Migalastat
(Fabry disease)

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

EXTRACT

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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 was received in the framework of the present dossier assessment.

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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
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLA	α-galactosidase A gene
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MCS	Mental Component Summary
mGFR	measured glomerular filtration rate
mITT	modified intention to treat
PCS	Physical Component Summary
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form 36 – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TIA	transient ischaemic attack

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 migalastat. 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 16 August 2023.

Research question

The aim of this report is to assess the added benefit of migalastat compared with the appropriate comparator therapy (ACT) for the treatment of 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.

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 migalastat

Therapeutic indication	**ACT**[a]
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
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company defined enzyme replacement therapy with agalsidase alfa or agalsidase beta as the ACT. This concurs with the ACT specified by the G-BA.

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 ATTRACT study is used for the benefit assessment of migalastat. This is an open-label RCT with several study phases. The study included patients aged 16 to 74 years with a confirmed diagnosis of Fabry disease. In addition, eligible patients had to have a migalastat-sensitive mutation of the gene coding for α-galactosidase A (GLA gene), confirmed by genotyping. Enzyme replacement therapy had to be initiated at least 12 months before baseline. A glomerular filtration rate ≥ 30 mL/min/1.73m² was another inclusion criterion.

A total of 60 patients were randomized in a 1.5:1 ratio either to treatment with migalastat (N = 36) or to enzyme replacement therapy with agalsidase alfa or agalsidase beta (N = 24). Randomization was stratified according to sex and urine protein (< 100 mg/24 h; ≥ 100 mg/24 h). Treatment with migalastat or enzyme replacement therapy lasted 18 months and was largely in compliance with the recommendations of the Summary of Product Characteristics (SPC). In the comparator arm, patients continued their baseline enzyme replacement therapy with agalsidase alfa or agalsidase beta during the study. Patients in the intervention arm had to discontinue their ongoing enzyme replacement therapy before initiating treatment with migalastat.

This 18-month randomized study phase represents the comparison of the intervention to be assessed with the ACT and is relevant for the present benefit assessment. The 18-month randomized phase was followed by an optional 12-month extension phase for all patients included in the study, in which open-label migalastat was administered in one study arm.

Primary outcomes of the study were the change in the measured glomerular filtration rate with iohexol (mGFR) per year after 18 months, and the change in the estimated glomerular filtration rate (eGFR) per year after 18 months. Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and adverse events (AEs) categories.

Analysis population a presented by the company

In Module 4 A, the company presented data on an analysis population, which it referred to as "modified intention to treat (mITT)". It excluded a total of 8 patients from this population. Firstly, it excluded 2 patients each from the intervention arm and from the comparator arm, and justified this by stating that the determination of the migalastat-sensitive mutation was not confirmed by a validated good laboratory practice (GLP) assay for these 4 patients. In the present benefit assessment, it is assumed that the validated GLP assay provides the more accurate results, so that the exclusion of the 4 patients is adequate. Furthermore, the company excluded another 3 patients due to withdrawal of consent before administration of the first dose of study medication. The exclusion of these 3 patients is not appropriate, as it violates the intention to treat (ITT) principle. This is taken into account in the assessment of the risk of bias.

Risk of bias

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

Due to violation of the ITT principle, the risk of bias is rated as high for the results of the outcomes of all-cause mortality, cardiac morbidity, cerebrovascular morbidity, health-related quality of life (recorded using the Short Form 36 – version 2 Health Survey [SF-36v2]), serious adverse events (SAEs) and discontinuation due to AEs. There is also a high risk of bias for the

results of the outcome of health-related quality of life (recorded using SF-36v2) due to lack of blinding in subjective recording of outcomes. There is an additional high risk of bias for the results of the outcome of SAEs because they include a relevant proportion of events that can be both side effects and symptoms of the disease.

Results

Mortality

All-cause mortality

No deaths occurred in the course of the study. There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Cardiac morbidity and cerebrovascular morbidity

No statistically significant difference between treatment groups was shown for the outcomes of cardiac morbidity (consisting of myocardial infarction, unstable angina pectoris, new symptomatic arrhythmia and cardiac failure) and cerebrovascular morbidity (consisting of stroke and transient ischaemic attack [TIA]). In each case, there is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy; an added benefit is therefore not proven.

Pain (recorded using the Brief Pain Inventory-Short Form [BPI-SF]), outcome on clinical morbidity of Fabry disease, renal morbidity

No suitable data are available for the outcomes of pain, outcome on clinical morbidity of Fabry disease (consisting of renal, cardiac and cerebrovascular morbidity), and renal morbidity (consisting of decrease in eGFR ≥ 15 mL/min/1.73 m² and increase in 24-hour urine protein ≥ 33%). In each case, 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

Health-related quality of life outcomes were recorded using the SF-36v2.

A statistically significant difference in favour of migalastat compared with enzyme replacement therapy was shown for the Physical Component Summary (PCS) of the SF-36v2. However, the 95% confidence interval of the standardized mean difference was not fully outside the irrelevance range of [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy for the outcome of PCS; an added benefit is therefore not proven.

No statistically significant difference between the treatment groups was shown for the Mental Component Summary (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

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from migalastat in comparison with enzyme replacement therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. There is no hint of greater or lesser harm from migalastat in comparison with enzyme replacement therapy for the outcome of discontinuation due to AEs; 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 migalastat in comparison with enzyme replacement therapy; greater or lesser harm is therefore not proven.

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 migalastat in comparison with the ACT is assessed as follows:

Overall, neither positive nor negative effects were found for migalastat in comparison with enzyme replacement therapy. In summary, there is no hint of an added benefit of migalastat in comparison with the ACT agalsidase alfa or agalsidase beta for patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation; an added benefit is therefore not proven.

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

[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: 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. ACT: appropriate comparator therapy; 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.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted in the context of market access in 2016 and of the extension of the therapeutic indication in 2021, where the G-BA found a non-quantifiable added benefit in 2016 and a hint of a non-quantifiable added benefit of migalastat in 2021. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data due to orphan drug status.

I 2 Research question

The aim of this report is to assess the added benefit of migalastat compared with the ACT for the treatment of 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.

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 migalastat

Therapeutic indication	**ACT[a]**
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
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company defined enzyme replacement therapy with agalsidase alfa or agalsidase beta as the ACT. This concurs with the ACT specified by the G-BA.

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 are 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 migalastat (status: 15 May 2023)
- bibliographical literature search on migalastat (last search on 15 May 2023)
- search in trial registries/trial results databases for studies on migalastat (last search on 15 May 2023)
- search on the G-BA website for migalastat (last search on 15 May 2023)

To check the completeness of the study pool:

- search in trial registries for studies on migalastat (last search on 4 September 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 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: migalastat vs. enzyme replacement therapy[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
AT1001-012 (ATTRACT[e])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6,7]

a. Agalsidase alfa or agalsidase beta.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
e. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

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

In Module 4 A, the company additionally presented results of the single-arm studies AT1001-041 and AT1001-042 [8,9]. The 2 studies AT1001-041 and AT1001-042 included

patients diagnosed with Fabry disease who had already received migalastat as monotherapy in a previous study. Instead of using these 2 single-arm studies to derive any added benefit, it presented their results only as supplementary information. This is appropriate.

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: migalastat vs. enzyme replacement therapy[a]

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ATTRACT	RCT, parallel, open-label	Patients aged 16 to 74 years with a confirmed diagnosis of Fabry disease and an underlying mutation of the gene coding for α-galactosidase A (GLA gene)[c], classified as migalastat-sensitive	Migalastat (N = 36) Enzyme replacement therapy[a] (N = 24) Relevant analysis population thereof[d]: migalastat (n = 34) enzyme replacement therapy[a] (n = 18)	Screening: 2 months Treatment: 18 months Follow-up: 1 month[e]	25 centres in: Australia, Austria, Belgium, Brazil, Denmark, France, Italy, Japan, United Kingdom and United States 9/2011–5/2015 Data cut-off at 18 months: 27 May 2014	Primary: ▪ change in $mGFR_{Iohexol}$ per year after 18 months ▪ change in eGFR per year[f] after 18 months Secondary: ▪ mortality, morbidity, health-related quality of life, AEs

a. Agalsidase alfa or agalsidase beta.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. According to the study protocol, measured with the in vitro HEK-293 cell-based assay. After recruitment was completed, the HEK-293 cell-based assay was switched to the validated good laboratory practice (GLP) assay. As a result, 4 patients with mutations initially classified as "responsive" were categorized as patients with mutations that are not sensitive to migalastat.
d. Population with confirmed GLA mutation for which a response to migalastat could be demonstrated in vitro by GLP assay. For the analysis population, 2 patients in each treatment arm were excluded from the randomized population due to lack of confirmation of the migalastat-sensitive mutation by GLP assay. In addition, another 4 patients were excluded for the analysed population in the comparator arm due to missing mGFR measurement (one patient) and withdrawal of consent before administration of the first dose of study medication (3 patients).
e. The follow-up visit was omitted for patients who participated in the optional extension phase for another 12 months after completing the 18-month treatment phase.
f. Measured as eGFR CKD-EPI.

AE: adverse event; CKD-EPI: chronic kidney disease epidemiology collaboration equation; eGFR: estimated glomerular filtration rate; GLA: α-galactosidase A deficiency; GLP: good laboratory practice; HEK-293: human embryonic kidney 293; mGFR: measured glomerular filtration rate; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: migalastat vs. enzyme replacement therapy[a]

Study	Intervention	Comparison
ATTRACT	Migalastat 123 mg orally, every 2 days[b]	Enzyme replacement therapy IV[c]
	Allowed prior and concomitant treatment ▪ required: enzyme replacement therapy ≥ 12 months before baseline, with stable dosage over the last 3 months[d]; continuation of this treatment for all included patients during the 2-month screening phase ▪ if ACE inhibitor or angiotensin receptor blocker use was stable for ≥ 4 weeks before baseline, continued use was permitted during the study[e] **Prohibited prior and concomitant treatment** ▪ miglitol, miglustat	

a. Agalsidase alfa or agalsidase beta.
b. On the other, alternating days, an inactive "reminder capsule" was taken during the study period. This capsule differed from migalastat in terms of appearance.
c. Patients in the control arm continued their pretreatment with agalsidase alfa or agalsidase beta during the study.
d. The stable dose had to be ≥ 80% of the approved dose.
e. Adjustment or initiation of concomitant treatment with ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, NSAIDs, or other drugs that affect renal perfusion (e.g. drugs for hypertension), only with caution for patients with CKD.

ACE: angiotensin converting enzyme; CKD: chronic kidney disease; IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SPC: Summary of Product Characteristics

The ATTRACT study is an open-label RCT with several study phases. The study included patients aged 16 to 74 years with a confirmed diagnosis of Fabry disease. In addition, eligible patients had to have a migalastat-sensitive mutation of the gene coding for α-galactosidase A (GLA gene), confirmed by genotyping. Enzyme replacement therapy had to be initiated at least 12 months before baseline. A glomerular filtration rate ≥ 30 mL/min/1.73m² was another inclusion criterion.

A total of 60 patients were randomized in a 1.5:1 ratio either to treatment with migalastat (N = 36) or to enzyme replacement therapy with agalsidase alfa or agalsidase beta (N = 24). Randomization was stratified according to sex and urine protein (< 100 mg/24 h; ≥ 100 mg/24 h). Treatment with migalastat or enzyme replacement therapy lasted 18 months and was largely in compliance with the recommendations of the SPC [10-12]. In the intervention arm, migalastat was taken every 2 days. An inactive "reminder capsule" was taken on the days between the migalastat intake. The SPC for migalastat does not provide for the intake of a "reminder capsule". This has no consequences for the present benefit assessment, however. In the comparator arm, patients continued their baseline enzyme replacement therapy with agalsidase alfa or agalsidase beta during the study. Patients in the

intervention arm had to discontinue their ongoing enzyme replacement therapy before initiating treatment with migalastat.

This 18-month randomized study phase represents the comparison of the intervention to be assessed with the ACT and is relevant for the present benefit assessment. The 18-month randomized phase was followed by an optional 12-month extension phase for all patients included in the study, in which open-label migalastat was administered in one study arm.

Primary outcomes of the study were the change in the measured glomerular filtration rate with iohexol (mGFR) per year after 18 months, and the change in the estimated glomerular filtration rate (eGFR) per year after 18 months. Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and AEs categories.

Data cut-off

The company used the analysis at the final 18-month data cut-off of the ATTRACT study conducted on 27 May 2014 for the benefit assessment. This final data cut-off was planned a priori and took place when the last patient had completed the 18-month randomized study phase.

Characteristics of the study population

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: migalastat vs. enzyme replacement therapy[a]

Study Characteristic Category	Migalastat N[b] = 34	Enzyme replacement therapy[a] N[b] = 18
ATTRACT study		
Age [years], mean (SD)	51 (13)	45 (15)
Sex [F/M], %	59/41	56/44
Family origin, n (%)		
White	28 (82)	17 (94)
Asian	5 (15)	1 (6)
Various	1 (3)	0 (0)
Time since Fabry diagnosis [years], mean (SD)	9.6 (10.9)	13.9 (13.5)
Enzyme replacement therapy at baseline, n (%)		
Agalsidase alfa	22 (65)	11 (61)
Agalsidase beta	11 (32)	7 (39)
No data	1 (3)	0 (0)
Use of ACEi/ARB/Ri at baseline, n (%)	16 (47)	10 (56)
24-hour urine protein at baseline [mg/24 h]		
Mean (SD)	260 (422)	417 (735)
Median [min; max]	124 [0; 2282]	172 [0; 3154]
Urine albumin:creatinine ratio [mg/mmol]		
Mean (SD)	13.6 (28.9)	21.9 (47.1)
Median [min; max]	2.6 [0.3; 155.9]	5.8 [0.5; 197.0]
$mGFR_{iohexol}$ [mL/min/1.73 m²], mean (SD)	82.3 (16.9)	81.4 (23.9)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)[c]	ND	ND

a. Agalsidase alfa or agalsidase beta.
b. Number of patients in the analysis population.
c. No data on the analysis population are available. In the ITT population, 3 patients in the control arm discontinued the study before administration of the first dose of the study medication, and 2 patients in the intervention arm and 3 patients in the control arm discontinued the study after the start of treatment. The reason for the discontinuation of the study for all patients was the withdrawal of consent.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; F: female; M: male; max: maximum; mGFR: measured glomerular filtration rate; min: minimum; n: number of patients in the category, N: number of randomized patients; ND: no data; RCT: randomized controlled trial; Ri: renin inhibitor; SD: standard deviation

The patients' demographic and clinical characteristics were largely comparable between the 2 treatment arms. The mean age of the patients in the analysis population was 51 and 45 years, just over half of the patients were male and most patients were of white family origin. The time since diagnosis differed between the 2 treatment arms (on average 10 years

in the intervention arm and 14 years in the control arm). The urine albumin:creatinine ratio also differed between the treatment arms (on average 14 mg/mmol in the intervention arm and 22 mg/mmol in the control arm). In this therapeutic indication, however, it is assumed that the patient characteristics are sufficiently comparable overall. Data on treatment discontinuation and study discontinuation are not available for the analysis population.

Analysis population a presented by the company

In Module 4 A, the company presented data on the analysis population, which it referred to as "mITT". It excluded a total of 8 patients. Firstly, it excluded 2 patients each from the intervention arm and from the comparator arm, and justified this by stating that during the study the determination of the migalastat-sensitive GLA mutation was switched from a human embryonic kidney 293 cell-based assay to the validated GLP assay, which did not confirm the migalastat-sensitive mutation for these 4 patients. In the present benefit assessment, it is assumed that the validated GLP assay provides the more accurate results, so that the exclusion of the 4 patients with unconfirmed GLA mutation is adequate. Furthermore, the company excluded another 3 patients due to withdrawal of consent before administration of the first dose of study medication. The exclusion of these 3 patients is not appropriate, as it violates the ITT principle. This is taken into account in the assessment of the risk of bias (see Section I 4.2).

Limitations of the ATTRACT study

No information on the procedure in the event of a drop of efficacy of the existing enzyme replacement therapy

According to the S1 guideline on Fabry disease, patients on enzyme replacement therapy may experience a drop in efficacy [13]. If this is the case, they should have an antibody test and a change of preparation could be considered. It is not clear from the study documents how to proceed in the study if there was a drop in efficacy of the enzyme replacement therapy and whether a change of drug was possible. There are no clear criteria for the definition of a drop in efficacy for this therapeutic indication. There is also no information available in which cases and how often a change of drug is necessary. This uncertainty therefore remains without consequence for the present benefit assessment.

Uncertainties in the documentation of concomitant treatment

Regarding concomitant treatment, it was recorded in the study documents that, in the intervention arm, 4 to 5 patients of the safety population received agalsidase alfa and/or agalsidase beta as concomitant treatment. However, it is unclear whether migalastat and agalsidase alfa or agalsidase beta were actually administered concomitantly, as drugs were documented as part of the concomitant therapy as early as one month before the start of the study medication. It is therefore assumed that these few cases are a documentation of the

therapy prior to the study intervention. Overall, this has no consequence for the present benefit assessment.

Further limitations of the study population

Only patients aged 16 years and older were enrolled in the ATTRACT study, and the youngest patient was 18 years old. The company has not submitted any data on adolescents aged 12 years and older.

Furthermore, only patients who had been on enzyme replacement therapy for at least 12 months before baseline were included in the ATTRACT study. Data for patients who had not yet received prior treatment with enzyme replacement therapy are not available for the assessment.

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: migalastat vs. enzyme replacement therapy[a]

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			
ATTRACT	Yes	Yes	No	No	Yes	Yes	Low

a. Agalsidase alfa or agalsidase beta.

RCT: randomized controlled trial

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

Limitations resulting from the open-label study design are described in Section I 4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the company's opinion, the results of the ATTRACT study are transferable to the German health care context. The characteristics of the patients included in the study showed very good comparability with published characteristics of Fabry patients from Europe and Germany.

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
  - pain, recorded using the BPI-SF
  - outcome on the clinical morbidity of Fabry disease
  - renal morbidity
  - cardiac morbidity
  - cerebrovascular morbidity
- Health-related quality of life
  - recorded using the SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infusion-related reactions

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

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

Table 10: Matrix of outcomes – RCT, direct comparison: migalastat vs. enzyme replacement therapy[a]

Study	Outcomes									
	All-cause mortality	Pain (BPI-SF)	Outcome on the clinical morbidity of Fabry disease (composite outcome)[b]	Renal morbidity (composite outcome)[c]	Cardiac morbidity (composite outcome)[d]	Cerebrovascular morbidity (composite outcome)[e]	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infusion-related reactions
ATTRACT	Yes	No[f]	No[f]	No[e]	Yes	Yes	Yes	Yes	Yes	No[f]

a. Agalsidase alfa or agalsidase beta.
b. Composite outcome, consisting of the components of renal, cardiac and cerebrovascular morbidity.
c. Composite renal outcome, consisting of the individual components of decrease in eGFR ≥ 15 mL/min/1.73 m² and increase in 24-hour urine protein ≥ 33%, component of the composite outcome on clinical morbidity of Fabry disease.
d. Composite cardiac outcome, consisting of the individual components of myocardial infarction, unstable angina, new symptomatic arrhythmia and heart failure, component of the composite outcome on clinical morbidity of Fabry disease.
e. Composite cerebrovascular outcome, consisting of the individual components of stroke and transient ischaemic attack.
f. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey

Notes on the outcomes

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 ATTRACT study recorded these late complications with a composite clinical morbidity outcome comprising the following components:

- renal morbidity
- cardiac morbidity
- cerebrovascular morbidity
- death

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be both patient relevant and of similar severity. The

composite outcome on clinical morbidity of Fabry disease is not suitable in the present operationalization and is not used for the assessment. However, it is possible to use individual components whose analysis was also planned according to the planning of the study. This is explained below using the individual components.

Renal morbidity

Renal morbidity was operationalized using the following individual components:

- decrease in eGFR ≥ 15 mL/min/1.73 m² (with the lower eGFR < 90 mL/min/1.73 m² relative to baseline)
- increase in 24-hour urine protein ≥ 33% (with the higher protein ≥ 300 mg relative to baseline)

In principle, the investigation of renal morbidity is relevant for the therapeutic indication of Fabry disease. However, the outcome of renal morbidity is not patient relevant in the present situation. This is explained below for the individual components. A decrease in eGFR ≥ 15 mL/min/1.73 m² is not necessarily patient relevant. Due to the high mean mGFR values at baseline (see Table 8), it cannot be assumed that a decrease in eGFR by ≥ 15 mL/min/1.73 m² represents a noticeable deterioration in renal function for the majority of affected patients. Similarly, taking into account the mean 24-hour urine protein values at baseline (see Table 8), it cannot be assumed that an increase by ≥ 33% represents a noticeable deterioration in renal function for the majority of affected patients.

Cardiac morbidity

Cardiac morbidity was operationalized using the following individual components:

- myocardial infarction
- unstable angina pectoris according to the American College of Cardiology/American Heart Association
- new, symptomatic arrhythmia with need for anti-arrhythmic medication, direct current cardioversion, cardiac pacemaker, or defibrillator implant
- New York Heart Association class III or IV heart failure

All of these individual components are patient-relevant outcomes. Although these individual components can vary in severity, they are all characterized by pronounced symptoms and can be life threatening. Myocardial infarction and unstable angina pectoris did not occur in the study. The outcome of cardiac morbidity is used for the benefit assessment.

Cerebrovascular morbidity

Cerebrovascular morbidity was operationalized using the following individual components:

- stroke
- TIA

Both stroke and TIA are patient-relevant events. However, no strokes occurred in the study. One TIA event occurred. Considering the AEs, it is assumed that the TIA that occurred was serious. The outcome of cerebrovascular morbidity is used for the benefit assessment.

To be able to use composite outcomes, information on the results of the included individual components is required. The company did not present any corresponding information in Module 4 A, which was available for the assessment. It did not justify its approach. This is incomprehensible insofar as it had presented this information in the G-BA's 2016 benefit assessment, which was also based on the ATTRACT study. This information is therefore used in the present assessment [6,7].

Pain recorded using the BPI-SF

For the outcome of pain, the company presented both responder analyses and analyses of continuous data. For the BPI-SF, the company's dossier presents responder analyses of the proportion of patients with improvement or deterioration by ≥ 15% (≥ 1.5 points) of the scale range (scale range 0 to 10). A change of ≥ 1.5 points is considered a clinically relevant change for the benefit assessment procedure. For the responder analyses, the company considered the analysis period until Month 18. Thus, patients with deterioration or improvement at (any) point in time during the course of the study are considered responders in the company's analyses. 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 at the end of the study at Month 18). However, such responder analyses at the analysis date at Month 18 are not available for the outcome of pain. In the presented continuous BPI-SF analyses of the change at Month 18 compared with baseline, the difference in the proportion of patients included in the analysis between the treatment arms is > 15 percentage points (19 percentage points). Therefore, these analyses are also not suitable for use in the present assessment.

Health-related quality of life recorded using the SF-36v2

For the outcome of health-related quality of life, the company presented both responder analyses and analyses of continuous data. For the SF-36v2, the company's dossier presents responder analyses of the proportion of patients with deterioration or improvement by 9.4 points (PCS) and 9.6 points (MCS). This corresponds to 15% of the scale range in each case and is considered a clinically relevant improvement or deterioration (more detailed reasoning can be found in benefit assessment A21-86 [14]). For the responder analyses, the company considered the analysis period until Month 18. As described for the outcome of pain recorded with the BPI-SF, in the present therapeutic indication of a chronic, progressive disease, it is relevant to consider the outcomes as late as possible (i.e. in the ATTRACT study at the end of

the study at Month 18). However, such responder analyses at the analysis date at Month 18 are also not available for the outcome of health-related quality of life. The analyses of the change at Week 18 compared with baseline are therefore used for this benefit assessment.

Outcome category of side effects

The company presented analyses of the side effects that include all AEs regardless of the symptoms of the disease or side effects of the study medication. 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. This is taken into account in the assessment of the outcome-specific risk of bias (see Section I 4.2).

Infusion-related reactions

Infusion-related reactions are a relevant side effect for the present benefit assessment because, according to the SPC, the administration of agalsidase alfa and agalsidase beta often leads to infusion-related reactions [11,12]. This outcome was not recorded in the ATTRACT study, however.

Outcome of change in renal function

The outcome of change in renal function per year (determined on the basis of the annualized change in eGFR and mGFR) 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 mean mGFR values at baseline (see Table 8) and the small change in renal function measured in the study (mean change per year of approx. −3 or −4 mL/min/1.73 m² based on mGFR), it cannot be assumed that the outcome represents a noticeable deterioration in renal function for the majority of patients affected.

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: migalastat vs. enzyme replacement therapy[a]

Study	Study level	Outcomes									
		All-cause mortality	Pain (BPI-SF)	Outcome on the clinical morbidity of Fabry disease (composite outcome)[b]	Renal morbidity (composite outcome)[c]	Cardiac morbidity (composite outcome)[d]	Cerebrovascular morbidity (composite outcome)[e]	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Infusion-related reactions
ATTRACT	L	H[f]	–[h]	–[h]	–[h]	H[f]	H[f]	H[f, i]	H[f, g]	H[f, i]	–[h]

a. Agalsidase alfa or agalsidase beta.
b. Composite outcome, consisting of the components of renal, cardiac and cerebrovascular morbidity.
c. Composite renal outcome, consisting of the individual components of decrease in eGFR ≥ 15 mL/min/1.73 m² and increase in 24-hour urine protein ≥ 33%.
d. Composite cardiac outcome, consisting of the individual components of myocardial infarction, unstable angina pectoris, new symptomatic arrhythmia and heart failure.
e. Composite cerebrovascular outcome, consisting of the individual components of stroke and transient ischaemic attack.
f. High risk of bias across outcomes due to violation of the ITT principle; see Section I 3.2 of the present dossier assessment for the reasoning.
g. Including a relevant proportion of events that can be both side effects and symptoms.
h. No suitable data available (see Section I 4.1).
i. Lack of blinding in subjective recording of outcomes.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey

For the results of the outcomes on all-cause mortality, cardiac morbidity, cerebrovascular morbidity, health-related quality of life (recorded using SF-36v2), SAEs, and discontinuation due to AEs, the risk of bias due to violation of the ITT principle is rated as high (see Section I 3.2 for the reasoning). There is an additional high risk of bias for the results of the outcome of health-related quality of life (recorded using SF-36v2) due to lack of blinding in subjective recording of outcomes. There is an additional high risk of bias for the results of the outcome of SAEs because they include a relevant proportion of events that can be both side effects and symptoms of the disease. No suitable data are available for the outcomes of pain (recorded using BPI-SF), outcome on clinical morbidity of Fabry disease, renal morbidity, and infusion-related reactions (see Section I 4.1 for the reasoning).

I 4.3 Results

Table 12 and Table 13 summarize the results of the comparison of migalastat with enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. Where necessary, calculations conducted by the Institute are provided to supplement the data from the company's dossier.

The results on common AEs are presented in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – 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[b]
ATTRACT					
Mortality					
All-cause mortality	34	0 (0)	18	0 (0)	–
Morbidity					
Outcome on the clinical morbidity of Fabry disease (composite outcome)	No suitable data[c]				
Renal morbidity (composite outcome)	No suitable data[c]				
Cardiac morbidity (composite outcome)	34	2 (6)	18	3 (17)	0.39 [0.08; 1.96]; 0.254
Symptomatic arrhythmia in need of anti-arrhythmic medication	34	1 (3)	18	1 (6)	ND
Ventricular tachycardia	34	1 (3)	18	0 (0)	ND
Cardioversion	34	0 (0)	18	1 (6)	ND
Heart failure	34	0 (0)	18	1 (6)	ND
Cerebrovascular morbidity (composite outcome)	34	0 (0)	18	1 (6)	0.38 [0.07; 2.06]; 0.261
Stroke	34	0 (0)	18	0 (0)	–
TIA	34	0 (0)	18	1 (6)	ND
Side effects					
AEs (supplementary information)	34	32 (94)	18	18 (100)	–
SAEs[d]	34	7 (21)	18	7 (39)	0.59 [0.26; 1.34]; 0.207
Discontinuation due to AEs	34	0 (0)	18	0 (0)	–
Infusion-related reactions	No suitable data[c]				

a. Agalsidase alfa or agalsidase beta.
b. Cochran-Mantel-Haenszel method, stratified according to sex and urine protein (< 100 mg/24 h; ≥ 100 mg/24 h).
c. See Section I 4.1 of the present dossier assessment for the reasoning.
d. Including a relevant proportion of events that can be both side effects and symptoms.

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 13: Results (morbidity, health-related quality of life, continuous) – 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[b]	Values at baseline mean (SD)	Change at Month 18 mean (SE)[c]	N[b]	Values at baseline mean (SD)	Change at Month 18 mean (SE)[c]	MD [95% CI]; p-value[c]
ATTRACT							
Morbidity							
Pain (BPI-SF)	No suitable data[d]						
Health-related quality of life							
SF-36v2							
Physical Component Summary (PCS)[e]	31	47.81 (10.81)	1.67 (1.21)	16	40.45 (10.65)	−3.35 (1.67)	5.02 [0.75; 9.30]; 0.022 SMD [95% CI]: 0.70 [0.08; 1.32][f]
Mental Component Summary (MCS)[e]	31	49.26 (10.58)	−0.04 (1.56)	16	50.60 (10.30)	−0.01 (2.21)	−0.02 [−5.48; 5.43]; 0.993

a. Agalsidase alfa or agalsidase beta.
b. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
c. Mean and SE (change at Month 18 per treatment group) as well as MD, CI and p-value (group comparison): ANCOVA analysis; adjusted for sex, age and baseline; the estimated effect represents the difference in change (from baseline) between the treatment groups at Month 18.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
f. Institute's calculation based on effect estimate of the mean difference and CI of the ANCOVA.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36v2: Short Form 36 – version 2 Health Survey; SMD: standardized mean difference

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

Mortality

All-cause mortality

No deaths occurred in the course of the study. There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Cardiac morbidity and cerebrovascular morbidity

No statistically significant difference between treatment groups was shown for the outcomes of cardiac morbidity (consisting of myocardial infarction, unstable angina pectoris, new symptomatic arrhythmia and cardiac failure) and cerebrovascular morbidity (consisting of stroke and TIA). In each case, there is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy; an added benefit is therefore not proven.

Pain (recorded using the Brief Pain Inventory-Short Form [BPI-SF]), outcome on clinical morbidity of Fabry disease, renal morbidity

No suitable data are available for the outcomes of pain, outcome on clinical morbidity of Fabry disease (consisting of renal, cardiac and cerebrovascular morbidity), and renal morbidity (consisting of decrease in eGFR ≥ 15 mL/min/1.73 m² and increase in 24-hour urine protein ≥ 33%) (see Section I 4.1 for the reasoning). In each case, 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

Health-related quality of life outcomes were recorded using the SF-36v2.

A statistically significant difference in favour of migalastat compared with enzyme replacement therapy was shown for the PCS of the SF-36v2. However, the 95% confidence interval of the standardized mean difference was not fully outside the irrelevance range of [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of migalastat in comparison with enzyme replacement therapy for the outcome of PCS; an added benefit is therefore not proven.

No statistically significant difference between the treatment groups was shown for 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

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from migalastat in comparison with enzyme replacement therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no discontinuations due to AEs during the course of the study. There is no hint of greater or lesser harm from migalastat in comparison with enzyme replacement therapy for the outcome of discontinuation due to AEs; greater or lesser harm is therefore not proven.

Infusion-related reactions

No suitable data are available for the outcome of infusion-related reactions (see Section I 4.1 for the reasoning). There is no hint of greater or lesser harm from migalastat in comparison with enzyme replacement therapy; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

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

No suitable analyses are available for the characteristic of disease severity.

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.

In the present benefit assessment, both dichotomous analyses (cardiac and cerebrovascular morbidity, side effects) and analyses of continuous data (health-related quality of life) are used (see Section I 4.1). However, the company did not present any subgroup analyses for the continuous analyses. When applying the methods described above, the available subgroup results do not reveal any effect modifications in the dichotomous outcomes.

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 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 14).

Table 14: Extent of added benefit at outcome level: migalastat vs. enzyme replacement therapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier**	**Migalastat vs. enzyme replacement therapy[a]** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Pain (BPI-SF)	No suitable data[d]	Lesser/added benefit not proven
Outcome on the clinical morbidity of Fabry disease	No suitable data[d]	Lesser/added benefit not proven
Renal morbidity	No suitable data[d]	Lesser/added benefit not proven
Cardiac morbidity	6% vs. 17% RR: 0.39 [0.08; 1.96] p = 0.254	Lesser/added benefit not proven
Cerebrovascular morbidity	0% vs. 6% RR: 0.38 [0.07; 2.06] p = 0.261	Lesser/added benefit not proven
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS)	1.67 vs. −3.35 MD: 5.02 [0.75; 9.30] p = 0.022 SMD: 0.70 [0.08; 1.32][e]	Lesser/added benefit not proven
Mental Component Summary (MCS)	−0.04 vs. −0.01 MD: −0.02 [−5.48; 5.43] p = 0.993	Lesser/added benefit not proven
Side effects		
SAEs[f]	21% vs. 39% RR: 0.59 [0.26; 1.34] p = 0.207	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0% RR: –	Greater/lesser harm not proven
Infusion-related reactions	No suitable data[d]	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: migalastat vs. enzyme replacement therapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier**	**Migalastat vs. enzyme replacement therapy[a]** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. Agalsidase alfa and agalsidase beta. b. Probability provided if a statistically significant and relevant effect is present. c. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L). d. See Section I 4.1 of the present dossier assessment for the reasoning. e. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived. f. Includes events that can be both side effects and symptoms of the disease. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of the confidence interval; CI_L: lower limit of the confidence interval; MD: mean difference; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SMD: standardized mean difference		

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of migalastat in comparison with enzyme replacement therapy[a]

Positive effects	**Negative effects**
–	–
No suitable data are available for the outcomes of pain (BPI-SF), outcome on clinical morbidity of Fabry disease, renal morbidity, and infusion-related reactions.	
a. Agalsidase alfa and agalsidase beta. BPI-SF: Brief Pain Inventory – Short Form	

Overall, neither positive nor negative effects were found for migalastat in comparison with enzyme replacement therapy.

In summary, there is no hint of an added benefit of migalastat in comparison with the ACT agalsidase alfa or agalsidase beta for patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation; an added benefit is therefore not proven.

Table 16 summarizes the result of the assessment of the added benefit of migalastat in comparison with the ACT.

Table 16: 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.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted in the context of market access in 2016 and of the extension of the therapeutic indication in 2021, where the G-BA found a non-quantifiable added benefit in 2016 and a hint of a non-quantifiable added benefit of migalastat in 2021. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data due to orphan drug status.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-88.html.