Luspatercept (non-transfusion-dependent beta-thalassaemia)

Addendum to Project A23-20 (dossier assessment)[1]

ADDENDUM

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[1] Translation of addendum A23-80 *Luspatercept (nicht transfusionsabhängige Beta-Thalassämie) – Addendum zum Projekt A23-20 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	Appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 8 August 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-20 (Luspatercept– Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- analysis of the outcome of transfusion avoidance, taking into account the entire observation period

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) BEYOND was used for the benefit assessment of luspatercept [1] in comparison with the appropriate comparator therapy (ACT) in adult patients with anaemia associated with non-transfusion-dependent beta-thalassaemia.

The analyses for the outcome of transfusion avoidance presented by the company in its dossier [3] were unsuitable for the benefit assessment, as they included only packed red blood cell 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". Secondly, this also meant that transfusions from patients who discontinued therapy before Week 48 may not have been included in the analyses at Week 48 presented by the company.

With its comments [2], the company subsequently submitted analyses of the outcome of transfusion avoidance that included all events during the full observation period, even after treatment discontinuation.

These subsequently submitted analyses are considered usable.

2.1 Results

Risk of bias

The risk of bias for the results of the outcome of transfusion avoidance is rated as low.

Results

Table 1 shows the results of the analyses subsequently submitted for the outcome of transfusion avoidance up to Week 48.

Table 1: Results (morbidity) – RCT, direct comparison: luspatercept vs. placebo

Study Outcome category Outcome	Luspatercept		Placebo		Luspatercept vs. placebo
	N	Patients with event[a] n (%)	N	Patients with event[a] n (%)	RR [95% CI]; p-value[b]
BEYOND					
Morbidity					
Transfusion avoidance (Week 48)	96	81 (84.4)	49	30 (61.2)	1.36 [1.08; 1.72]; 0.009

a. Patients without complete observation until Week 48 were not rated as transfusion-free (this applies to 3 patients in each of the 2 treatment arms).
b. 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.

CI: confidence interval; Hb: haemoglobin; n: number of patients with event; N: number of analysed patients; NTDT-PRO: non-transfusion-dependent thalassaemia-patient-reported outcome; RCT: randomized controlled trial; RR: relative risk

Transfusion avoidance

A statistically significant difference between the treatment arms in favour of luspatercept was shown for the outcome of transfusion avoidance. The extent of the effect was no more than marginal, however. There is no evidence of an added benefit of luspatercept in comparison with the ACT; an added benefit is therefore not proven.

Assessment of the added benefit at outcome level

The extent of the added benefit at outcome level is estimated from the results presented in Table 1. Table 2 presents only the results of the outcome of transfusion avoidance relevant in the present addendum.

Determination of the outcome category for the morbidity outcomes

The company presented no information for categorizing the severity of the outcome of transfusion avoidance. The outcome of transfusion avoidance is therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 2: Extent of added benefit at outcome level: luspatercept versus placebo

Outcome category **Outcome**	**Luspatercept vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Transfusion avoidance (Week 48)	84.4% vs. 61.2% RR: 1.36 [1.08; 1.72] RR: 0.74 [0.58; 0.93][c] p = 0.009	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]

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.

CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of luspatercept from dossier assessment A23-20.

The following Table 3 shows the result of the benefit assessment of luspatercept under consideration of dossier assessment A23-20 and the present addendum.

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; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; RBC: red blood cells

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Luspatercept (nicht transfusionsabhängige Beta-Thalassämie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a23-20_luspatercept_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 933: Luspatercept (nicht transfusionsabhängige Beta-Thalassämie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. 2023: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/940/#stellungnahmen in the document "Zusammenfassende Dokumentation".

3. Bristol-Myers Squibb. Luspatercept (Reblozyl); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 11.08.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/940/#dossier.