Pegunigalsidase alfa (Fabry disease)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment Pegunigalsidase alfa *(Morbus Fabry) – Nutzenbewertung gemäß § 35a SGB V*. 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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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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADA	American Diabetes Association
AE	adverse event
ARB	angiotensin receptor blocker
BPI-SF	Brief Pain Inventory-Short Form
CI_u	upper limit of the confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention-to-treat
MSSI	Mainz Severity Score Index
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UPCR	urine protein/creatinine ratio
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pegunigalsidase alfa. 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 29 September 2023.

Research question

The aim of this report is to assess the added benefit of pegunigalsidase alfa in comparison with agalsidase beta as appropriate comparator therapy (ACT) in patients with a confirmed diagnosis of Fabry disease.

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

Table 2: Research question of the benefit assessment of pegunigalsidase alfa

Therapeutic indication	**ACT**[a, b]
Adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).	Agalsidase alfa or agalsidase beta or migalastat
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The approval and dosing information of the drugs' Summary of Product Characteristics (SPCs) must be adhered to, and any deviations justified separately. 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 provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Study pool and study design

The benefit assessment of pegunigalsidase alfa is based on the double-blind RCT BALANCE, which compares pegunigalsidase alfa with agalsidase beta.

The study included adult patients with a confirmed diagnosis of Fabry disease who had been treated with agalsidase beta for at least 1 year prior to the start of the study and had a linear decrease in the estimated glomerular filtration rate (eGFR) of at least 2 mL/min/1.73 m²/year. Patients with an eGFR below 40 ml/min/1.73 m² were excluded from participation in the study. Treatment-naive patients were also excluded, although they are included in the

approved therapeutic indication for pegunigalsidase alfa. Hence, no usable data are available for these patients.

In the BALANCE study, a total of 78 patients were randomly assigned to treatment with pegunigalsidase alfa (N = 53) or continuation of their treatment with agalsidase beta (N = 25) in a 2:1 ratio. Randomization was stratified by the urine protein/creatinine ratio category at baseline (< 1 g/g vs. ≥ 1 g/g).

Treatment with pegunigalsidase alfa and agalsidase beta was carried out in compliance with the respective Summary of Product Characteristics (SPC). However, there were deviations in the administration of premedication to avoid infusion-related reactions.

Patients were treated for 24 months. The primary outcome of the study was the annual change in the kidney function (eGFR slope). Patient-relevant secondary outcomes were recorded in the categories “mortality”, “morbidity” and side effects.

Uncertainties of the BALANCE study

Reduction of premedication administered prior to study inclusion to avoid infusion-related reactions

In the BALANCE study, the patients retained their premedication existing under the pretreatment with agalsidase beta only during the first administration of the study medication, after which the premedication was gradually reduced for all patients within the first 3 months. It is not clear from the documents that the decision to initiate a reduction was reviewed on an individualized basis according to the respective tolerability. The clinical study report (CSR) describes that infusion-related reactions occurred primarily in patients who had previously received a premedication during treatment with agalsidase beta. The proportion of patients who received premedication at baseline was 39% in the intervention arm and 60% in the comparator arm. Overall, the risk of infusion-related reactions appears to be increased, particularly after discontinuation of the premedication. The SPC for pegunigalsidase alfa provides recommendations on how to proceed when switching from treatment with agalsidase beta or agalsidase alfa to pegunigalsidase alfa with an ongoing premedication. This should be maintained for the first 3 months (6 infusions) of treatment. In case of corresponding tolerability, a gradual reduction can then be carried out.

Antibodies against the active substance

The presence of antibodies against the drug may not only favour infusion reactions but also impair the effectiveness of the respective therapy. The S1 guideline for the diagnosis and treatment of Fabry disease recommends testing for the presence of antibodies against the drug if the effectiveness of the treatment decreases. If antibodies are present, a treatment switch can be considered, and there is also the option of immunomodulating therapy. It was

also noted in the minutes of the counselling interview that although it is generally appropriate to continue treatment with agalsidase beta, the antibody status must be taken into account. There is no information available that corresponding measures for patients with a positive antibody status were investigated in the BALANCE study. At the start of the study, the proportion of patients with antibodies against the respective drug administered was comparable in both arms (pegunigalsidase alfa: 34.6% vs. agalsidase beta 32.0%).

Decreasing renal function under pretreatment with agalsidase beta

Patients were included in the study if their renal function had decreased by at least 2 mL/min/1.73 m²/year. The guideline describes that under enzyme replacement therapy, women lose approx. 1 mL/min/1.73 m²/year of renal filtration capacity and men approx. 3 mL/min/1.73 m²/year, while untreated patients can lose up to 8 to 12 mL/min/1.73m^2 per year. Prior to inclusion in the study, the patients were all receiving treatment with agalsidase beta and had a mean decrease in renal function of around 8 mL/min/1.73 m²/year at baseline. In view of the fact that enzyme replacement therapy certainly enables a greater treatment response in terms of renal function, the company's inclusion criterion of restricting itself to patients with a continued severe decline in renal function during treatment with agalsidase beta is not appropriate. Although it remains to be seen whether further treatment with agalsidase beta is adequate for these patients in the comparator arm, there was a comparable improvement in renal function in both treatment arms during the course of the study

Uncertainties do not lead to study exclusion

Overall, the uncertainties described do not lead to the exclusion of the study from the benefit assessment. However, the described aspects are taken into account when assessing the certainty of conclusions of the results and lead to a limitation of the certainty of conclusions.

Risk of bias

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

For the results on all-cause mortality and the outcomes on morbidity, the risk of bias is rated as low. There is a high risk of bias for the results of the side effects outcomes because they include a relevant proportion of events that can be both side effects and symptoms of the disease. In the present therapeutic indication, it is not possible to differentiate between side effects of the treatment and events of the underlying disease

Results

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Morbidity

Worst pain (Brief Pain Inventory-Short Form [BPI-SF] Item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (BPI-SF Item 3). There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Pain interference (BPI-SF Items 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (BPI-SF Item 9a–g). There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Outcome on the clinical morbidity/symptoms of Fabry disease

No suitable data are available for the outcome of clinical morbidity/symptoms of Fabry disease. There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status recorded with the EQ-5D visual analogue scale (VAS). There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Health-related quality of life

There were no data for the outcome "health-related quality of life". There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. There is no

hint of greater or lesser harm from pegunigalsidase alfa in comparison with agalsidase beta; greater or lesser harm is therefore not proven.

Infusion-related reactions

No suitable data are available for the outcome of infusion-related reactions. There is no hint of greater or lesser harm from pegunigalsidase alfa in comparison with agalsidase beta; greater or lesser harm is therefore not proven.

Chest pain (SAEs), respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference between treatment groups in favour of pegunigalsidase alfa was shown for the outcomes of chest pain (SAEs) and respiratory, thoracic and mediastinal disorders severe AEs). There is a hint of lesser harm from pegunigalsidase alfa in comparison with agalsidase beta.

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 the added benefit of the drug pegunigalsidase alfa in comparison with the ACT is assessed as follows:

Overall, pegunigalsidase alfa shows positive effects over agalsidase beta for patients with Fabry disease.

These are significant effects in the outcomes of chest pain (SAE) and respiratory, thoracic and mediastinal disorders (severe AEs). However, due to the low number of events (2 events in the outcome “chest pain” and 3 events in the outcome “respiratory, thoracic and mediastinal disorders”) and the existing limitations of the BALANCE study, these effects are not considered sufficient to derive an overall added benefit for pegunigalsidase alfa.

In summary, there is no hint of an added benefit of pegunigalsidase alfa over the ACT agalsidase beta for patients with a confirmed diagnosis of Fabry disease.

Table 3 shows a summary of probability and extent of the added benefit of pegunigalsidase alfa.

[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: Pegunigalsidase alfa – extent and probability of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).	Agalsidase alfa or agalsidase beta or migalastat	Added benefit not proven[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The approval and dosing information of the drugs' Summary of Product Characteristics (SPCs) must be adhered to, and any deviations justified separately.
c. The BALANCE study only included pretreated patients and patients with an eGFR of ≥ 40 mL/min/1.73m^2 whose renal function had previously decreased by at least 2 mL/min/1.73 m^2/year. It remains unclear whether the observed results are transferable to treatment-naive patients and to patients with better renal functions.

eGFR: estimated glomerular filtration rate; min: minute; 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.

I 2 Research question

The aim of this report is to assess the added benefit of pegunigalsidase alfa in comparison with agalsidase beta as ACT in patients with a confirmed diagnosis of Fabry disease.

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

Table 4: Research question of the benefit assessment of pegunigalsidase alfa

Therapeutic indication	**ACT**[a, b]
Adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase)	Agalsidase alfa or agalsidase beta or migalastat
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately. 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 provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pegunigalsidase alfa (status: 19 September 2023)
- bibliographical literature search on pegunigalsidase alfa (last search on 24 July 2023)
- search in trial registries/trial results databases for studies on pegunigalsidase alfa (last search on 25 July 2023)
- search on the G-BA website for pegunigalsidase alfa (last search on 25 July 2023)

To check the completeness of the study pool:

- search in trial registries for studies on pegunigalsidase alfa (last search on 10 October 2023); for search strategies, see I Appendix 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: pegunigalsidase alfa versus agalsidase beta

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
BALANCE	Yes	No	Yes	Yes [3]	Yes [4,5]	No

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

The BALANCE study is used for the benefit assessment. The study pool concurs with that of the company.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BALANCE	RCT, double-blind, parallel	Adults (18-60 years) with a confirmed diagnosis of Fabry disease and ▪ at least 1 year under treatment with agalsidase beta ▪ a linear decrease in the eGFR value ≥ -2 mL/min/1.73 m²/year ▪ a screening eGFR value (according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI formula]) of 40-120 mL/min/1.73 m²	Pegunigalsidase alfa (N = 53) agalsidase beta (N = 25)[b]	Screening: 1 month treatment: 24 months[b] follow-up[c]: 3 months	29 study centres in Czech Republic, Finland, France, Great Britain, Hungary, Italy, Netherlands, Norway, Slovenia, Spain, Switzerland, USA 08/2016–10/2021 data cut-offs: ▪ 12 October 2020 (interim analysis) ▪ 12 October 2021 (final analysis)	Primary: annual change in renal function (eGFR slope) secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. After the end of the study, the patients were eligible for participating in an open-label extension study in which the patients continued their treatment with pegunigalsdiase alfa or switched to treatment with pegunigalsidase alfa.
c. Only for patients who did not participate in the open-label extension study.

AE: adverse event; CKD-EPI: chronic kidney disease epidemiology collaboration equation; eGFR: estimated glomerular filtration rate; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta

Study	Intervention	Comparison
BALANCE	Pegunigalsidase alfa 1 mg/kg body weight IV every 2 weeks as an infusion	Agalsidase beta 1 mg/kg body weight IV every 2 weeks as an infusion
	Dose adjustment: ▪ adjustment of the permitted infusion rate, depending on the patient's signs and symptoms ▪ dose adjustment in case of changes in patient weight at months 6, 12 or 18 ≥ 25% compared to baseline	
	Allowed prior and concomitant treatment ▪ required: treatment with agalsidase beta for at least 1 year and administration of at least 80% of the dose within the last 6 months (i.e. at least 10.4 mg/kg body weight) ▪ individualized treatment with ACE inhibitors or angiotensin receptor blockers ▪ analgesics as required ▪ premedication to control infusion-related reactions (corticosteroids, antihistamines, paracetamola) **disallowed concomitant treatment** ▪ agalsidase alfa and other drugs for the treatment of Fabry disease	

a. Patients who were already on premedication prior to participation in the study received this premedication upon the 1st infusion whereafter it was phased out over the following 3 months.

ACE: angiotensin-converting enzyme; RCT: randomized controlled trial

The BALANCE study is a double-blind RCT comparing pegunigalsidase alfa with agalsidase beta.

The study included adult patients with a confirmed diagnosis of Fabry disease who had been treated with agalsidase beta for at least 1 year prior to the start of the study and had a linear decrease in the eGFR of at least 2 mL/min/1.73 m²/year. Patients with an eGFR below 40 ml/min/1.73 m² were excluded from participation in the study. Treatment-naive patients were also excluded, although they are included in the approved therapeutic indication for pegunigalsidase alfa. Hence, no usable data are available for these patients.

In the BALANCE study, a total of 78 patients were randomly assigned to treatment with pegunigalsidase alfa (N = 53) or continuation of their treatment with agalsidase beta (N = 25) in a 1:1 ratio. Randomization was stratified by the urine protein/creatinine ratio category at baseline (< 1 g/g vs. ≥ 1 g/g).

Treatment with pegunigalsidase alfa and agalsidase beta was carried out in compliance with the respective SPC [6,7]. However, there were deviations in the administration of premedication to avoid infusion-related reactions (see below).

Patients were treated for 24 months. The primary outcome of the study was the annual change in the kidney function (eGFR slope). Patient-relevant secondary outcomes were recorded in the categories “mortality”, “morbidity” and side effects.

Data cut-offs

According to the study protocol, an interim analysis after 12 months was planned for the BALANCE study in addition to the final analysis after 24 months. For the benefit assessment, the company presented the analysis on the final data cut-off at Month 24; this time point is considered for the present benefit assessment. This final data cut-off took place when the last patient had completed the 24-month randomized study phase.

Analysis population a presented by the company

The population referred to by the company in the dossier as the intention-to-treat (ITT) population deviates from the population of randomized patients (pegunigalsidase alfa N = 53 vs. agalsidase beta N = 25) and comprises those patients who received at least one dose of the study medication (pegunigalsidase alfa N = 52 vs. agalsidase beta N = 25). One patient in the intervention arm discontinued participation in the study by withdrawing consent before administration of the first study medication. In this case, it is not assumed that the exclusion of one patient has any consequences although using the treated patients as the ITT population is not appropriate.

Uncertainties of the BALANCE study

Reduction of premedication administered prior to study inclusion to avoid infusion-related reactions

In the BALANCE study, the patients retained their premedication existing under the pretreatment with agalsidase beta only during the first administration of the study medication, after which the premedication was gradually reduced for all patients within the first 3 months. It is not clear from the documents that the decision to initiate a reduction was reviewed on an individualized basis according to the respective tolerability. The CSR describes that infusion-related reactions occurred primarily in patients who had previously received a premedication during treatment with agalsidase beta. The proportion of patients who received premedication at baseline was 39% in the intervention arm and 60% in the comparator arm. Overall, the risk of infusion-related reactions appears to be increased, particularly after discontinuation of the premedication. The SPC for pegunigalsidase alfa provides recommendations on how to proceed when switching from treatment with agalsidase beta or agalsidase alfa to pegunigalsidase alfa with an ongoing premedication. This should be maintained for the first 3 months (6 infusions) of treatment. In case of corresponding tolerability, a gradual reduction can then be carried out [6].

One possible cause for the occurrence of infusion reactions is the presence of antibodies against the infused proteins [8].

Antibodies against the active substance

The presence of antibodies against the drug may not only favour infusion reactions but also impair the effectiveness of the respective therapy. The S1 guideline for the diagnosis and treatment of Fabry disease recommends testing for the presence of antibodies against the drug if the effectiveness of the treatment decreases. If antibodies are present, a treatment switch can be considered, and there is also the option of immunomodulating therapy [8]. It was also noted in the minutes of the counselling interview that although it is generally appropriate to continue treatment with agalsidase beta, the antibody status must be taken into account [9]. There is no information available that corresponding measures for patients with a positive antibody status were investigated in the BALANCE study. At the start of the study, the proportion of patients with antibodies against the respective drug administered was comparable in both arms (pegunigalsidase alfa: 34.6% vs. agalsidase beta 32.0%). Thus, a bias with regard to the antibody status between the two study arms is not assumed.

Decreasing renal function under pretreatment with agalsidase beta

Patients were included in the study if their renal function had decreased by at least 2 mL/min/1.73 m²/year. The guideline describes that under enzyme replacement therapy, women lose approx. 1 mL/min/1.73 m²/year of renal filtration capacity and men approx. 3 mL/min/1.73 m²/year, while untreated patients can lose up to 8 to 12 mL/min/1.73m²/year [8]. Prior to inclusion in the study, the patients were all receiving treatment with agalsidase beta and had a mean decrease in renal function of around 8 mL/min/1.73 m²/year at baseline (see Table 8). In view of the fact that enzyme replacement therapy certainly enables a greater treatment response in terms of renal function, the company's inclusion criterion of restricting itself to patients with a continued severe decline in renal function during treatment with agalsidase beta is not appropriate. Although it remains to be seen whether further treatment with agalsidase beta is adequate for these patients in the comparator arm, there was a comparable improvement in renal function in both treatment arms during the course of the study.

Uncertainties do not lead to study exclusion

Overall, the uncertainties described do not lead to the exclusion of the study from the benefit assessment, but are taken into account when assessing the certainty of conclusions of the results and lead to a limitation of the certainty of conclusions (see Section I 4.2).

Characteristics of the study population

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

Table 8: Characteristics of the study population and discontinuation of the study/treatment – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta (multipage table)

Study characteristic category	Pegunigalsidase alfa N[a] = 52	Agalsidase beta N[a] = 25
BALANCE study		
Age [years], mean (SD)	44 (10)	45 (10)
Sex [F/M], %	44/56	28/72
Ethnic origin, n (%)		
Asian	2 (4)	0
Black/African American	1 (2)	2 (8)
White	49 (94)	23 (92)
eGFR [mL/min/1.73 m^2], mean (SD)	73.5 (20.2)	74.2 (21.0)
eGFR slope at baseline [ml/min/1.73 m^2], mean (SD)	-8.0 (6.6)	-8.3 (4.3)
Urine protein/creatinine ratio (UPCR) stratification at screening, n (%)		
< 1 g/g	41 (79)	21 (84)
≥ 1 g/g	11 (21)	4 (16)
Treatment with ACE inhibitors/angiotensin receptor blockers (ARB), n (%)		
Yes	26 (50)	16 (64)
No	26 (50)	9 (36)
Region, n (%)		
United States	33 (63)	18 (72)
Outside the USA	19 (37)	7 (28)
Duration of the last continuous agalsidase beta treatment [months], mean (SD)	65.0 (48.0)	77.3 (41.3)
Classification of Fabry disease, n (%)		
Classical	27 (52)	14 (56)
Non-classical	25 (48)	11 (44)
American Diabetes Association (ADA) status at baseline[b], n (%)		
Positive	18 (35)	8 (32)
Negative	34 (65)	17 (68)
Treatment discontinuation, n (%)[c, d,e]	5 (9)	1 (4)
Study discontinuation, n (%)[c,d, e]	5 (9)	1 (4)

Table 8: Characteristics of the study population and discontinuation of the study/treatment – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta (multipage table)

Study characteristic category	Pegunigalsidase alfa N[a] = 52	Agalsidase beta N[a] = 25
a. Number of patients who received at least one dose of the study medication. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant. b. The ADA status was determined with reference to the drug administered in the respective treatment arm. c. In Module 4 A, the company describes the 6 patients as both treatment and study dropouts and gives the same reasons for discontinuation in each case. The study report only contains information on study dropouts. It therefore remains unclear whether the information actually relates to those who have dropped out of treatment. d. Data based on the number of randomized patients (pegunigalsidase alfa: N = 53 vs. agalsidase beta: N = 25). e. Reasons for treatment or study discontinuation in the intervention vs. the control arm were (in each case number of patients): AEs (2 vs. 0) and withdrawal of consent (3 vs. 1). ACE: angiotensin-converting enzyme; ADA: anti-drug antibody; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; F: female, M: male; mL: millilitre; min: minute; n: Number of patients in the category; N: Number of patients who received at least one dose of the study medication; RCT: randomized controlled trial; SD: standard deviation; UPCR: urine protein/creatinine ratio		

The patient characteristics were largely balanced between the study arms. The mean age of the patients was about 45 years and about half of them had classic Fabry disease. The proportion of female patients was higher in the intervention arm than in the comparator arm. Renal function was comparable in both arms and decreased on average by around 8 mL/min/1.73m^2/year before the start of the study.

The dossier provides inconsistent information on study or treatment discontinuations. The company describes the 6 patients partly as treatment dropouts and partly as study dropouts. For example, the dossier describes that 1 patient had discontinued the study before the first administration of the study medication and thereafter 4 further patients discontinued treatment. Module 4 provides no information on whether the discontinuation of treatment also led to discontinuation of the study. Module 5 describes 5 patients in the intervention arm as study dropouts, stating the identical reasons as for the treatment discontinuation, so that it can be assumed that the respective treatment discontinuations also led to study discontinuation.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta

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

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

Transferability of the study results to the German health care context

The company considers the results of the BALANCE study to be transferable to the German health care context. According to the company, the characteristics of the patients included in the study with regard to general patient characteristics such as ethnic origin, average height and body weight suggest a transferability to the German health care context. Moreover, as Fabry disease is a rare disease, patients would only be cared for by experienced and appropriately specialized physicians. In addition, the patients were treated in Europe and the USA, which according to the company is a comparable 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
  - worst pain (measured using the Brief Pain Inventory-Short Form [BPI-SF] Item 3)
  - pain interference (measured using the BPI-SF Item 9a–g)
  - outcome on the clinical morbidity/symptoms of Fabry disease
  - health status, recorded using the EQ-5D VAS
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infusion-related reactions
  - 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 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta

Study	Outcomes											
	All-cause mortality	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a–g)	Outcome on the clinical morbidity/symptoms of Fabry disease	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions	Chest pain (Preferred Term [PT], SAEs)	Respiratory, thoracic and mediastinal disorders (SOC, severe AEs[a])
BALANCE	Yes	Yes	Yes	No[b]	Yes	No[c]	Yes	Yes	Yes	No[d]	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The company presented a composite outcome on the clinical morbidity of Fabry disease and the outcome of symptoms recorded with the Mainz Severity Score Index (MSSI). However, in each case, suitable data are missing; for justification see Section I 4.1 of the present dossier assessment.
c. Outcome not recorded.
d. No suitable data available; for the reasoning, see Section I 4.1.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Outcome of change in renal function

The outcome of change in renal function (eGFR slope) per year is not used for the benefit assessment. A change in renal function based on the glomerular filtration rate is not necessarily patient relevant. Taking into account the high median baseline mGFR values of 73.45 mL/min/1.73m^2 in the intervention arm and 74.85 mL/min/1.73m^2 in the comparator arm and the small change in renal function measured in the study (median change per year of approx. −2.5 or −2.2 mL/min/1.73 m²), it cannot be assumed that the outcome represents a noticeable deterioration in renal function for the majority of patients affected.

Comment on outcomes on the clinical morbidity/symptoms of Fabry disease

Composite outcome on the clinical morbidity of Fabry disease

Fabry disease is a multi-organ disease with late complications manifesting in various organ systems. The BALANCE study recorded these with a composite outcome on the clinical morbidity comprising the following components:

- renal morbidity

- cardiac morbidity
- cerebrovascular morbidity
- death without cardiac cause

Events were recorded under the respective components that were categorized as relevant by a clinical monitor either as part of the AE survey or from the clinical information stored in the database. These include PTs according to MedDRA (Medical Dictionary for Regulatory Activities) as well as other events. The events that occurred in the study are coded as PTs in the study report.

The operationalization of the components is not fully comprehensible. For example, the dossier describes events for the respective components of the composite outcome that are recorded under this component. However, it is unclear, for example, which PTs should be assigned to the event "proof of progressive heart disease requiring a pacemaker". The study report also shows that 1 event of the cardiac morbidity component was a troponin elevation and 1 was a grade 2 atrioventricular block. However, it is not clear from the operationalization of the cardiac morbidity component that these two events were to be recorded. It therefore remains unclear to what extent the coding of events by the clinical monitor, especially those taken from the clinical documentation, was standardized. Moreover, individual events of the respective components comprise non-directly patient-relevant events.

Due to the incomprehensible operationalization of the outcome, the results for the composite outcome on clinical morbidity of Fabry disease and its individual components were not used in the present benefit assessment.

Symptoms recorded using the Mainz Severity Score Index (MSSI)

To assess the symptoms and categorize the severity of the disease, the company presented results from the disease-specific instrument MSSI. The MSSI is used to assess the presence of symptoms in the 4 domains of general symptoms, renal symptoms, neurological symptoms and cardiovascular symptoms. Physicians check for the presence of certain symptoms, which are assigned a defined score value if they are present. For example, the symptom diarrhoea is awarded 1 point, while the presence of pulmonary symptoms is awarded 2 points. The total score is calculated from the sum of the scores and ranges from 0 to 76, with higher scores indicating more severe symptoms. The different degrees of severity are categorized into mild (0 to 19 points), moderate (20 to 40 points) and severe (> 40 points) based on the scores achieved.

Although the MSSI is a disease-specific instrument for recording the symptom burden of patients with Fabry disease, there are uncertainties in the operationalization. On the one hand, it is not comprehensible for which events a symptom is considered to be present. For

example, neither the information in the validation publication [10] nor the instrument itself makes clear whether the pulmonary symptoms only comprise certain symptoms or also, for example, the occurrence of an acute infection. Furthermore, it remains unclear whether the varying degrees of scoring of the individual symptoms, which are based on expert assessments [10], are adequate, or how this expert decision was made. The company also describes that the mapping of the symptoms was validated both for the 4 individual domains and for the total score. The validation publication, however, does not address an isolated analysis of the individual domains with corresponding limits for categorizing symptom severity [10].

In addition, the MSSI contains some components, such as abnormalities in the electrocardiogram, which are not directly relevant to the patient.

Due to the uncertainties described, the results for the outcome "symptoms", recorded via the MSSI, were not used for the benefit assessment. However, the analyses on the change in the MSSI total score at Week 104 compared to baseline are presented as supplementary information in I Appendix B.

Worst pain (BPI-SF Item 3) and pain interference (BPI-SF Items 9a–g)

For the outcomes “worst pain” and “pain interference”, the company presented responder analyses for the proportion of patients with an improvement by ≥ 15% of the scale range at Week 104 (scale range 0 to 10). This is appropriate, as the reduction of pain is an essential treatment goal in the present therapeutic indication [8]. In the dossier, however, the company provides no information as to which score 15% of the scale range corresponds to. A change of ≥ 1.5 points is considered a clinically relevant change for the benefit assessment procedure.

The pain intensity based on BPI-SF Items 3–6 represents an equally weighted average of different pains. Of these, the worst pain felt by the patient (Item 3) is of particular importance. It therefore appears meaningful to present the results for this item separately and to use them for the derivation of the added benefit. The results on average pain intensity (BPI-SF Items 3–6) are only presented as supplementary information in the present assessment. The results of the BPI-SF Items 3–6 were not used for the derivation of the added benefit, as otherwise the results of Item 3 would have been considered twice. If there are discrepant results compared with the results of worst pain (Item 3), these are discussed. Pain interference (BPI-SF Items 9 a–g) was also included in the present assessment.

Health status (EQ-5D VAS)

For the outcome “health status”, the company presented responder analyses for the proportion of patients with an improvement by ≥ 15% of the scale range at Week 104 (scale range 0 to 100). This is appropriate, as an improvement of the general condition of patients with Fabry disease represents a further treatment goal [8].

Side effects

The company presented both analyses on side effects that include all AEs regardless of the symptoms of the disease or side effects of the study medication, and on side effects without disease-related events. The company defined disease-related events as the events that it recorded as part of the composite outcome on the clinical morbidity of Fabry disease, as well as infusion-related reactions. As explained above, there are uncertainties in the operationalization of the composite outcome on clinical morbidity of Fabry disease, and the analyses presented cannot be used for the benefit assessment. Moreover, the exclusion of infusion-related reactions from the analyses on side effects as disease-related events is not appropriate. Therefore, the results on side effects without disease-related events presented by the company are not considered in the benefit assessment.

Since the underlying disease manifests itself in numerous different symptoms due to the failure of various organs, it is not possible to clearly differentiate between side effects of the therapy and events of the underlying disease for numerous events. This is taken into account in the assessment of the outcome-specific risk of bias (see Section I 4.2).

Infusion-related reactions

Due to the uncertainties described in Section I 3.2 regarding the tapering of the premedication that was ongoing before study participation in order to avoid infusion-related reactions, it cannot be ruled out that the events that occurred were significantly influenced by the discontinuation of the premedication ongoing before study inclusion as specified in the study protocol. Hence, no suitable data are available for the outcome of infusion-related reactions.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pegunigalsidase alfa vs. agalsidase beta

Study		Outcomes											
	Study level	All-cause mortality	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Items 9a–g)	Outcome on the clinical morbidity/symptoms of Fabry disease	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reactions	Chest pain (PT, SAEs)	Respiratory, thoracic and mediastinal disorders (SOC, severe AEs[a])
BALANCE	L	L	L	L	–[b]	L	–[c]	H[d]	H[d]	H[d]	–[b]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
c. Outcome not recorded.
d. Including a relevant proportion of events that can be both side effects and symptoms of the disease.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

For the results on all-cause mortality and the outcomes on morbidity, the risk of bias is rated as low. There is a high risk of bias for the results of the side effects outcomes because they include a relevant proportion of events that can be both side effects and symptoms of the disease. In the present therapeutic indication, it is not possible to differentiate between side effects of the treatment and events of the underlying disease.

I 4.3 Results

Table 12 summarizes the results on the comparison of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Tables on common AEs, common SAEs, common severe AEs and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. Results on the outcome of symptoms (recorded using the MSSI) are presented as supplementary information in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: pegunigalsidase alfa versus agalsidase beta (multipage table)

Study outcome category outcome	Pegunigalsidase alfa		Agalsidase beta		Pegunigalsidase alfa vs. agalsidase beta
	L	patients with event n (%)	L	patients with event n (%)	RR [95% CI]; p-value
BALANCE study					
Mortality					
All-cause mortality	52	0	25	0	–
Morbidity					
Worst pain (BPI-SF item 3)[a]	*45*	*12 (26.7)*	*22*	*3 (13.6)*	*1.96 [0.61; 6.22]* *0.300*[b]
Pain intensity (BPI-SF Items 3–6, improvement at Week 104)[d] (supplementary information)	*45*	*5 (11.1)*	*22*	*1 (4.5)*	*2.44 [0.30; 19.68];* *0.433*[b]
Pain interference (BPI-SF Items 9a–g, improvement at week 104)[a]	45	5 (11.1)	22	2 (9.1)	1.22 [0.26; 5.81]; 0.800[b]
Outcome on the clinical morbidity/symptoms of Fabry disease	No suitable data[c]				
Health status (EQ-5D VAS, improvement at Week 104)[d]	46	7 (15.2)	22	4 (18.2)	0.84 [0.27; 2.56]; 0.756[b]
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	52	47 (90.4)	25	24 (96.0)	–
SAEs	52	8 (15.4)	25	6 (24.0)	0.64 [0.25; 1.65]; 0.413[b]
Severe AEs[e]	52	15 (28.9)	25	7 (28.0)	1.03 [0.48; 2.20]; 0.987[b]
Discontinuation due to AEs	52	2 (3.8)	25	0 (0.0)	2.45 [0.12; 49.26][f]; 0.403[b]
Infusion-related reactions	No suitable data[c]				
Chest pain (PT, SAEs)	52	0 (0.0)	25	2 (8.0)	0.10 [0.00; 1.97][f]; 0.042[b, g]
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs)[h]	52	0 (0.0)	25	3 (12.0)	0.07 [0.00; 1.31][f]; 0.011[b, g]

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: pegunigalsidase alfa versus agalsidase beta (multipage table)

Study outcome category outcome	Pegunigalsidase alfa		Agalsidase beta		Pegunigalsidase alfa vs. agalsidase beta
	L	patients with event n (%)	L	patients with event n (%)	RR [95% CI]; p-value

a. A decrease by ≥ 15% from baseline is considered a clinically relevant improvement (scale range 0 to 10). The company provides no information on how many points correspond to the 15 % response criterion.
b. Institute's calculation, unconditional exact test (CSZ method according to [11]).
c. See Section I 4.1 for reasons.
d. A score increase by ≥ 15 points from baseline is defined as a clinically relevant (scale range 0 to 100).
e. Operationalized as CTCAE grade ≥ 3.
f. In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
g. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
h. Includes 1 event each of the PTs "acute respiratory insufficiency", "chronic obstructive pulmonary disease" and "pulmonary embolism".

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.2).

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Morbidity

Worst pain (BPI-SF Item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (BPI-SF Item 3). There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Pain interference (BPI-SF Items 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (BPI-SF Item 9a–g). There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Outcome on the clinical morbidity/symptoms of Fabry disease

No suitable data are available for the outcome of clinical morbidity/symptoms of Fabry disease. There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status recorded with the EQ-5D VAS. There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Health-related quality of life

There were no data for the outcome "health-related quality of life". There is no hint of an added benefit of pegunigalsidase alfa in comparison with agalsidase beta; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. There is no hint of greater or lesser harm from pegunigalsidase alfa in comparison with agalsidase beta; greater or lesser harm is therefore not proven.

Infusion-related reactions

No suitable data are available for the outcome of infusion-related reactions. There is no hint of greater or lesser harm from pegunigalsidase alfa in comparison with agalsidase beta; greater or lesser harm is therefore not proven.

Chest pain (SAEs), respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference between treatment groups in favour of pegunigalsidase alfa was shown for the outcomes of chest pain (SAEs) and respiratory, thoracic and mediastinal disorders severe AEs). There is a hint of lesser harm from pegunigalsidase alfa in comparison with agalsidase beta.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- sex (male versus female)
- GFR at baseline (≤ 60/> 60 and ≤ 90/> 90 [mL/min/1.73 m²])

No suitable analyses are available for the characteristic “age”.

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

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

Using the methods described above, the available subgroup results do not reveal any effect modifications.

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 General Methods of IQWiG [1].

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 13).

Table 13: Extent of added benefit at outcome level: pegunigalsidase alfa vs. agalsidase beta (multipage table)

Outcome category **outcome**	**Pegunigalsidase alfa vs. agalsidase beta** **proportion of events (%)** **RR [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% –	Lesser/added benefit not proven
Morbidity		
Worst pain (BPI-SF Item 3, improvement at Week 104)	26.7% vs. 13.6% 1.96 [0.61; 6.22] p = 0.300	Lesser/added benefit not proven
Pain interference (BPI-SF Items 9a–g, improvement at Week 104)	11.1% vs. 9.1% 1.22 [0.26; 5.81] p = 0.800	Lesser/added benefit not proven
Outcome on the clinical morbidity/symptoms of Fabry disease	No suitable data	
Health status (EQ-5D VAS, improvement at Week 104)	15.2% vs. 18.2% 0.84 [0.27; 2.56] p = 0.756	Lesser/added benefit not proven
Health-related quality of life	Outcome not recorded	
Side effects		
SAEs	15.4% vs. 24.0% 0.64 [0.25; 1.65] p = 0.413	Greater/lesser harm not proven
Severe AEs	28.9% vs. 28.0% 1.03 [0.48; 2.20] p = 0.987	Greater/lesser harm not proven
Discontinuation due to AEs	3.8% vs. 0.0% 2.45 [0.12; 49.26] p = 0.403	Greater/lesser harm not proven
Infusion-related reactions	No suitable data	
Chest pain (SAEs)	0.0% vs. 8.0% 0.10 [0.00; 1.97][c] p = 0.042 probability: “hint”	Outcome category: serious/severe side effects lesser harm; extent: “minor”[d]
Respiratory, thoracic and mediastinal disorders (severe AEs)	0.0% vs. 12.0% 0.07 [0.00; 1.31][c] p = 0.011 probability: “hint”	Outcome category: serious/severe side effects lesser harm; extent: “minor”[d]

Table 13: Extent of added benefit at outcome level: pegunigalsidase alfa vs. agalsidase beta (multipage table)

Outcome category **outcome**	**Pegunigalsidase alfa vs. agalsidase beta** **proportion of events (%)** **RR [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
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. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. d. The result of the statistical test is determinative for the derivation of added benefit. Its extent is rated as "minor". AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of pegunigalsidase alfa in comparison with agalsidase beta

Positive effects	**Negative effects**
Serious/severe side effects[a] ▪ chest pain: hint of lesser harm – extent: minor ▪ respiratory, thoracic and mediastinal disorders: hint of lesser harm – extent: "minor"	–
The outcome "health-related quality of life" was not recorded in the relevant study. No suitable data are available for the outcome of clinical morbidity/symptoms of Fabry disease and for the outcome of infusion-related reactions.	
a. Including a relevant proportion of events that can be both side effects and symptoms.	

Overall, pegunigalsidase alfa shows positive effects over agalsidase beta for patients with Fabry disease.

These are significant effects in the outcomes of chest pain (SAE) and respiratory, thoracic and mediastinal disorders (severe AEs). However, due to the low number of events (2 events in the outcome "chest pain" and 3 events in the outcome "respiratory, thoracic and mediastinal disorders") and the existing limitations of the BALANCE study (see Section I 3.2), these effects are not considered sufficient to derive an overall added benefit for pegunigalsidase alfa in comparison with agalsidase beta.

In summary, there is no hint of an added benefit of pegunigalsidase alfa over the ACT agalsidase beta for patients with a confirmed diagnosis of Fabry disease.

Table 15 summarizes the result of the assessment of added benefit of pegunigalsidase alfa in comparison with the ACT.

Table 15: Pegunigalsidase alfa – extent and probability of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).	Agalsidase alfa or agalsidase beta or migalastat	Added benefit not proven[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.
c. The BALANCE study only included pretreated patients and patients with an eGFR of ≥ 40 mL/min/1.73m^2 whose renal function had previously decreased by at least 2 mL/min/1.73 m²/year. It remains unclear whether the observed results are transferable to treatment-naive patients and to patients with better renal functions.

eGFR: estimated glomerular filtration rate; min: minute; G-BA: Federal Joint Committee

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

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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