Migalastat (Fabry disease)

Addendum to Project A23-88 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
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
MCS	Mental Component Summary
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SF-36v2	Short Form 36-version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class

1 Background

On 16 January 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-88 (Migalastat – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the following 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]:

- Responder analyses for the outcomes of pain and health-related quality of life at the end of the study (Month 18)
- Assessment of the suitability of the subsequently submitted analyses for the outcome of infusion related reactions (side effects)

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) ATTRACT was included for the benefit assessment of migalastat in comparison with the appropriate comparator therapy (ACT) agalsidase alfa or agalsidase beta in adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. A detailed description of the study can be found in dossier assessment A23-88 [1].

Below, the analyses subsequently submitted by the company in the commenting procedure [2] on the outcomes recorded using the Brief Pain Inventory-Short Form (BPI-SF) and the Short Form 36-version 2 Health Survey (SF-36v2) are assessed as commissioned. The analyses on infusion related reactions are additionally assessed.

2.1 Assessment of subsequently submitted data on morbidity, health-related quality of life and side effects

2.1.1 Responder analyses on patient-reported outcomes recorded using BPI-SF und SF-36v2

Consideration of improvement in the responder analyses is relevant for the benefit assessment

In its comments, the company presented responder analyses for the patient-relevant outcomes on morbidity and health-related quality of life on the proportions of patients with improvement or deterioration by a response threshold of ≥ 15% of the respective scale range of the instrument. In the present therapeutic indication, the therapeutic goals are to reduce symptoms, e.g. pain relief, and to improve quality of life [4]. Therefore, the improvement of these outcomes is considered in the present assessment.

Analysis date at Month 18 is relevant for the benefit assessment

The dossier contained responder analyses for the analysis period until Month 18 for the morbidity outcome of worst pain (BPI-SF) and for health-related quality of life (SF-36v2) [3]. In these analyses conducted by the company, patients were considered responders if they experienced improvement by the response criterion at (any) point in time during the course of the study (until Month 18). In the present therapeutic indication of a chronic, progressive disease, however, it is relevant to consider the outcomes as late as possible (i.e. in the ATTRACT study by the end of the study at Month 18). The responder analyses presented by the company were therefore unsuitable for the benefit assessment. In its comments, the company presented responder analyses for the outcomes recorded using BPI-SF and SF-36v2 at the time of analysis at Month 18. This is appropriate.

Response criterion of 15% is relevant for the benefit assessment

In its analyses of the BPI-SF, the company considered a change by ≥ 15% of the respective scale range of the instrument to be the response threshold. This corresponds to a threshold of ≥ 1.5 points.

For the SF-36v2 Physical Component Summary (PCS) and Mental Component Summary (MCS), the company also stated that it had considered the response criterion of ≥ 15% of the respective scale range. It used ≥ 9.4 points for the PCS and ≥ 9.6 points for the MCS as response criteria. These values correspond to ≥ 15% of the scale range calculated using the 2009 standard sample (PCS: standardized scale with a minimum of approx. 7 and a maximum of approx. 70, and MCS: standardized scale with a minimum of approx. 6 and a maximum of approx. 70). However, it can be inferred from the study documents that the 1998 standard sample was used to analyse the SF-36v2 in the ATTRACT study. The following scale ranges and values for the response criterion of ≥ 15% result from using this standard sample:

- PCS: scale range 4 to 71 points and ≥ 10.05 points
- MCS: scale range 2 to 74 points and ≥ 10.80 points

The analyses presented by the company can nevertheless be used as an approximation.

The response criterion of ≥ 15% of the respective scale range, which was used in the analyses presented by the company, fulfils the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the *General Methods* of the Institute [5]. The analyses of this response threshold are therefore used for the benefit assessment.

Worst pain measured by BPI-SF (Item 3) is relevant for the assessment

In the ATTRACT study, Items 3–6 of the BPI-SF (worst, least, average, and current pain) were planned to be recorded. The recording of pain interference (BPI-SF Items 9a–g) was not planned and corresponding data are not available. Therefore, only the outcome of worst pain (Item 3) is used in the present assessment. The outcome of pain intensity (Items 3 to 6) is presented as supplementary information.

2.1.2 Analyses on infusion related reactions

The ATTRACT study compared migalastat (oral administration) with enzyme replacement therapy administered as an infusion. Infusion related reactions are therefore a relevant side effect. The recording of infusion related reactions was not planned in the ATTRACT study. In its comments, the company presented analyses on infusion related reactions operationalized post hoc. It only considered procedural events (Preferred Terms [PTs]) to be relevant. To identify these, the company considered the events occurring in the System Organ Class (SOC)

of injury, poisoning and procedural complications and selected the PTs it considered relevant: procedural hypotension, procedural nausea, infusion related reaction, procedural pain, procedural hypertension, procedural vomiting.

The analyses subsequently submitted by the company for the outcome of infusion related reactions are unsuitable for the benefit assessment. Due to the selective consideration of exclusively procedural events, which can only occur in the comparator arm, no comparative data is available. To obtain the necessary comparative data for the benefit assessment, it would be necessary to conduct an aggregated analysis of all symptomatic adverse events (AEs) potentially relevant for infusion related reactions (e.g. chills, headache, nausea, or fever, irrespective of whether or not they were temporally related to an infusion). Specific AEs that represent infusion related reactions should either be predefined or refer to content-based compilations based on publications or compilations of the Medical Dictionary for Regulatory Activities system (Standardized MedDRA Query [SMQ]) and be recorded in both study arms. This allows taking these events into account in the benefit assessment even if they occurred in studies comparing orally and intravenously administered drugs. Irrespective of this, the individual AEs were included in the AE analyses of the ATTRACT study.

2.2 Risk of bias

The risk of bias of the results for the outcome of worst pain (recorded using BPI-SF) and for the outcomes in the health-related quality of life category (recorded using SF-36v2) was rated as high due to a violation of the intention-to-treat (ITT) principle (for detailed justification, see A23-88). In addition, there is a high risk of bias due to a lack of blinding in subjective recording of outcomes. No suitable data are available for the outcome of infusion related reactions.

2.3 Results

Table 1 shows the results on the outcomes of worst pain (BPI-SF) and health-related quality of life (SF-36v2). As described in the previous sections, no suitable data are available for the outcome of infusion related reactions.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: migalastat vs. enzyme replacement therapy[a]

Study Outcome category Outcome	Migalastat		Enzyme replacement therapy[a]		Migalastat vs. enzyme replacement therapy[a]
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
ATTRACT					
Morbidity					
BPI-SF (improvement by 15% at Month 18)					
Worst pain (Item 3)[b]	34	5 (15)	18	3 (17)	0.87 [0.21; 3.69]; 0.855
Supplementary information:					
Pain intensity (BPI-SF Items 3-6)[d]	*34*	*3 (9)*	*18*	*3 (17)*	*0.53 [0.10; 2.72]; 0.446*
Health-related quality of life					
SF-36v2 (improvement by 15% at Month 18)[c]					
Physical Component Summary (PCS)[d]	34	1 (3)	18	2 (11)	0.32 [0.04; 2.89]; 0.309
Mental Component Summary (MCS)[d]	34	3 (9)	18	2 (11)	0.80 [0.13; 4.85]; 0.804
Side effects					
Infusion related reactions	No suitable data[e]				

a. Agalsidase alfa or agalsidase beta.
b. A decrease by ≥ 1.5 points from baseline is defined as a clinically relevant improvement (scale range 0 to 10).
c. No data are available on the SF-36v2 subscales.
d. For the used response criteria and scale ranges, see the explanations in Section 2.1.2. An increase in the values compared with baseline indicates improvement.
e. For the reasoning, see Section 2.1.2.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36-version 2 Health Survey

Based on the available information, at most hints, e.g. of an added benefit, can be derived for the outcomes of worst pain (BPI-SF) and health-related quality of life (SF-36v2) due to the high risk of bias.

Morbidity

Worst pain (recorded using the BPI-SF)

No statistically significant difference between the treatment arms was shown for the outcome of worst pain (BPI-SF). There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy; an added benefit is therefore not proven.

Health-related quality of life (SF-36v2)

No statistically significant difference between the treatment arms was shown for the PCS and the MCS of the SF-36v2. There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy; an added benefit is therefore not proven.

Side effects

Infusion related reactions

No suitable data are available for the outcome of infusion related reactions. There is no hint of an added benefit of migalastat in comparison with the ACT; an added benefit is therefore not proven.

2.3.1 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment (see also dossier assessment A23-88):

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

Interaction tests are performed if 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.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of migalastat from dossier assessment A23-88.

Table 2 below shows the result of the benefit assessment of migalastat, taking into account dossier assessment A23-88 and the present addendum.

Table 2: Migalastat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation	Agalsidase alfa or agalsidase beta	Added benefit not proven[b]

a. Presented is the ACT specified by the G-BA.
b. The ATTRACT study only enrolled patients aged 16 years and older with pretreatment. The youngest patient in the study was 18 years old. It remains unclear whether the observed results can be transferred to adolescents aged 12 years and older.

ACT: appropriate comparator therapy; 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.

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