Pegunigalsidase alfa (Fabry disease 1)

Addendum to Project A23-95 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 06 February 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-95 (Pegunigalsidase alfa – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the outcome of infusion-related reactions taking into account the information in the dossier [2] and the analyses additionally submitted by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [3].

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) BALANCE was included for the benefit assessment of pegunigalsidase alfa compared to the appropriate comparator therapy (ACT) in adults with confirmed Fabry disease (deficiency of α-galactosidase). A detailed description of the study can be found in dossier assessment A23-95.

The analyses for the outcome of infusion-related reactions are assessed below in compliance with the commission.

Uncertainty remains due to the attempt to phase out premedication

As described in dossier assessment A23-95, the premedication that was ongoing in about half of all patients at the start of the study should be phased out or reduced from the 2nd infusion onwards according to the study protocol. The individualized adjustment of the rate or speed of tapering described by the company in the commenting procedure was carried out depending on the recurrence of infusion-related reactions and at the investigator's discretion [3]. However, it remains unclear whether at the second infusion, infusion-related reactions have already occurred in a relevant proportion of patients as a result of the tapering attempt.

The uncertainty described in the dossier assessment therefore remains and there are still no suitable data available for the outcome of infusion-related reactions.

Irrespective of this relevant uncertainty, the analyses on infusion-related reactions used by the company to derive the added benefit are not suitable for the benefit assessment also for further reasons. This is described below.

Operationalization and presented analyses of infusion-related reactions

Operationalization only suitable to a limited extent

In the BALANCE study, infusion-related reactions were operationalized as adverse events (AEs) that occurred during or shortly after (time window 2 h and 24 h) the end of the infusion of the study medication and whose causality was assessed by the investigator as definitely, probably or possibly related. Reactions at the injection site were not taken into account.

Basically, a limitation for the interpretation of the results is that no specific criteria were specified in the BALANCE study (e.g. a predefined list of Preferred Terms [PTs]) for the investigators' assessment of whether an AE should be classified as an infusion-related AE. In certain data constellations, e.g. in the presence of marked effects (see dossier assessment A21-60 Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2021 #23}), it is nevertheless conceivable to derive greater or lesser harm based on such an operationalization. However, the present analysis of the number of patients with at least 1

infusion-related reaction shows no statistically significant difference between the treatment arms either after 2 h or after 24 h.

Analyses with consideration of recurrent events not suitable for benefit assessment

In addition to the analyses on the proportion of patients with at least 1 infusion-related reaction (already mentioned in the previous section), the company primarily presents analyses on the number of infusion-related reactions and the rate of infusion-related reactions (number of infusion-related reactions*100/number of infusions; ratio of the rates [effect estimate rate ratio] without using a specific model for recurrent events) for the derivation of the added benefit. Analyses are available for infusion-related reactions that occurred within 2 hours and within 24 hours. As part of the comments, the company also presented analyses on the rate of infusion-related reactions for the subpopulations of patients who received premedication at baseline and for patients who received premedication at the time point of infusion. In its comments, the company also presented analyses of the cumulative number of infusion-related reactions over the course of treatment for patients who received premedication at baseline.

For the outcomes on side effects, analyses of the proportion of patients with at least 1 event (effect estimator hazard ratio [HR] or relative risk [RR]) are primarily presented and used in dossier assessments. Irrespective of this, analyses that take recurrent events into account are only selectively available for the AE “infusion-related reactions” in the present case. Patients who had more than 1 infusion-related reaction are included more than once in these analyses. Thereby, it is possible that individual patients with frequently recurring reactions account for a relevant proportion of the events. In the agalsidase beta arm, for example, pruritus (PT) was the most common event, with 21 events after 2 hours and 23 events after 24 hours. However, these events only occurred in 2 (after 2 hours) and 3 patients (after 24 hours).

Conclusion

Both the analyses on the number and rate of infusion-related reactions used by the company to derive the added benefit and the analyses on the number of patients with at least 1 infusion-related reaction, which are generally relevant for dossier assessments, are not suitable for the benefit assessment for the reasons described above.

2.1 Summary

The present addendum does not change the conclusions on the added benefit of pegunigalsidase alfa from dossier assessment A23-95.

The following Table 1 shows the result of the benefit assessment of pegunigalsidase alfa under consideration of dossier assessment A23-95 and the present addendum.

Table 1: Pegunigalsidase alfa – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy[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; 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 G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pegunigalsidase alfa (Morbus Fabry); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 04.01.2024]. URL: https://doi.org/10.60584/A23-95.

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3. Chiesi. Stellungnahme zum IQWiG-Bericht Nr. 1694: Pegunigalsidase alfa (Morbus Fabry); Nutzenbewertung gemäß § 35a SGB V. 2024: [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1001/#beschluesse im Dokument "Zusammenfassende Dokumentation"].