining endurance. It is used, e.g. in pneumological and cardiological diagnostics in the therapeutic indications of COPD or heart failure [14,15]. However, it is unclear whether the 6-minute walk test represents a meaningful interpretable outcome in the therapeutic indication of NTD beta-thalassaemia. The company does not provide any sources in its dossier to show the validity of the outcome in the present therapeutic indication. Hence, the 6-minute walk test was disregarded in the present benefit assessment.

Transfusion avoidance

In its dossier, the company presents analyses of the proportion of patients who had avoided transfusions by Week 24 and Week 48. According to the study protocol, RBC concentrate transfusions were to be documented until Week 48 even in patients who discontinued therapy. However, the analyses presented by the company include only RBC concentrate transfusions up to 20 days after treatment discontinuation. Firstly, patients who did not receive a transfusion within 20 days after treatment discontinuation were excluded from the analyses and counted as "missing" (5 [5.2%] of patients in the intervention arm and 11 [22.4%] in the control arm). Secondly, this also means that transfusions from patients who discontinued therapy before Week 48 may not have been included in the analyses presented by the company at Week 48. This approach is not appropriate. The assessment requires analyses of the proportion of patients who had avoided transfusions by Week 48, with complete observation even after treatment discontinuation of all patients with transfusion of an RBC concentrate up to Week 48. The responder analyses submitted by the company for the outcome of transfusion avoidance are therefore disregarded in the benefit assessment.

Notes on side effects

The analyses of the outcomes of SAEs, severe AEs, and discontinuation due to AEs include events such as the PTs of bone pain and hypotension or the System Organ Class (SOC) of infections and infestations, which may represent either side effects or 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 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: 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]	Symptoms (NTDT-PRO)	Beta-thalassaemia-related symptoms (PGIS, PGIC)	Transfusion avoidance[b]	Health-related quality of life (FACIT-F, SF-36v2)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Bone pain (PT, AEs)
BEYOND	L	L	H[d]	H[d]	–[e]	H[d]	H[f]	H[f]	L[g]	H[f]

a. Deaths were recorded as AEs.
b. Defined as the proportion of patients who did not require an RBC concentrate transfusion by Week 48.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. High proportion of patients not included at the time of analysis (Week 24 or 48, depending on the outcome).
e. No usable data available; see Section I 4.1 for the reasoning.
f. Incomplete observations for potentially informative reasons with different observation times and different proportions of treatment discontinuations.
g. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see body of text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; H: high; L: low; NTDT-PRO: Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2

The risk of bias is deemed high for the results of all outcomes except overall survival and discontinuation due to AEs. For the outcomes on symptoms (NTDT-PRO), beta-thalassaemia-related symptoms (PGIS, PGIC), and health-related quality of life (FACIT-F, SF-36v2), the response rate to the respective questionnaires markedly decreased in both treatment arms; therefore, a high proportion of patients is not included in the analysis. The outcomes in the side effects category (SAEs, severe AEs, and bone pain [PT, AEs]) suffer from incomplete observations for potentially informative reasons due to (a) the follow-up observation being linked to treatment duration and (b) the outcome and reason for treatment discontinuation being potentially linked.

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, it is possible for AEs to occur which would have led to discontinuation, but it was no longer possible to apply the criterion of discontinuation to them. It is impossible to estimate how many AEs are affected by this issue.

I 4.3 Results

Table 13 and Table 14 summarize the results from the comparison of luspatercept versus placebo in patients with anaemia associated with NTD beta thalassaemia. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The overall hospitalization rates are presented as supplementary information in I Appendix D of the full dossier assessment. The Kaplan-Meier curves for the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuation due to AEs can be found in I Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study	**Luspatercept**		**Placebo**		**Luspatercept vs. placebo**
Outcome category **Outcome** **Time point**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
BEYOND					
Mortality (by 14/09/2020)					
All-cause mortality[b]	96	0 (0)	49	0 (0)	NC
Morbidity (proportion of patients with improvement)					
Symptoms (NTDT-PRO) (Week 24)					
Tiredness/weakness[c]	76	27 (35.5)	39	7 (17.9)	2.06 [1.02; 4.17]; 0.043
Shortness of breath[c]	76	21 (27.6)	39	4 (10.3)	2.87 [1.09; 7.59]; 0.033
Beta-thalassaemia-related symptoms					
PGIS (Week 24)[c]	76	23 (30.3)	39	4 (10.3)	3.08 [1.19; 7.95]; 0.020
PGIC (Week 48)[d]	73	38 (52.1)	40	3 (7.5)	7.08 [2.29; 21.87]; 0.001
Transfusion avoidance (Week 48)	No suitable data available[e]				

Table 13: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: luspatercept versus placebo (multipage table)

Study	Luspatercept		Placebo		Luspatercept vs. placebo
Outcome category **Outcome** **Time point**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Health-related quality of life (proportion of patients with improvement)					
FACIT-F total score (Week 48)[f]	74	9 (12.2)	40	1 (2.5)	4.99 [0.67; 36.94]; 0.116
Subscales (Week 48; presented as supplementary information)					
Physical well-being	*74*	*8 (10.8)*	*40*	*1 (2.5)*	*4.43 [0.59; 33.41]*
Social/family well-being	*74*	*8 (10.8)*	*40*	*4 (10.0)*	*1.10 [0.36; 3.31]*
Emotional well-being	*74*	*9 (12.2)*	*40*	*3 (7.5)*	*1.66 [0.51; 5.43]*
Functional well-being	*74*	*5 (6.8)*	*40*	*1 (2.5)*	*2.77 [0.33; 23.02]*
FACT-G total score	*74*	*5 (6.8)*	*40*	*1 (2.5)*	*2.77 [0.35; 22.04]*
Fatigue-specific scale	*74*	*17 (23.0)*	*40*	*4 (10.0)*	*2.35 [0.88; 6.28]*
SF-36v2 (Week 48)					
Physical Component Summary (PCS)[g]	73	5 (6.8)	39	2 (5.1)	1.31 [0.27; 6.26]; 0.736
Mental Component Summary (MCS)[h]	73	11 (15.1)	39	1 (2.6)	5.93 [0.79; 44.22]; 0.083

a. RR using Mantel-Haenszel method, adjusted for baseline Hb value and baseline NTDT-PRO total score in the tiredness/weakness domain; CIs and p-value calculated using normal approximation.
b. Deaths were recorded as AEs.
c. Proportion of patients with a score decrease by ≥ 1.5 points from baseline by Week 24, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement of symptoms.
d. Proportion of patients who rated their beta-thalassaemia-related symptoms as very much better or much better compared to baseline.
e. See Section I 4.1 of the present dossier assessment for the reasoning.
f. Percentage of patients with FACIT-F score increase by ≥ 24 points from baseline at Week 48, given a scale range of 0 to 160. Higher (increasing) values indicate an improvement in health-related quality of life.
g. Percentage of patients with PCS score increase by ≥ 9.4 points from baseline by Week 48, at a scale range of 7 to 63. Higher (increasing) values indicate an improvement in health-related quality of life.
h. Percentage of patients with MCS score increase by ≥ 9.6 points from baseline at Week 48, at a scale range of 6 to 64. Higher (increasing) values indicate an improvement in health-related quality of life.

CI: confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-G: Functional Assessment of Cancer Therapy - General; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: Number of patients analysed; NC: not calculable; NTDT-PRO: Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form-36 Health Survey version 2

Table 14: Results (side effects) – RCT, direct comparison: luspatercept versus placebo

Study Outcome category Outcome	Luspatercept N	Luspatercept Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Luspatercept vs. placebo HR [95% CI][a]; p-value[b]
BEYOND					
Side effects[c]					
AEs (supplementary information)	96	0.10 [0.07; 0.13]; 96 (100.0)	49	0.76 [0.46; 0.89]; 48 (98.0)	–
SAEs	96	NR 11 (11.5)	49	NR [18.00; NC] 12 (24.5)	0.29 [0.12; 0.69]; 0.003
Severe AEs[d]	96	NR 27 (28.1)	49	NR [16.62; NC] 12 (24.5)	1.07 [0.54; 2.14]; 0.842
Discontinuation due to AEs	96	NR 3 (3.1)	49	NR 4 (8.2)	0.29 [0.06; 1.34]; 0.092
Bone pain (PT, AEs)	96	NR 35 (36.5)	49	NR 3 (6.1)	7.11 [2.18; 23.15]; < 0.001

a. Cox regression model, stratified by baseline Hb level and baseline NTDT-PRO total score in the domain tiredness/weakness.
b. Log-rank test, stratified by baseline Hb value and baseline NTDT-PRO total score in the domain tiredness/weakness.
c. Events which occurred from the day of the first dose of the study medication until 9 weeks after the last dose, possibly also beyond Week 48.
d. Operationalized as CTCAE grade ≥ 3.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial

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

Mortality

All-cause mortality

No deaths occurred in either of the 2 treatment arms. There was no evidence of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (NTDT-PRO)

A statistically significant difference between treatment arms in favour of luspatercept was shown for the outcomes of tiredness/weakness as well as shortness of breath, surveyed with the NTDT-PRO. However, the extent of the effect was no more than minor in each case (see Section I 5.1). This results in no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Beta-thalassaemia-related symptoms (PGIS, PGIC)

A statistically significant difference between treatment arms in favour of luspatercept was shown for both of the outcomes of PGIS and PGIC. For each of them, this results in a hint of added benefit of luspatercept in comparison with the ACT.

Transfusion avoidance

No suitable data are available for the outcome of transfusion avoidance (see Section I 4.1 for reasons). This results in no hint of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

FACIT-F and SF-36v2

For the outcomes of FACIT-F or SF-36v2, there was no statistically significant difference between treatment arms. This results in no hint of an added benefit of luspatercept in comparison with the ACT for either of them; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference between the treatment arms in favour of luspatercept was shown for the outcome of SAEs. However, there is an effect modification by the characteristic of prior splenectomy (yes versus no), with a simultaneously unequal distribution of patients with splenectomy between the treatment arms (35% in the intervention arm versus 53% in the control arm). For patients who have undergone splenectomy, there is a hint of lesser harm from luspatercept compared to the ACT. For patients without splenectomy, there is no hint of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm for this patient group is therefore not proven for this patient group (see Section I 4.4).

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of severe AEs or discontinuation due to AEs. For each of them, this results in no hint

of greater or lesser harm from luspatercept in comparison with the ACT; greater or lesser harm is therefore not proven.

For the outcome of severe AEs, the Kaplan-Meier curves cross at about Month 17 (see Figure 3 of the full dossier assessment). At the timepoint where the Kaplan-Meier curves intersect, however, few patients in the control arm are still under observation. Hence, the hazard ratio can be used as an effect estimator.

Specific AEs

Bone pain

For the outcome of bone pain (PT, AEs), there is a statistically significant difference to the disadvantage of luspatercept. This results in a hint of greater harm from luspatercept in comparison with the ACT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (≤ 32 years versus > 32 years)
- sex (female versus male)
- prior splenectomy (yes versus no)

Interaction tests are performed if 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.

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 1 subgroup.

Table 15 summarizes the subgroup results from the comparison of luspatercept versus placebo in patients with anaemia associated with NTD beta thalassaemia.

Table 15: Subgroups (side effects) – RCT, direct comparison: luspatercept versus placebo

Study Outcome Characteristic Subgroup	Luspatercept N	Luspatercept Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Luspatercept vs. placebo HR [95% CI][a]	Luspatercept vs. placebo p-value[b]
BEYOND						
Side effects[c]						
SAEs						
Splenectomy						
Yes	34	NR [28.81; NC] 3 (8.8)	26	19.48 [12.42; NC] 10 (38.5)	0.08 [0.02; 0.37]	< 0.001
No	62	NR 8 (12.9)	23	NR [18.00; NC] 2 (8.7)	1.18 [0.25; 5.62]	0.832
Total					Interaction:	0.037[d]

a. Unstratified Cox regression model.
b. Unstratified log-rank test.
c. Events which occurred from the day of the first dose of the study medication until 9 weeks after the last dose, possibly also beyond Week 48.
d. Unstratified Cox regression model with treatment, subgroup characteristic, and the interaction term "treatment x subgroup characteristic".

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

Side effects

SAEs

For the outcome of SAEs, there is a statistically significant interaction for the characteristic of prior splenectomy, with a simultaneously unequal distribution of patients with splenectomy between the treatment arms (35% in the intervention arm versus 53% in the control arm).

A statistically significant difference to the benefit of luspatercept is shown for patients with prior splenectomy. This results in a hint of lesser harm from luspatercept in comparison with the ACT.

There was no statistically significant difference between the treatment groups for patients without splenectomy. For this subgroup, this results in no hint of greater or lesser harm from luspatercept in comparison with the ACT; therefore, there is no proof of greater or lesser harm for this outcome.

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 the 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).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms (NTDT-PRO)

The NTDT-PRO records the symptoms of tiredness/weakness and shortness of breath. At baseline, patients had a median score of 4.3 for tiredness/weakness and a score of 3.5 for shortness of breath (scale range in both cases from 0 to 10, corresponding to no to extremely/very severe symptoms). These values correspond to mild to moderate symptoms. Therefore, the outcome of symptoms (NTDT-PRO) was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Beta-thalassaemia-related symptoms (PGIS, PGIC)

The median PGIS score, which indicates the severity of symptoms on a scale from 0 "no symptoms" to 10 "very severe symptoms", was approximately 4 at baseline, corresponding to mild to moderate symptoms. Therefore, the outcome of beta thalassaemia-related symptoms (surveyed with the PGIS and PGIC) was assigned to the outcome category of non-serious/non-severe symptoms / late complications.

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

Outcome category **Outcome**	**Luspatercept vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: -	Lesser/Added benefit not proven
Morbidity		
NTDT-PRO (Week 24; improvement)		
Tiredness/Weakness	35.5% vs. 17.9% RR: 2.06 [1.02; 4.17] RR: 0.49 [0.24; 0.98][c] p = 0.043	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/Added benefit not proven[d]
Shortness of breath	27.6% vs. 10.3% RR: 2.87 [1.09; 7.59] RR: 0.35 [0.13; 0.92][c] p = 0.033	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/Added benefit not proven[d]
Beta-thalassaemia-related symptoms (improvement)		
PGIS (Week 24)	30.3% vs. 10.3% RR: 3.08 [1.19; 7.95] RR: 0.32 [0.13; 0.84][c] p = 0.020 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit; extent: minor
PGIC (Week 48)	52.1% vs. 7.5% RR: 7.08 [2.29; 21.87] RR: 0.14 [0.05; 0.44] p = 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Transfusion avoidance ≥ 48 weeks (Week 48)	No suitable data	Lesser/Added benefit not proven
Health-related quality of life (improvement)		
FACIT-F total score (Week 48)	12.2% vs. 2.5% RR: 4.99 [0.67; 36.94] p = 0.116	Lesser/Added benefit not proven
SF-36v2 (Week 48)		
Physical Component Summary (PCS)	6.8% vs. 5.1% RR: 1.31 [0.27; 6.26] p = 0.736	Lesser/Added benefit not proven

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

Outcome category **Outcome**	**Luspatercept vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mental Component Summary (MCS)	15.1% vs. 2.6% RR: 5.93 [0.79; 44.22] p = 0.083	Lesser/Added benefit not proven
Side effects		
SAEs Prior splenectomy Yes	8.8% vs. 38.5% HR: 0.08 [0.02; 0.37] p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm; extent: major
No	12.9% vs. 8.7% HR: 1.18 [0.25; 5.62] p = 0.832	Greater/Lesser harm not proven
Severe AEs	28.1% vs. 24.5% HR: 1.07 [0.54; 2.14] p = 0.842	Greater/Lesser harm not proven
Discontinuation due to AEs	3.1% vs. 8.2% HR: 0.29 [0.06; 1.34] p = 0.092	Greater/Lesser harm not proven
Bone pain	36.5% vs. 6.1% HR: 7.11 [2.18; 23.15] HR: 0.14 [0.04; 0.46] 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, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
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_U: upper limit of confidence interval; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; MCS: Mental Component Summary; NTDT-PRO: Non-Transfusion-Dependent Thalassemia – Patient Reported Outcomes; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 17: Favourable and unfavourable effects from the assessment of luspatercept in comparison with the ACT

Favourable effects	**Unfavourable effects**
Morbidity Non-serious/non-severe symptoms / late complications ▪ PGIS (Week 24): hint of an added benefit – extent minor ▪ PGIC (Week 48): hint of added benefit – extent considerable	-
Serious/severe side effects ▪ SAEs ▫ Prior splenectomy yes: hint of lesser harm – extent major	-
-	Non-serious/non-severe side effects ▪ Bone pain (AEs): hint of greater harm - extent: considerable
No suitable data are available for the outcome of transfusion avoidance.	
AE: adverse event; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; SAE: serious adverse event	

Overall, both favourable and unfavourable effects were found, each with the probability of hint, but of different extents. In the outcome category of morbidity, the 2 outcomes on beta-thalassaemia-related symptoms (PGIC, PGIS) each show a hint of added benefit, of minor and considerable extent, respectively. The overall interpretation, however, must take into account that some of the patients were only slightly symptomatic at baseline and potentially unable to achieve any measurable symptomatic improvement. Furthermore, only patients with prior splenectomy exhibit a hint of lesser harm of major extent for SAEs. It cannot be ruled out that the SAEs also include events due to the symptoms or late complications of the underlying disease. On the other hand, there is a hint of greater harm of considerable extent for the AE of bone pain. However, this unfavourable effect did not completely call into question the favourable effects.

In summary, there is a hint of minor added benefit of luspatercept in comparison with the ACT for patients with anaemia associated with NTD 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 non-transfusion-dependent beta-thalassaemia[b]	Transfusion therapy with packed red blood cells as needed in combination with chelation therapy as per approval, preferably as monotherapy[c]	Hint of minor added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. 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.
c. RBC transfusions and chelation therapy, if indicated, are presumed to be performed in both arms of the study. The reasons are to be documented.
d. The BEYOND study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RBC: red blood cell

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

The approach for deriving 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Celgene. A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study To Determine The Efficacy And Safety Of Luspatercept (Ace-536) Versus Placebo In Adults With Non-Transfusion Dependent Beta (B)-Thalassemia (THE BEYOND STUDY); study ACE-536-B-THAL-002; Clinical Study Report [unpublished]. 2021.

4. Celgene. A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) versus Placebo in Adults with Non Transfusion Dependent Beta (β)-Thalassemia [online]. [Accessed: 17.04.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003225-33.

5. Celgene. A Study to Determine the Efficacy and Safety of Luspatercept in Adults With Non Transfusion Dependent Beta (β)-Thalassemia [online]. 2022 [Accessed: 17.04.2023]. URL: https://ClinicalTrials.gov/show/NCT03342404.

6. Taher AT, Cappellini MD, Kattamis A et al. Luspatercept for the treatment of anaemia in non-transfusion-dependent β-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial. Lancet Haematology 2022; 9(10): e733-e744. https://dx.doi.org/10.1016/S2352-3026(22)00208-3.

7. Bristol-Myers Squibb. Reblozyl 25 mg/75 mg Pulver zur Herstellung einer Injektionslösung [online]. 2023 [Accessed: 29.03.2023]. URL: https://www.fachinfo.de/.

8. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Beta Thalassämie Leitlinie [online]. 2022 [Accessed: 20.02.2023]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/beta-thalassaemie/@@guideline/html/index.html.

9. Taher A, Vichinsky E, Musallam K et al. Guidelines for the Management of non transfusion dependent Thalassaemia (NTDT), 2nd Edition [online]. 2017 [Accessed: 20.02.2023]. URL: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf.

10. Gesellschaft für Pädiatrische Onkologie und Hämatologie. S2k-Leitlinie Diagnostik und Therapie der sekundären Eisenüberladung bei Patienten mit angeborenen Anämien [online]. 2022 [Accessed: 20.02.2023]. URL: https://register.awmf.org/assets/guidelines/025-029l_S2k_Diagnostik-Therapie-der-sekundaeren-Eisenueberladung-bei-Patienten-mit-angeborenen-Anaemien_2022-03_1.pdf.

11. Taher A, Viprakasit V, Cappellini MD et al. Development of a patient-reported outcomes symptom measure for patients with nontransfusion-dependent thalassemia (NTDT-PRO). Am J Hematol 2019; 94(2): 171-176.

12. Taher A, Cappellini MD, Viprakasit V et al. Validation of a patient-reported outcomes symptom measure for patients with nontransfusion-dependent thalassemia (NTDT-PRO). Am J Hematol 2019; 94(2): 177-183.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 29.06.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

14. Hien P, Morr H. [Six-minute walk test in chronic lung and heart disease - technical aspects, interpretation, limitations]. Pneumologie 2002; 56(9): 558-566. https://dx.doi.org/10.1055/s-2002-33850.

15. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1): 111-117. https://dx.doi.org/10.1164/ajrccm.166.1.at1102.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-20.html.