Elosulfase alfa (mucopolysaccharidosis type IVA)

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

EXTRACT

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Medical and scientific advice

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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

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization ‘MPS e. V.’ for participating in the written exchange and for their support. The respondent and ‘MPS e. V.’ were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
3MSCT	3-minute stair climb test
6MWT	6-minute walk test
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CI	confidence interval
CSR	clinical study report
EMA	European Medicines Agency
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IAR	infusion-associated reaction
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MARS	Morquio A Registry Study
MedDRA	Medical Dictionary for Regulatory Activities
MPS	mucopolysaccharidosis
MPS-HAQ	Mucopolysaccharidosis Health Assessment Questionnaire
PT	Preferred Term
QOW	every other week
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class

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 elosulfase alfa. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 30 April 2025.

Research question

The aim of this report is the assessment of the added benefit of elosulfase alfa in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients of all ages with mucopolysaccharidosis type IVA.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of elosulfase alfa

Therapeutic indication	**ACT**[a]
Patients of all ages with mucopolysaccharidosis type IVA (Morquio A Syndrome, MPS IVA)	Best supportive care[b, c]
a. Presented is the ACT specified by the G-BA. b. Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. The assessment was 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.

Approach of the company

To derive the added benefit, the company presented an RCT with a duration of 24 weeks and a comparison of individual arms of different studies with confounder adjustment using propensity score matching with a longer observation period. In addition, it presented a comparison of individual arms of different studies without confounder adjustment for children < 5 years, although it did not use this for the derivation of the added benefit. The RCT presented was used for the benefit assessment. Comparisons of individual arms of different studies were not suitable for the benefit assessment.

Direct comparison in randomized controlled trials

Study pool and study design

The MOR-004 study was included for the benefit assessment. MOR-004 is a double-blind, 3-arm multicentre RCT comparing elosulfase alfa administered weekly or every other week (QOW) versus placebo for the treatment of patients with mucopolysaccharidosis IVA. The study included patients aged 5 years and older who covered a walking distance of between 30 and 325 m in the 6-minute walk test (6MWT) during screening, averaged over 2 tests. Patients who had undergone major surgery within 3 months of study entry or who were scheduled to undergo major surgery during the study were excluded.

A total of 177 patients were included in the study and randomly assigned in a 1:1:1 ratio to treatment with elosulfase alfa weekly (N = 58), elosulfase alfa QOW alternating with placebo (N = 59) or placebo (N = 60). The study arm with elosulfase alfa QOW was not relevant for this benefit assessment and is not considered further in the following. Randomization was stratified by age group (5 to 11 versus 12 to 18 versus ≥ 19 years) and the result of the 6MWT (≤ 200 m versus > 200 m).

In the intervention arm, elosulfase alfa was administered in compliance with recommendations of the summary of product characteristics (SmPC). Placebo consisted of the carrier solution of the drug and was administered intravenously analogous to the administration of elosulfase alfa, including premedication with oral or intravenous antihistamine. The treatment duration was 24 weeks or until treatment discontinuation as decided by the investigator or the withdrawal of informed consent. The primary outcome of the study was the change in 6MWT at Week 24. Further patient-relevant outcomes were recorded in the categories of morbidity and side effects.

After completion of the study, all patients had the option of switching to the extension study MOR-005, in which all patients received elosulfase alfa weekly or QOW.

Implementation of the appropriate comparator therapy best supportive care

BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The concomitant medication used in the study, for example for pain therapy or anti-infective therapies, suggested guideline-compliant supportive health care in both arms of the study.

In the comparator arm of the MOR-004 study, a placebo infusion was used with the same carrier solution (excipients in addition to physiological saline: sodium acetate trihydrate, sodium dihydrogen phosphate, arginine hydrochloride, sorbitol, polysorbate 20) and premedication as in the intervention arm. However, the carrier solution used in the study, the weekly intravenous administration over several hours and the premedication were not part

of the ACT BSC. Furthermore, the carrier solution was potentially not an ineffective placebo. The influence of the administration of the placebo infusion with the carrier solution, the premedication and the necessary creation and use of peripheral/central venous access on the observed effects in the MOR-004 study was unclear.

In the MOR-004 study, the implementation of the ACT BSC was limited overall due to the administration of a potentially effective placebo and the associated additional measures. The study was used for the benefit assessment, but at most hints, e.g. of an added benefit, could be derived for the results of all outcomes.

Study duration

It should be noted that the study duration of 24 weeks was short in relation to the chronic course of the disease, which slowly progresses, sometimes over decades. The long-term effect of elosulfase alfa on patient-relevant outcomes can therefore only be assessed to a limited extent on the basis of the MOR-004 study.

No data on children up to 5 years

An age ≥ 5 years at screening was an inclusion criterion of the study. Based on the study, it is therefore not possible to draw any conclusions on the added benefit for children up to 5 years of age with MPS IVA.

Risk of bias

The risk of bias across outcomes was rated as low for the MOR-004 study, as was the risk of bias for the results of all outcomes with suitable data. However, due to the limited implementation of the ACT, at most hints, e.g. of an added benefit, could be derived for the results of all outcomes.

Results

Mortality

All-cause mortality

There were no events in the outcome of all-cause mortality. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Walking ability (6-minute walk test)

A statistically significant difference between the treatment arms was shown for the outcome walking ability (6MWT). As explained below, the clinical relevance of the effect was unclear, however.

The mean improvement in walking distance between the intervention and the comparator arm was 22.5 m; the lower limit of the 95% confidence interval (CI) was 4.0 m, which appeared too small to rate the observed effect in isolation as clinically relevant. A distribution diagram in the study documents indicated that the mean difference in the 6MWT was largely due to a group of patients who achieved a particularly large improvement (> 60 m) in walking distance. However, it was not possible to differentiate these patients on the basis of the available data using subgroup analyses. A meaningful assessment of the clinical relevance of the effect in the 6MWT was not possible for all patients in the study on the basis of the mean difference and the CI.

Regardless of the aforementioned aspects, the improvement in walking distance was not confirmed in other outcomes on exercise capacity such as the 3-minute stair climb test (3MSCT) and the forced expiratory volume in 1 second (FEV1) measurement. Neither the 3MSCT nor the FEV1 measurement showed statistically significant differences between the treatment arms. In addition, the data from the extension study MOR-005 showed no improvement in walking distance in those patients who switched from the control arm (placebo) in MOR-004 to treatment with elosulfase alfa at the approved dose in MOR-005. The patients who were treated with elosulfase alfa in the intervention arm in MOR-004 and continued this treatment in the extension study MOR-005, initially blinded and then unblinded after the analysis of MOR-004, also showed no further increase in walking distance after the transition.

Another uncertainty regarding the observed effect resulted from the fact that blinding may not have been consistently ensured, particularly in the intervention arm. For example, the proportion of infusion interruptions with intervention due to AEs of 22.4% in the intervention arm versus 0% in the comparator arm and the use of elective premedication with glucocorticoids during the course of the study of 36% (intervention arm) versus 12% (placebo arm) showed the sometimes very specific side effect profile of enzyme replacement therapy. In a subjectively influenceable outcome such as the 6MWT, which depends on the motivation and cooperation of the subjects [3,4], knowledge of the treatment can influence the outcome.

Against the background of the aspects described, the relevance of the statistically significant effect therefore remained unclear. The effect was taken into account in the overall assessment of the added benefit.

Use of wheelchairs and walking aids

No suitable data were available for the outcomes of wheelchair use and walking aid use. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Height (z-score)

There was no statistically significant difference between the treatment arms for the outcome height. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

No data were recorded for the outcome of health-related quality of life. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of elosulfase alfa compared with placebo was shown for the outcome serious adverse events (SAEs). There is a hint of greater harm of elosulfase alfa + BSC versus BSC.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Infusion-related reactions

No suitable data are available for the outcome of infusion-related reactions. This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Anaphylactic reactions (SMQ)

There was no statistically significant difference between the treatment arms for the outcome anaphylactic reactions. This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Specific AEs

There was a statistically significant difference to the disadvantage of elosulfase alfa compared with placebo for the outcome infections and infestations (System Organ Class [SOC], SAEs). There is a hint of greater harm of elosulfase alfa + BSC versus BSC.

Indirect, non-randomized comparison

Evidence provided by the company

Comparison of individual arms from different studies, age ≥ 5 years

The company presented a comparison of individual arms of different studies. It conducted this comparison to draw conclusions regarding the efficacy of elosulfase alfa beyond the 24-week observation period in the RCT MOR-004.

On the intervention side, the company used individual data from patients from the elosulfase alfa arm with weekly administration from the RCT MOR-004 and its extension study MOR-005. To represent the ACT, the company used individual data from a selection of patients from the observational study MOR-001. An adjustment for confounders was made using propensity score matching.

Data sources for the intervention elosulfase alfa: MOR-004 / MOR-005

For the intervention side of the indirect comparison, the company used data from the study MOR-004 and the associated extension study MOR-005. It considered the 56 patients who received therapy with elosulfase alfa at the approved dosage in MOR-004 and continued this regimen in MOR-005. The duration of treatment and observation in MOR-005 was a maximum of 240 weeks, and outcomes on morbidity (especially the 6MWT) and side effects were recorded.

Data sources for the ACT BSC: study MOR-001

MOR-001 was initiated in 2008 as a non-interventional, observational cross-sectional study to characterize the spectrum of the condition MPS IVA. From 2011, it was amended to continue as a longitudinal study to characterize the natural course of the disease with data collection from annual visits. MOR-001 included patients with MPS IVA without any restrictions, e.g. with regard to age or disease severity. The annual visits included measurements of walking distance in the 6MWT and height. Side effects were not systematically recorded. A total of 353 patients in 11 countries were observed in the study.

Analysis time points and outcomes of the indirect comparison

In the intervention arm (MOR-005), data from the visit at Week 72 were used for the comparison; in the comparator arm (MOR-001), data were used from the visit in the 1-year time window, which took place on average on Day 447. MOR-005 collected data on morbidity outcomes (6MWT, respiratory function test, body measurements) and data on side effects; MOR-001 also collected data on morbidity outcomes (6MWT, respiratory function test, body measurements), but no outcomes in the side effects category. Among other things, the company presented a comparison for the morbidity outcomes 6MWT, FEV1, height and weight.

Assessment of the methods of the adjusted comparison

Overall, the indirect, non-randomized comparison presented by the company was not suitable for the benefit assessment. Firstly, the company markedly limited the study pool and thus the eligible patients on both sides of the comparison: In addition to the studies used, the company identified 8 further studies in its information retrieval that concurred with the inclusion criteria for the comparison according to the research question. It briefly justified the exclusion of the evidence from these studies and registries by referring to the sometimes small sample sizes, differences in the baseline characteristics or too high a proportion of missing values. These justifications for the exclusion of the identified studies were neither sufficient nor appropriate. On the other hand, sufficient structural equality of the patient groups was not guaranteed even after the propensity score matching. Relevant confounders and selection bias were not sufficiently taken into account in the adjustment. The company followed the process proposed by Pufulete 2022 for the identification of confounders, but the further approach to reducing the number of identified confounders was not adequate: The exclusion of a potential confounder based on content considerations must be justified based on the literature, and consideration must not be guided by the available data or the possibility or impossibility of operationalizing the confounder. For example, it remained unproven and implausible that the company did not take into account characteristics identified as confounders such as 'use of wheelchair/walking aids', 'skeletal abnormalities', 'concomitant therapies/medication' and 'motivation/cooperation'. It cannot be ruled out either that the selection of the few characteristics considered from the large number of identified confounders (4 of initially more than 120) was not made independently of the availability of the data.

In addition, there were possible causes of selection bias that could not be adequately captured by the confounders.

Regardless of the deficiencies described above, the observed effect was not large enough to be explained solely by a systematic bias in the given data situation. The data presented therefore did not allow for an adequate comparison of elosulfase alfa with the ACT.

Indirect, non-randomized, unadjusted indirect comparison for children < 5 years of age

In addition to the adjusted comparison for patients aged ≥ 5 years, the company also presented the single-arm phase 2 study MOR-007, which investigated the safety and efficacy of elosulfase alfa in the approved dosage for the duration of 52-weeks in children aged < 5 years with MPS IVA. In Module 4 of the dossier, the company compared results on growth from this study with data on similar outcomes for selected children under 5 years of age without treatment with elosulfase alfa who had been included in the MPS IV observational study MOR-001 prior to the marketing authorization of elosulfase alfa. This comparison was unadjusted and was only available for outcomes relating to height. Non-comparative data on

outcomes in the side effects category were not available. Results from the MOR-007 study and from the comparison with MOR-001 were not used for the derivation of the added benefit, analogous to the company's approach.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

The indirect comparison presented by the company was not suitable and was not used for the assessment. The added benefit of elosulfase alfa was therefore determined exclusively on the basis of the RCT MOR-004.

On the basis of the results presented, the probability and extent of the added benefit of the drug elosulfase alfa in comparison with the ACT was assessed as follows:

Compared with the ACT, negative effects of elosulfase alfa were shown for the overall rate of SAEs and a subcategory of SAEs at SOC level. The extent of the effect was minor in each case. For the outcome 6MWT, there was a statistically significant advantage in favour of elosulfase alfa, but the clinical relevance of this effect was unclear. In the given data situation, the positive and negative effects were therefore assessed as balanced. No data were recorded for the category health-related quality of life, and no suitable data were available for the outcome infusion-related reactions.

No suitable data were available for children aged < 5 years.

In the overall assessment of the available data, there is no proof of an added benefit of elosulfase alfa versus the ACT for patients with mucopolysaccharidosis type IVA.

Table 3 shows a summary of probability and extent of added benefit of elosulfase 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: Elosulfase alfa – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients of all ages with mucopolysaccharidosis type IVA (Morquio A Syndrome, MPS IVA)	Best supportive care[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group.

ACT: appropriate comparator therapy; BSC: best supportive care; 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 result of the G-BA's assessment conducted in the context of the market launch in 2014 and of the reassessment in 2018. In both cases, the G-BA had determined a minor added benefit of elosulfase alfa.

I 2 Research question

The aim of this report is the assessment of the added benefit of elosulfase alfa in comparison with BSC as the ACT in patients of all ages with mucopolysaccharidosis type IVA.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of elosulfase alfa

Therapeutic indication	**ACT**[a]
Patients of all ages with mucopolysaccharidosis type IVA (Morquio A Syndrome, MPS IVA)	Best supportive care[b, c]
a. Presented is the ACT specified by the G-BA. b. Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. The assessment was 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.

Approach of the company

To derive the added benefit, the company presented an RCT with a duration of 24 weeks and a comparison of individual arms of different studies with confounder adjustment using propensity score matching with a longer observation period. In addition, it presented a comparison of individual arms of different studies without confounder adjustment for children < 5 years, although it did not use this for the derivation of the added benefit. The RCT presented was used for the benefit assessment and its assessment can be found in Chapter I 3. Comparisons of individual arms of different studies were not suitable for the benefit assessment; this is explained in Chapter I 4. Chapter I 5 then provides an overall assessment of the probability and extent of the added benefit.

I 3 Direct comparison in randomized controlled trials

I 3.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on elosulfase alfa (status: 6 February 2025)
- Bibliographical literature search on elosulfase alfa (last search on 6 February 2025)
- Search in trial registries/trial results databases for studies on elosulfase alfa (last search on 6 February 2025)
- Search on the G-BA website for elosulfase alfa (last search on 21 February 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on elosulfase alfa (last search on 15 May 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant RCTs.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: elosulfase alfa + BSC vs. BSC

Study	Study category			Available sources		
	Study for the marketing authorization 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])
MOR-004	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8-11]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on 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.

ACT: appropriate comparator therapy; BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: elosulfase alfa vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MOR-004	RCT, double-blind, parallel	Patients with MPS IVA[b] ▪ 5 years and older ▪ Mean 6MWT ≥ 30 m and ≤ 325 m at screening ▪ No major surgery within 3 months prior to study entry and no planned major surgery during the study	▪ elosulfase alfa 2 mg/kg/week (N = 58) ▪ elosulfase alfa 2 mg/kg, every 2 weeks alternating with placebo (N = 59)[c] ▪ placebo (N = 59[d])	Screening: up to 3 weeks Treatment: 24 weeks or until treatment discontinuation at the physician's decision or withdrawal of consent Follow-up: up to a maximum of 30 days after the end of treatment[e]	33 study centres in Argentina, Brazil, Canada, Colombia, Denmark, France, Germany, Italy, Japan, Netherlands, Portugal, Qatar, Saudi Arabia, South Korea, Taiwan, United Kingdom, United States 1/2011–8/2012	Primary: change in 6MWT at Week 24 Secondary: morbidity outcomes, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Diagnosis based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte GALNS enzyme activity or genetic testing.
c. The elosulfase alfa dose of 2.0 mg/kg every 2 weeks does not concur with the approved dose in Germany. This arm is therefore not relevant for the assessment and is not presented in the following tables.
d. One of the originally 60 randomized individuals in the placebo arm was not included. After randomization, it was determined that the diagnosis of MPS IVA was not confirmed for this individual.
e. Patients had the opportunity to participate in the open-label extension study MOR-005 after completing the MOR-004 study.

6MWT: 6-minute walk test; AE: adverse event; GALNS: N-acetylgalactosamine-6-sulphate sulphatase; MPS IVA: mucopolysaccharidosis type IVA / Morquio A Syndrome; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: elosulfase alfa vs. placebo

Study	Intervention	Comparison
MOR-004	elosulfase alfa 2 mg/kg/week[a], IV	Placebo (vehicle solution[b] of elosulfase alfa)
	No dose modifications planned; in case of infusion reactions, depending on the severity of the reaction: interruption of the infusion[c], reduction of the infusion rate or termination of the infusion	
	Prohibited prior treatments ▪ Haematopoietic stem cell transplantation ▪ elosulfase alfa ▪ Any investigational medicinal product or medical device being tested ≤ 30 days before screening ▪ Major surgery ≤ 3 months before start of study **Concomitant treatment** <u>Premedication required before each infusion:</u> ▪ Antihistamines (preferably non-sedating, e.g. cetirizine, loratadine) <u>Allowed</u> ▪ For patients with known infusion reactions, sedating antihistamines and additional premedication if required, e.g. H2 blockers, montelukast sodium or glucocorticoids ▪ Antipyretics at the discretion of the investigator ▪ Best supportive care (any concomitant medication other than investigational drugs, and other medical interventions other than medical devices being tested)	

a. Minimum interval between infusions: 4 days
b. According to the SmPC [12], the carrier solution contains sodium acetate trihydrate, sodium dihydrogen phosphate, arginine hydrochloride, sorbitol and polysorbate 20.
c. After interruption, continuation of the infusion at half the infusion rate from the time the infusion reaction occurred.

H2 blocker: histamine-2 blocker; IV: intravenous; RCT: randomized controlled trial; SmPC: summary of product characteristics

Study design

The MOR-004 study is a double-blind, 3-arm multicentre RCT comparing elosulfase alfa administered weekly or QOW versus placebo for the treatment of patients with mucopolysaccharidosis IVA. The study included patients aged 5 years and older who covered a walking distance of between 30 and 325 m in the 6MWT during screening, averaged over 2 tests. Patients who had undergone major surgery within 3 months of study entry or who were scheduled to undergo major surgery during the study were excluded.

A total of 177 patients were included in the study and randomly assigned in a 1:1:1 ratio to treatment with elosulfase alfa weekly (N = 58), elosulfase alfa QOW alternating with placebo (N = 59) or placebo (N = 60). The study arm with elosulfase alfa QOW was not relevant for this benefit assessment and is not considered further in the following. One person in the placebo arm was excluded from the study and not treated because the diagnosis of MPS IVA was not

confirmed. This person was not included in the analysis population. Randomization was stratified by age group (5 to 11 versus 12 to 18 versus ≥ 19 years) and the result of the 6MWT (≤ 200 m versus > 200 m).

In the intervention arm, elosulfase alfa was administered in compliance with recommendations of the SmPC [12]. Placebo consisted of the carrier solution of the drug and was administered intravenously analogous to the administration of elosulfase alfa, including premedication with oral or intravenous antihistamine. The treatment duration was 24 weeks or until treatment discontinuation as decided by the investigator or the withdrawal of informed consent. The primary outcome of the study was the change in 6MWT at Week 24. Further patient-relevant outcomes were recorded in the categories of morbidity and side effects.

After completion of the study, all patients had the option of switching to the extension study MOR-005, in which all patients received elosulfase alfa weekly or QOW (see Chapter I 4).

Implementation of the appropriate comparator therapy best supportive care

BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The study protocol did not restrict the supportive therapy measures recommended in guidelines [13,14] (e.g. physiotherapy, vaccinations, infection therapy), measures for the early detection of possible complications (including those affecting the musculoskeletal system, but also the eyes and ears) or the recommendations for early surgical interventions. The concomitant medication used in the study, for example for pain therapy or anti-infective therapies, suggested guideline-compliant supportive health care in both arms of the study.

In the comparator arm of the MOR-004 study, a placebo infusion was used with the same carrier solution (excipients in addition to physiological saline: sodium acetate trihydrate, sodium dihydrogen phosphate, arginine hydrochloride, sorbitol, polysorbate 20 [12]) and premedication as in the intervention arm (see Table 7). However, the carrier solution used in the study, the weekly intravenous administration over several hours and the premedication were not part of the ACT BSC. Furthermore, the carrier solution was potentially not an ineffective placebo. The fact that the carrier solution administered as a placebo was not completely without effect was shown in particular by the need to administer additional glucocorticoids as premedication in 12% of the patients in the comparator arm (36% in the intervention arm). The influence of the administration of the placebo infusion with the carrier solution, the premedication and the necessary creation and use of peripheral/central venous access on the observed effects in the MOR-004 study was unclear.

In the MOR-004 study, the implementation of the ACT BSC was limited overall due to the administration of a potentially effective placebo and the associated additional measures. The

study was used for the benefit assessment, but at most hints, e.g. of an added benefit, could be derived for the results of all outcomes.

Study duration

It should be noted that the study duration of 24 weeks was short in relation to the chronic course of the disease, which slowly progresses, sometimes over decades. The long-term effect of elosulfase alfa on patient-relevant outcomes can therefore only be assessed to a limited extent on the basis of the MOR-004 study. This applies in particular to potential adverse events (AEs) that may only occur later as a result of the necessary concomitant treatments. For example, optional premedication with corticosteroids was given to 36% of patients in the intervention arm during the course of the study.

No data on children up to 5 years

An age ≥ 5 years at screening was an inclusion criterion of the study. Based on the study, it is therefore not possible to draw any conclusions on the added benefit for children up to 5 years of age with MPS IVA, see Section I 5.2.

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: elosulfase alfa vs. placebo (multipage table)

Study Characteristic Category	elosulfase alfa N[a] = 58	Placebo N[a] = 59
MOR-004		
Age [years]		
Mean (SD)	13.1 (8.1)	15.0 (11.3)
Median [min; max]	11.1 [5; 42]	11.9 [5; 57]
Age groups [years], n (%)		
5–11	32 (55)	30 (51)
12–18	16 (28)	15 (25)
≥ 19	10 (17)	14 (24)
Sex [F/M], %	55/45	54/46
Region, n (%)		
North America	15 (26)	16 (27)
Europe	25 (43)	27 (46)
Other	18 (31)	16 (27)
Body weight [kg]		
Mean (SD)	22.9 (10.5)	25.4 (11.5)
Median [min; max]	19.1 [12; 69]	23.0 [13; 67]

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: elosulfase alfa vs. placebo (multipage table)

Study **Characteristic** **Category**	**elosulfase alfa** **N[a] = 58**	**Placebo** **N[a] = 59**
Height[b] [cm]		
Mean (SD)	101.3 (13.1)	105.5 (16.8)
Median [min; max]	98.8 [83; 141]	100.0 [86; 165]
Height (z-score)		
Mean (SD)	-6.4 (2.55)	-6.0 (2.77)
Median [min; max]	-6.5 [-11.0; -2.1]	-5.6 [-11.4; -1.4]
6MWT [m]		
Mean (SD)	203.9 (76.3)	211.9 (69.9)
Median [min; max]	216.5 [42; 322]	228.9 [36; 312]
Stratified 6MWT walking distance [m], n (%)		
≤ 200	23 (40)	23 (39)
> 200	35 (60)	36 (61)
Wheelchair use in everyday life[c], n (%)	30 (52)	22 (37)
Walking aid use in everyday life[d], n (%)	17 (29)	18 (31)
Walking aid use during the 6MWT, n (%)	9 (16)	11 (19)
Crutches n%	1 (2)	4 (7)
Walking frame / rollator n%	7 (12)	6 (10)
Cane / walking stick n%	1 (2)	1 (2)
3MSCT [steps/minute]		
Mean (SD)	29.6 (16.4)	30.0 (14.1)
Median [min; max]	30.5 [0; 72]	30.8 [0; 59]
Time since MPS IVA diagnosis [years]		
Mean (SD)	6.5 (6.3)	8.7 (9.6)
Median [min; max]	4.8 [0; 26]	4.1 [0; 38]
Age at the time of MPS IVA diagnosis [years]		
Mean (SD)	6.6 (7.1)	6.4 (6.4)
Median [min; max]	4.2 [1; 31]	4.4 [0; 37]
Treatment discontinuation[e], n (%)	1 (1.7)	0 (0)
Study discontinuation[e], n (%)	1 (1.7)	0 (0)

a. N: in the intervention arm: number of randomized patients, in the control arm: number of randomized patients minus 1 person for whom the diagnosis of MPS IVA was not confirmed after randomization; values based on other patient numbers are marked in the corresponding line if deviation is relevant.
b. Data from 55 vs. 56 patients are included; measured in standing position.
c. Any, even occasional, wheelchair use.
d. Walking aids include orthoses, braces, crutches, walking stick or rollator.
e. One person in the intervention arm withdrew their consent after the first infusion.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: elosulfase alfa vs. placebo (multipage table)

Study Characteristic Category	elosulfase alfa N[a] = 58	Placebo N[a] = 59
3MSCT: 3-minute stair climb test; 6MWT: 6-minute walk test; F: female; M: male; max: maximum; min: minimum; MPS IVA: mucopolysaccharidosis type IVA / Morquio A Syndrome; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation		

Most demographic and clinical characteristics of the patients in both treatment arms were largely comparable. The mean patient age at study inclusion was 13 years in the intervention arm and 15 years in the comparator arm; the proportion of adults was > 20%. Almost all patients were of very short stature with a mean height z-score of –6.4 in the intervention arm and –6.0 in the comparator arm. The baseline walking distance in the 6MWT was approximately 200 metres in both arms. The baseline wheelchair use as an aid in everyday life was higher in the intervention arm (52%) than in the comparator arm (37%). At the time of study inclusion, the median time since diagnosis was more than 4 years.

Over the course of the entire 24-week study, there was one study discontinuation and thus treatment discontinuation. This occurred in the intervention arm by withdrawing consent after the first infusion.

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: elosulfase alfa vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MOR-004	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the MOR-004 study.

Transferability of the study results to the German health care context

The company considered the study results to be transferable to the German health care context. It justified this with the large proportion of patients in the study who were from Europe, and specifically from Germany. In addition, the subgroup analyses stratified by origin and region did not indicate any significant interactions. Furthermore, the company justified the inclusion and exclusion criteria of the MOR-004 study and discussed the relevance of the measured outcomes.

The company did not provide any further information on the transferability of the study results to the German health care context.

For the transferability of the study results, see also the comments on the study in this section above and in Section I 3.2.3.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Walking ability (6MWT)
  - Wheelchair use
  - Walking aid use
  - Height (z-score)
- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to AEs
- Infusion-related reactions
- Anaphylactic reactions (AE, Standardized Medical Dictionary for Regulatory Activities Query [SMQ])
- Other specific AEs, if any

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

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

Table 10: Matrix of outcomes – RCT, direct comparison: elosulfase alfa vs. placebo

Study	Outcomes										
	All-cause mortality[a]	Walking ability (6MWT)	Wheelchair use	Walking aid use	Height (z-score)	Health-related quality of life	SAEs	Discontinuation due to AEs	Infusion-related reactions	Anaphylactic reactions (SMQ, AEs)	Infections and infestations (SOC, SAEs)
MOR-004	Yes	Yes	No[b]	No[b]	Yes[c]	No[d]	Yes	Yes	No[b]	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. No suitable data available; see running text below for reasons.
c. Analysis for female patients ≤ 15 years and male patients ≤ 18 years at baseline.
d. Outcomes in this category were not recorded.

6MWT: 6-minute walk test; AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class

Notes on outcomes

Walking ability (6MWT)

The progressive loss of the ability to walk and physical endurance due to the progressive disease is a common symptom in patients with MPS IVA. The 6MWT is a standardized and established instrument for determining physical endurance (distance a patient can walk within 6 minutes [3]) and was considered relevant for this assessment. In the MOR-004 study, the 6MWT was conducted at screening and in Weeks 12 and 24, and within 1 week following early study discontinuation. The patient was asked to walk (not run or jog) as far as possible on a flat surface for 6 minutes. The use of an aid (e.g. cane, crutch or rollator) to conduct the 6MWT was permitted. The patient had to use the same walking aid for all subsequent tests.

In the dossier, the company presented both prespecified analyses on the mean change in 6MWT distance at Week 24 versus baseline and non-prespecified responder analyses with a threshold value of 9% for improvement and deterioration in relation to the baseline value of

the respective patient. This assessment used the ANCOVA mean difference in the 6MWT from Week 24 versus baseline as planned in the study protocol as the primary analysis .

The presented responder analyses based on the threshold value of 9% were not used for the benefit assessment. This is due to the fact that these analyses were conducted post hoc. In addition, it remained unclear what the selected response threshold of 9% means for the patients. This threshold value was therefore also not justified in terms of content.

The implementation of the prespecified imputation method for missing values in the analysis of the mean change in 6MWT distance was insufficiently documented in Module 4. However, based on information in the clinical study report (CSR), it is presumed that missing values in the 6MWT only had to be replaced for one patient at Week 24.

Use of wheelchairs and walking aids

Being dependent on a wheelchair or walking aid to cope with everyday life is a patient-relevant restriction. In the study, the company asked about the current use of wheelchairs and walking aids. This was done as part of the recording of the Mucopolysaccharidosis Health Assessment Questionnaire (MPS-HAQ, see also the following text in this section). The isolated analysis of the items of the questionnaire on wheelchair and walking aid use was carried out post hoc and recorded any current use. The company considered both improvement (no need for further use) and deterioration (new need for use). However, the analyses presented were not suitable for the benefit assessment: The analyses presented by the company only included those patients who were dependent on the respective mobility aids at enrolment (analysis on improvement) or who were not dependent on the respective mobility aids at enrolment (analysis on deterioration). A relevant proportion of randomized patients was not included in these outcome definitions. This was not appropriate. Instead, an analysis based on all randomized patients would be necessary, e.g. as the proportion of patients who required a walking aid or wheelchair at Week 24.

Height (z-score)

Z-scores for height are derived using age and sex-specific reference data for the population of average stature. The available data on height were presented as z-scores (number of standard deviations) above or below the age-specific reference for the United States (data from the Centers for Disease Control and Prevention). The reference corresponds to a z-score of 0. Short stature is defined as a height deficit of at least 2.0 standard deviations below the population-specific mean height for age and sex, corresponding to a z-score of −2.

The outcome height (z-score) in the given therapeutic indication with pronounced short stature (z-score at baseline < –5, see Table 8) was used for the benefit assessment. However, it is difficult to estimate how a specific change in the outcome of height (z-score) will ultimately affect the patient.

The company presented a prespecified operationalization of the outcome as change in standing height at Week 24, which was limited to the analysis of female patients aged ≤ 15 years at baseline and male patients aged ≤ 18 years at baseline. This analysis was appropriate.

MPS-HAQ

The MPS-HAQ is a 52-question instrument for the assessment of functional abilities and performance in patients with MPS IV, which comprises 3 subdomains: self-care, mobility and caregiver-assistance. It was developed for patients with type I MPS.

The MPS-HAQ was not assessed to be a validated instrument for measuring morbidity in patients with MPS IVA. This was due to a lack of information on the development of the instrument, in particular on the involvement of patients in the therapeutic indication. In addition, there is no manual or publication by the developers of the instrument describing the standardized analysis of the instrument, nor are there any standardized criteria available specifying under which circumstances or up to what age the questionnaire should be completed by caregivers. In Module 5 of the dossier, the company provided a manuscript that has not been published yet [15], which, according to the company, is currently in the peer review process and investigated the validity and reliability of the instrument. However, the described shortcomings of the instrument validation cannot be remedied by this subsequent investigation of some psychometric properties of the instrument in the therapeutic indication. The analyses presented on the MPS-HAQ were therefore not used for the benefit assessment.

Health-related quality of life

Outcomes in the health-related quality of life category were not recorded in the MOR-004 study.

Side effects

In the comparator arm of the study, placebo infusion with a carrier solution (in addition to physiological saline) and the corresponding premedication were used for blinding (see Section I 3.1.2). On the one hand, this enables blinding in the study, which is particularly appropriate when using influenceable outcomes such as the 6MWT. On the other hand, however, this infusion constituted a continually repeated, invasive procedure that would not be performed in standard care practice and entailed risks and burdens such as infusion-related reactions (see Section I 3.1.2 on the implementation of the ACT BSC). The observed effects in the outcome category of side effects of the MOR-004 study were thus potentially underestimated.

Infusion-related reactions

In the MOR-004 study, infusion-related reactions were recorded as ‘infusion-associated reactions (IARs)’. According to the study design, any AEs that occurred after infusion onset and within 24 hours after infusion end were documented as IARs. The company did not

present any analyses on severe or serious IAR events. This operationalization was too unspecific to represent infusion-related reactions. In the given therapeutic indication and against the background of the invasive procedure of a placebo infusion with premedication in the comparator arm, an AE was documented in almost all patients within the time window of observation from the start of the infusion to 24 hours after the end of the infusion during the course of the study: 89.7% in the intervention arm versus 91.5% in the placebo arm. However, when looking at individual symptoms typical of infusion-related reactions within 24 hours of infusion, there were marked differences in the results between the treatment arms, for example for pyrexia (36.2% versus 18.6%), chills (10.3% versus 1.7%), vomiting (37.9% versus 15.3%) and nausea (27.6% versus 13.6%) (for a more comprehensive, supplementary presentation of AEs according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) that occurred within 24 hours after infusion, see Appendix D of the full dossier assessment).

The analyses of infusion-related reactions that required interruption and medical intervention also showed clear differences between the treatment arms. According to the study protocol, medical intervention was to consist of the administration of oxygen, IV antihistamines, IV steroids or IV fluids. Such an interruption with intervention was considered necessary and conducted by the investigators in 22.4% of patients in the intervention arm, compared with 0% in the comparator arm. However, this operationalization was largely based on the assessment of the investigators and therefore did not represent all patient-relevant events in the context of infusion-related symptoms.

None of the above operationalizations enabled a comprehensive assessment of infusion-related reactions. Thus, no suitable data were available for this outcome. However, the results described above suggested that elosulfase alfa potentially has disadvantages in the outcome infusion-related reactions.

Anaphylactic reactions

Anaphylactic reactions are a specific and potentially fatal infusion-related reaction that can occur during enzyme replacement therapy with elosulfase alfa. The company operationalized this outcome using the SMQ ‘broad’ anaphylactic reaction, which is based on the combination of 2 relevant but unspecific symptoms (e.g. blood pressure drop and simultaneous swelling of the lips). It was assumed that this combination of several PTs allowed the anaphylactic reaction syndrome to be recorded with sufficient specificity in this context. This operationalization was therefore used for the benefit assessment in the present research question.

Missing outcomes on symptoms

Outcomes on symptoms were only observed to a limited extent in the study. Pain, fatigue, lack of stamina, dyspnoea and joint stiffness are typical symptoms of the disease. Most of these symptoms were not recorded in the study with corresponding outcomes. It was therefore not possible to assess the effect of treatment with elosulfase alfa on the symptoms described above in the benefit assessment.

Outcomes additionally presented

In the MOR-004 study, the FEV1 was recorded as an outcome as part of the respiratory function test. The test was not used as a patient-relevant outcome for the benefit assessment, but the results are presented as supplementary information in I Appendix E of the full dossier assessment.

In the MOR-004 study, the 3MSCT, which indicates the number of stairs patients can climb within 3 minutes as steps per minute, was recorded as a secondary outcome. The company described neither the results nor the relevance and validity of this outcome in Module 4 of its dossier. The references regarding the 3MSCT cited in the study protocol described various stair climb tests as a measure of lung function in older men. The company did not provide a manual for the standardized conduct of 3MSCT in the MOR-004 study, although it referred to one in the study protocol. A conclusive assessment of the suitability of this outcome for the assessment was therefore not possible. The 3MSCT outcome was therefore not used for the benefit assessment. In addition, the 6MWT is an established and standardized outcome for recording mobility and walking ability for the present assessment. Therefore, the results for the outcome 3MSCT are only presented as a supplement (I Appendix E of the full dossier assessment). Together with the FEV1, they were considered as supporting information in the assessment of the outcome 6MWT, see Section I 3.2.3.

I 3.2.2 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: elosulfase alfa vs. placebo

Study		Outcomes										
	Study level	All-cause mortality[a]	Walking ability (6MWT)	Wheelchair use	Walking aid use	Height (z-score)[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Infusion-related reactions	Anaphylactic reactions (SMQ, AEs)	Infections and infestations (SOC, SAEs)
MOR-004	L	L	L	–[c]	–[c]	L	–[d]	L	L[e]	–[c]	L	L

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Analysis for female patients ≤ 15 years and male patients ≤ 18 years at baseline.
c. No suitable data available; see Section I 3.2.1 for reasoning.
d. Outcomes in this category were not recorded.
e. Despite the low risk of bias, limited certainty of results is assumed for the outcome 'discontinuation due to AEs'.

6MWT: 6-minute walk test; AE: adverse event; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SOC: System Organ Class

The risk of bias was assessed as low for the results of all outcomes with suitable data.

I 3.2.3 Results

Table 12 and Table 13 summarize the results from RCTs comparing elosulfase alfa with placebo in patients with mucopolysaccharidosis type IVA. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results for the outcomes 3MSCT and FEV1 are presented in I Appendix E of the full dossier assessment. Tables on common AEs and SAEs are presented in I Appendix C of the full dossier assessment.

Table 12: Results (mortality, side effects) – RCT, direct comparison: elosulfase alfa vs. placebo

Study Outcome category Outcome	elosulfase alfa		Placebo		elosulfase alfa vs. placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
MOR-004 (Week 24)					
Mortality					
All-cause mortality[c]	58	0	59	0	–
Side effects					
AEs (supplementary information)	58	56 (96.6)	59	57 (96.6)	–
SAEs	58	9 (15.5)	59	2 (3.4)	4.58 [1.03; 20.28]; 0.026
Discontinuation due to AEs	58	0	59	0	–
Infusion-related reactions				No suitable data[d]	
Anaphylactic reactions (SMQ, AEs)	58	3 (5.2)	59	1 (1.7)	3.05 [0.33; 28.49]; 0.320
Infections and infestations (SOC, SAEs)	58	5 (8.6)	59	0	11.19 [0.63; 197.8]; 0.026[e]

a. In the intervention arm: number of randomized patients, in the control arm: number of randomized patients minus 1 person for whom the diagnosis of MPS IVA was not confirmed after randomization.
b. Institute's calculation, unconditional exact test (CSZ method according to [16]).
c. The results on all-cause mortality are based on the data on fatal AEs.
d. See Section I 3.2.1 of this dossier assessment for reasoning.
e. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; MPS IVA: mucopolysaccharidosis type IVA / Morquio A; n: number of patients with (at least one) event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Table 13: Results (morbidity) – RCT, direct comparison: elosulfase alfa vs. placebo

Study Outcome category	elosulfase alfa			Placebo			elosulfase alfa vs. placebo
Outcome	N[a]	Baseline values Mean[b] [95% CI]	Change at Week 24 Mean[b] [95% CI]	N[a]	Baseline values Mean[b] [95% CI]	Change at Week 24 Mean[b] [95% CI]	MD [95% CI]; p-value[b]
MOR-004 (Week 24)							
Morbidity							
Walking ability (6MWT) [m]	58	202.3 [183.6; 221.0]	36.0 [22.9; 49.1]	59	213.4 [194.8; 232.0]	13.6 [0.6; 26.5]	22.5 [4.0; 40.9]; 0.017
Wheelchair use	No suitable data[c]						
Walking aid use	No suitable data[c]						
Height[d] (z-score)	44	−5.6 [−6.2; −5.0]	0.0 [−0.2; 0.1]	40	−5.2 [−5.8; −4.5]	−0.2 [−0.3; −0.0]	0.1 [−0.0; 0.3]; 0.115
Health-related quality of life							
No data recorded							

a. Number of patients included in the analysis with imputation of missing values, including using multiple imputation (MI). No information on the number of patients affected by each type of imputation.
b. Mean and CI per treatment group as well as effect, CI and p-value: ANCOVA (with imputation of missing values by multi-step procedure including multiple imputation) and t-test from ANCOVA. In addition to treatment arm in the model: age groups, 6MWT category and, when analysing a variable other than 6MWT, the baseline value of the respective variable as a continuous variable. The effect represents the difference in changes (from baseline) between the treatment groups at Week 24.
c. See Section I 3.2.1 for reasoning.
d. Analysis for female patients ≤ 15 years and male patients ≤ 18 years at baseline.

6MWT: 6-minute walk test; ANCOVA: analysis of covariance; CI: confidence interval; MD: mean difference; MPS IVA: mucopolysaccharidosis type IVA / Morquio A; RCT: randomized controlled trial

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (see Section I 3.1.2).

Mortality

All-cause mortality

There were no events in the outcome of all-cause mortality. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Walking ability (6-minute walk test)

A statistically significant difference between the treatment arms was shown for the outcome walking ability (6MWT). As explained below, the clinical relevance of this effect was unclear, however.

The mean improvement in walking distance between the intervention and the comparator arm was 22.5 m; the lower limit of the 95% CI was 4.0 m, which appeared too small to rate the observed effect in isolation as clinically relevant. A distribution diagram in the study documents indicated that the mean difference in the 6MWT was largely due to a group of patients who achieved a particularly large improvement (> 60 m) in walking distance (see I Appendix G of the full dossier assessment). However, it was not possible to differentiate these patients on the basis of the available data using subgroup analyses. A meaningful assessment of the clinical relevance of the effect in the 6MWT was not possible for all patients in the study on the basis of the mean difference and the CI.

Regardless of the aforementioned aspects, the improvement in walking distance was not confirmed in other outcomes on exercise capacity such as the 3MSCT and the FEV1 measurement (see I Appendix E of the full dossier assessment). Neither the 3MSCT nor the FEV1 measurement showed statistically significant differences between the treatment arms. In addition, the data from the extension study MOR-005 showed no improvement in walking distance in those patients who switched from the control arm (placebo) in MOR-004 to treatment with elosulfase alfa at the approved dose in MOR-005 (see Appendix I F of the full dossier assessment). The patients who were treated with elosulfase alfa in the intervention arm in MOR-004 and continued this treatment in the extension study MOR-005, initially blinded and then unblinded after the analysis of MOR-004, also showed no further increase in walking distance after the transition (see I Appendix F of the full dossier assessment).

Another uncertainty regarding the observed effect resulted from the fact that blinding may not have been consistently ensured, particularly in the intervention arm. For example, the proportion of infusion interruptions with intervention due to AEs of 22.4% in the intervention arm versus 0% in the comparator arm and the use of elective premedication with glucocorticoids during the course of the study of 36% (intervention arm) versus 12% (placebo arm) showed the sometimes very specific side effect profile. In a subjectively influenceable outcome such as the 6MWT, which depends on the motivation and cooperation of the subjects [3,4], knowledge of the treatment can influence the outcome.

Against the background of the aspects described, the relevance of the statistically significant effect therefore remained unclear. The effect was taken into account in the overall assessment of the added benefit.

Use of wheelchairs and walking aids

No suitable data were available for the outcomes of wheelchair use and walking aid use (see Section I 3.2.1 for reasoning). There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Height (z-score)

There was no statistically significant difference between the treatment arms for the outcome height. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

No data were recorded for the outcome of health-related quality of life. There is no hint of an added benefit of elosulfase alfa + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of elosulfase alfa compared with placebo was shown for the outcome SAEs. There is a hint of greater harm of elosulfase alfa + BSC versus BSC.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs. This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Infusion-related reactions

No suitable data were available for the outcome of infusion-related reactions (see Section I 3.2.1 for reasoning). This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Anaphylactic reactions (SMQ)

There was no statistically significant difference between the treatment arms for the outcome anaphylactic reactions. This resulted in no hint of greater or lesser harm of elosulfase alfa + BSC versus BSC; greater or lesser harm is therefore not proven.

Specific AEs

There was a statistically significant difference to the disadvantage of elosulfase alfa compared with placebo for the outcome infections and infestations (SOC, SAEs). There is a hint of greater harm of elosulfase alfa + BSC versus BSC.

I 3.2.4 Subgroups and other effect modifiers

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

- Age (5 to 11 years versus 12 to 18 years versus ≥ 19 years)
- Sex (female versus male)

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 1 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup analyses conducted by the company used the Breslow-Day test as a test for homogeneity for results on binary outcome measures. This test is suitable when using the effect measure odds ratio, but not for the effect measure relative risk (RR). Interaction tests using the Q-test based on the RR were therefore conducted in the dossier assessment, where relevant.

The dossier contained contradictory information on the testing of homogeneity between subgroups for (cardinally scaled) outcome measures assessed by mean difference. It was assumed that homogeneity was tested using an interaction term between the treatment group and the respective subgroup characteristic in an ANCOVA model.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

The probability and extent of the added benefit are determined in Chapter I 5.

I 4 Indirect, non-randomized comparison

I 4.1 Information retrieval

In addition to the direct, randomized comparison presented in Chapter I 3, the company presented a comparison of individual arms of different studies for the benefit assessment. To this end, it conducted an information retrieval relating to the therapeutic indication mucopolysaccharidosis type IVA, covering both the intervention side and the ACT. The purpose was to identify studies that may be suitable for an indirect comparison with or without a common comparator.

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

Sources used by the company in the dossier:

- Study list on mucopolysaccharidosis type IVA (status: 6 February 2025)
- Bibliographic literature search for mucopolysaccharidosis type IVA (last search on 6 February 2025)
- Search of trial registries/trial results databases for mucopolysaccharidosis type IVA (last search on 6 February 2025)
- Search on the G-BA website for mucopolysaccharidosis type IVA (last search on 21 February 2025)

I 4.2 Evidence provided by the company

I 4.2.1 Comparison of individual arms from different studies, age ≥ 5 years

The company presented a comparison of individual arms and patient groups from different studies. It conducted this comparison to draw conclusions regarding the efficacy of elosulfase alfa beyond the 24-week observation period in the RCT MOR-004.

On the intervention side, the company used individual data from patients from the elosulfase alfa arm with weekly administration from the RCT MOR-004 (see Chapter I 3) and its extension study MOR-005 [17]. To represent the ACT, the company used individual data from a selection of patients from the observational study MOR-001 [18]. An adjustment for confounders was made using propensity score matching.

Overall, the comparison presented by the company was not suitable for the derivation of an added benefit of elosulfase alfa in comparison with the ACT specified by the G-BA. This was mainly due to the following aspects:

- Exclusion of identified studies not appropriate

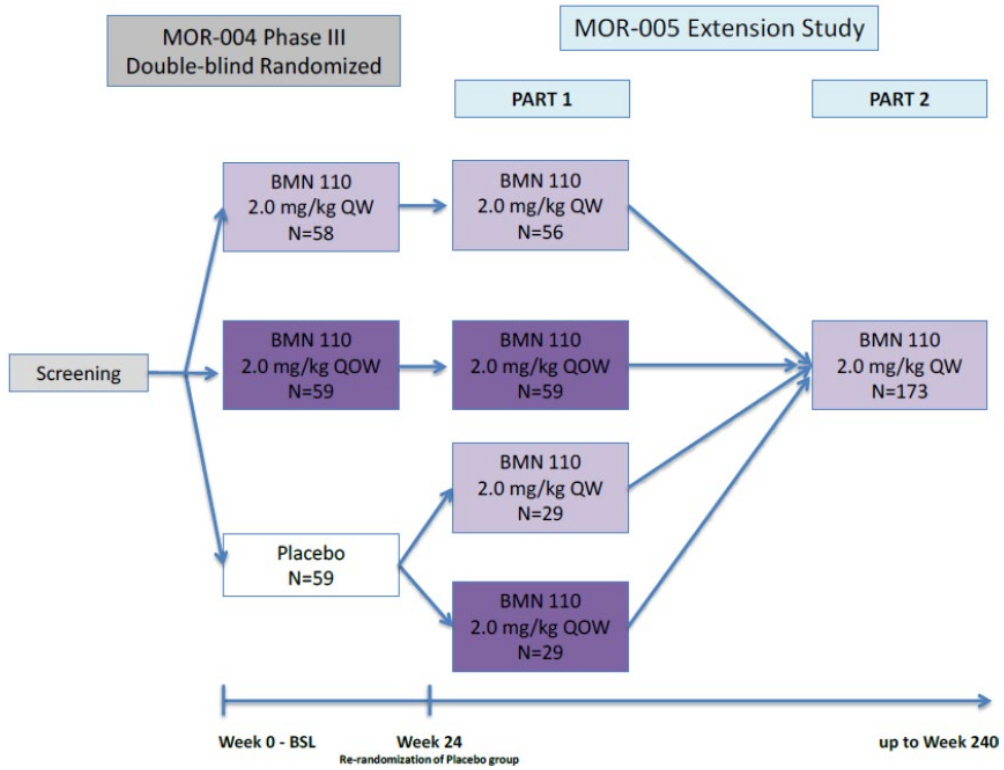
- Incompleteness of the confounders taken into account for the adjustment
- Possible selection bias due to transfer of patients from the observational study to treatment studies and due to lack of adjustment for the characteristic 'time since diagnosis'

The evidence presented by the company and the reasons for its unsuitability are described below.

Data sources provided

Data sources for the intervention elosulfase alfa: MOR-004 / MOR-005

For the intervention side of the indirect comparison, the company used data from the study MOR-004 and the associated extension study MOR-005. All patients who had completed the MOR-004 study (see Chapter I 3) were eligible to transfer to the MOR-005 study. Patients who transferred to study MOR-005 from the placebo arm of study MOR-004 were randomized in a 1:1 ratio to either elosulfase alfa administered weekly or elosulfase alfa QOW alternating with placebo. Treatment was initially continued blinded in all elosulfase alfa arms of MOR-005. Only after the analysis of efficacy data from MOR-004 was the prespecified unblinding of the study performed, and all participants continued treatment with weekly doses of elosulfase alfa. The duration of treatment and observation in MOR-005 was a maximum of 240 weeks, and outcomes on morbidity (especially the 6MWT) and side effects were recorded. The study design is shown in Figure 1; further information on the study characteristics can be found in I Appendix B of the full dossier assessment.



BMN 110: elosulfase alfa; QOW: every 2 weeks; QW: every week

Figure 1: Study scheme of MOR-004 / MOR-005

Analysis population

For the indirect comparison, the company initially only considered the 57 patients from the elosulfase alfa arm of MOR-004 with weekly administration who had completed MOR-004. Of these, 56 patients continued treatment in MOR-005. The 72-week data for walking distance in the 6MWT used for the comparison were available for 55 patients, for 52 there were data for all baseline characteristics used for matching for the adjusted comparison (see below). In the further course of the study, the company only used these 52 patients on the intervention side for the adjusted comparison. The patients who switched from the placebo arm of study MOR-004 to study MOR-005 and directly received weekly doses of elosulfase alfa (N = 29) were relevant to the intervention side of the research question, but were not used by the company for the indirect comparison, without any justification provided.

Data sources for the ACT BSC: study MOR-001

MOR-001 was initiated in 2008 as a non-interventional, observational cross-sectional study to characterize the spectrum of the condition MPS IVA. From 2011, it was amended to continue as a longitudinal study to characterize the natural course of the disease with data collection from annual visits. Following the establishment of the Morquio A Registry Study (MARS) [19], which was commissioned by the European Medicines Agency (EMA) upon marketing authorization of elosulfase alfa in 2014, the study was terminated prematurely. MOR-001

included patients with MPS IVA without any restrictions, e.g. with regard to age or disease severity. The annual visits included measurements of walking distance in the 6MWT and height. Side effects were not systematically recorded. A total of 353 patients in 11 countries were observed in the study. Further information on the study characteristics is presented in I Appendix B of the full dossier assessment. A CSR on the MOR-001 study was not available. The study protocol neither mandated nor restricted interventions apart from outcome recording and withdrawal from the study when enzyme replacement therapy was initiated. Observation took place in the respective care context of the patients. The implementation of the ACT BSC was unclear.

Analysis population

Of the 353 patients included in the study, 1-year data at the last available analysis date (8/2023) were only available for 184 patients (52%), defined post hoc as any data from visits between 270 and 609 days [mean: 446 days, i.e. approx. 64 weeks] after the baseline visit. Two-year data (from visits between 610 and 944 days [mean: 749 days, i.e. 107 weeks] after the baseline visit) were available for 78 patients (22%). For the indirect comparison, the company selected those 97 patients from the 184 patients with 1-year data who met the inclusion criteria of the MOR-004 study with regard to age (≥ 5 years) and 6MWT (30 to 325 m) at their respective baseline recording. For 77 of these 97 patients, a value for the 6MWT from the 1-year visit was also available, and for 71 patients, data were available on all 4 characteristics used in the adjustment (see below). Only these 71 patients were taken into account for the comparison with the intervention side.

Analysis time points and outcomes of the indirect comparison

In the intervention arm (MOR-005), data from the visit at Week 72 were used for the comparison; in the comparator arm (MOR-001), data were used from the visit in the 1-year time window, which took place on average on Day 447 (i.e. after approx. 64 weeks). MOR-005 collected data on morbidity outcomes (6MWT, respiratory function test, body measurements) and data on side effects; MOR-001 also collected data on morbidity outcomes (6MWT, respiratory function test, body measurements), but no outcomes in the side effects category. Among other things, the company presented a comparison for the morbidity outcomes 6MWT, FEV1, height and weight.

Assessment of the methods of the adjusted comparison

Exclusion of studies not appropriate

In addition to the studies used, the company's information retrieval identified 8 further studies that concurred with the inclusion criteria for the comparison according to the research question, which it did not take into account in the indirect comparison. These included the international patient registry MARS [19]required by the EMA as part of the marketing authorization. Between the marketing authorization of elosulfase alfa in 2014 and the 2/2023

data cut-off of the last available annual report, 419 patients with MPS IVA (355 with elosulfase alfa treatment, 64 without elosulfase alfa treatment) were included in this registry. Regular recordings of morbidity outcomes including the 6MWT were required. Furthermore, the company identified the observational programme under the Managed Access Agreement for elosulfase alfa by the National Health Service England, in which data were available for more than 50 patients in 2021 [20]. The company briefly justified the exclusion of the evidence from these studies and registries by referring to the sometimes small sample sizes, differences in the baseline characteristics or too high a proportion of missing values.

The justifications for the exclusion of the identified studies were neither sufficient nor appropriate, as the following examples show: The company justified the exclusion of the identified study MOR-008 [21] by stating that the baseline 6MWT values were not sufficiently similar to those in the MOR-001 study on the comparator side, relying exclusively on the mean values and standard deviations of the entire study population (e.g. mean baseline 6MWT in MOR-008 372 m [standard deviation 81 m] vs. 212 m [152 m] in MOR-001). Especially when using propensity score matching, which includes individual patient data, a study exclusion based solely on discrepancies in means is not adequate. Analogous to the exclusion of the MOR-008 study, the company justified the exclusion of the MARS registry on both sides of the comparison with the lack of similarity of the baseline characteristics for age and walking distance in the 6MWT. Furthermore, the company referred to a high proportion of missing data. This was also not an appropriate justification for the exclusion of the entire study. Rather, this study should have been included and the effect of the missing data should have been taken into account in the assessment of the results of the indirect comparison.

Due to the company's approach, a relevant proportion of patients who concurred with the given research question were not taken into account in the analyses. It was not possible to estimate the number of patients not included in the analyses. However, taking into account the small number of patients included in the company's indirect comparison (52 on each side), it can be assumed that this was a relevant proportion.

Incompleteness of the confounders considered by the company and selection bias

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors that are related to both the treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The first prerequisite for this is that relevant confounders are systematically identified.

For the identification of possible confounders of the non-randomized comparison without a common comparator, the company followed the process proposed by Pufulete 2022 [22] with the 3 steps:

1) Systematic literature search
2) Detailed interviews with experienced clinicians
3) Survey of treatment providers (different people than those in the expert interviews)

The company replaced the 3rd step with a new survey of the 3 experts already interviewed in step 2, who were now asked to classify the relevance of the previously identified possible confounders on a 5-point scale.

A large number (> 120) of possible confounders were identified in the systematic literature search. A few additional confounders were added based on the expert interviews. Characteristics with overlapping content were merged and organized in a list of around 40 remaining characteristics concurring with their relevance classification in the 3rd step of the approach outlined above. The company then discussed the necessity of their inclusion in the confounder adjustment only for the 12 characteristics on this list that exceeded a threshold value defined by the company in the relevance classification. As a result of this process, the company named the following 4 factors as the only confounders to be considered:

- Age at baseline
- Body height at baseline
- Walking distance in the 6MWT at baseline
- FEV1 at baseline

It is necessary and reasonable to reduce a large number of systematically identified possible confounders, but the company's approach was not appropriate. The exclusion of a potential confounder based on content considerations must be justified based on the literature, and consideration must not be guided by the available data or the possibility or impossibility of operationalizing the confounder [23]. For example, it remained unproven and implausible that the company did not take into account characteristics identified as confounders such as 'use of wheelchair/walking aids', 'skeletal abnormalities', 'concomitant therapies/medication' and 'motivation/cooperation'.

It cannot be ruled out that the selection of the few characteristics considered from the large number of identified confounders (4 of initially more than 120) was not made independently of the availability of the data. One example is the confounder 'participant's motivation/co-operation' identified in the expert interviews, but also in the guideline document for the 6MWT [3]. The relevance of this confounder was shown by the result of the 6MWT in the placebo arm of the MOR-004 study, where the walking distance improved over 24 weeks (13.6 m, 95% CI: [0.6 m; 26.5 m]) – while the disease is described as chronically progressive. This was in contrast with the deterioration found in the observational study MOR-001 in the

1-year data for the propensity score-matched population (−19.1 m, 95% CI: [−38.2 m; −0.1 m]). Simply participating in an intervention study involving weekly interventions lasting several hours appeared to have a marked effect on the change in walking distance compared with pure annual observation in a normal care context. Differences in expectation and motivation could be possible explanations for this difference. The non-consideration of the confounder motivation/co-operation was therefore not comprehensible in view of the available data.

In addition, the characteristic 'time since diagnosis to start of observation' was not identified, and hence not taken into account in the analyses, as a potentially relevant confounder that could lead to a selection bias. The median time since diagnosis in the intervention arm of the MOR-004 study was 4.8 years. Combined with the inclusion criterion of at least 30 m walking distance in the 6MWT, this means that the patients included in MOR-004 were still able to walk (> 30 m) a long time after diagnosis (median 4.8 years). Patients with rapidly progressive disease, who lose their ability to walk at an early stage, were therefore underrepresented in the MOR-004 study. Data for the time since diagnosis at study entry were not available for the MOR-001 study. However, the longer recruitment period of the MOR-001 study (> 4 years compared with approx. 1 year in MOR-004) favoured the inclusion of newly diagnosed patients shortly after diagnosis. A shorter time since diagnosis in MOR-001 is also supported by the fact that a relevant proportion of patients in the company's studies on elosulfase alfa had already been observed in the MOR-001 study (see also the next section). It was therefore possible that the MOR-004 study – in contrast to the MOR-001 study – preferentially included patients with slowly progressive disease and thus a better prognosis, without this being taken into account in the adjustment of the indirect comparison. Such a selection bias can notably impair the balance of the comparator arms.

An additional, independent cause of another possible selection bias in the present comparison was the transitioning from the observational study MOR-001 to intervention studies with elosulfase alfa. A CSR on the MOR-001 study was not available, but there were 2 publications in scientific journals [18,24]. These publications mention the transitioning of patients from MOR-001 to an intervention study of the company with elosulfase alfa as one of the main reasons for the notable decline in follow-up observations in the study as early as Year 1. At 123 out of 353 (35%), this affected a relevant proportion of patients in the MOR-001 study. The MOR-004 study is the largest of these intervention studies. The patient-specific exclusion criteria of the MOR-004 study included potentially relevant confounders such as accompanying diseases and any circumstances that could jeopardize long-term study participation, protocol adherence or patient safety. It was therefore conceivable that mainly patients with prognostically more favourable characteristics switched from the MOR-001 study to the MOR-004 study. This selection bias might have further compromised the balance of the comparator arms and was not sufficiently taken into account in the adjustment made.

In summary, the list of confounders considered by the company for the adjustment was incomplete, relevant confounders were missing. There were also possible causes of selection bias not sufficiently taken into account by the identified confounders.

Propensity score matching

From the MOR-004 / MOR-005 study, 52 patients were included for conducting the propensity score matching, for whom data on all 4 confounders used were available (see the above section *Analysis population* for the MOR-004 / MOR-005 study). Of the 77 patients from the MOR-001 study shown above, those 71 patients were included for whom baseline values were available for all 4 confounders used. From the group of these 71 patients, a partner was then identified for each of the 52 patients from MOR-004 / MOR-005 according to a nearest neighbour criterion. This left 52 matched pairs, each of which was included in the adjusted comparison with the same weight. As the earlier steps of the indirect comparison were already conducted inadequately, no further comments are made on the method of propensity score matching.

Result of the indirect comparison for the outcome walking distance (6MWT)

The difference in the development of walking distance in the 6MWT to Week 72 (in MOR-004 / MOR-005) or up to the 1-year visit (in MOR-001) was 47.5 m in the propensity score-adjusted comparison of the company (95% CI: [20.4 m; 74.6 m]) and was made up of the difference between the increase in walking distance in the elosulfase alfa arm of 28.4 m (95% CI: [9.1 m; 47.6 m]) and the decrease in walking distance in the observation arm −19.1 m (95% CI: [−38.2 m; −0.1 m]). Against the background of the uncertainties described above, the observed effect was not large enough to be explained solely by a systematic bias in the given data situation.

Summary

Overall, the indirect, non-randomized comparison presented by the company was not suitable for the benefit assessment. Firstly, the company markedly limited the study pool and thus the eligible patients on both sides of the comparison. On the other hand, sufficient structural equality of the patient groups was not guaranteed even after the propensity score matching. Relevant confounders and selection bias were not sufficiently taken into account in the adjustment. Furthermore, the observed effect was not large enough to be explained solely by a systematic bias in the given data situation. The data presented therefore did not allow for an adequate comparison of elosulfase alfa with the ACT.

I 4.2.2 Indirect, non-randomized, unadjusted indirect comparison for children < 5 years of age

In addition to the adjusted comparison for patients aged ≥ 5 years, the company also presented the single-arm phase 2 study MOR-007 [25], which investigated the safety and efficacy of elosulfase alfa in children aged < 5 years with MPS IVA.

In the study, 15 children aged between 9 months and 4.9 years were treated with elosulfase alfa at the currently approved dosage for a period of 52 weeks. The outcomes recorded included growth and side effects. In Module 4 of the dossier, the company compared results on growth from this study with data on similar outcomes for selected children under 5 years of age without treatment with elosulfase alfa who had been included in the MPS IV observational study MOR-001 prior to the marketing authorization of elosulfase alfa. This comparison was unadjusted and was only available for outcomes relating to height. Non-comparative data on outcomes in the side effects category were not available. Results from the MOR-007 study and from the comparison with MOR-001 were not used for the derivation of the added benefit, analogous to the company's approach.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, Only results from the randomized comparison (Chapter I 3) were included, as the indirect, non-randomized comparison was not suitable for the derivation of an added benefit (see Chapter I 4). The different outcome categories and effect sizes were taken into account. 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 was assessed based on the results presented in Section I 3.2 (see Table 14).

Table 14: Extent of added benefit at outcome level: elosulfase alfa + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
All-cause mortality	0 vs. 0 events	Lesser benefit not proven/added benefit not proven
Morbidity		
Walking ability (6MWT) [m]	36.0 vs. 13.6 22.5 [4.0; 40.9] p = 0.017	Statistically significant result with unclear relevance
Height (z-score)	0.0 vs. −0.2 0.1 [−0.0; 0.3] p = 0.115	Lesser benefit not proven/added benefit not proven
Wheelchair and walking aid use	No suitable data	Greater/lesser harm not proven
Health-related quality of life		
No data recorded		

Table 14: Extent of added benefit at outcome level: elosulfase alfa + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	15.5% vs. 3.4% RR: 4.58 [1.03; 20.28]; RR: 0.22 [0.05; 0.97][c] p = 0.026 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Discontinuation due to AEs	0 vs. 0 events	Greater/lesser harm not proven
Infections and infestations (SOC, SAE)	8.6% vs. 0% RR: 11.19 [0.63; 197.8]; RR: 0.09 [0.01; 1.59][c] p = 0.026 Probability: hint	Outcome category: serious/severe side effects $1 < CI_u$, $p < 0.05$ Greater harm, extent: minor[d]
Anaphylactic reactions (SMQ, AEs)	5.2% vs. 1.7% RR: 3.05 [0.33; 28.49] p = 0.320	Greater/lesser harm not proven
Infusion-related reactions	No suitable data	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discrepancy between CI and p-value. The result of the statistical test (p-value) is decisive for the derivation of the added benefit. Its extent is rated as minor.

6MWT: 6-minute walk test; AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; CI_L: lower limit of confidence interval; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; SMQ: Standardized Medical Dictionary for Regulatory Activities Query

I 5.2 Overall conclusion on added benefit

The indirect comparison presented by the company was not suitable and was not used for the assessment (see Chapter I 4). The added benefit of elosulfase alfa was therefore determined exclusively on the basis of the RCT MOR-004.

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

Table 15: Positive and negative effects from the assessment of elosulfase alfa in comparison with the ACT

Positive effects	Negative effects
–	**Serious/severe side effects** ▪ SAEs: hint of greater harm – extent: minor ▫ Specific AEs (SAEs): infections and infestations: hint of greater harm –extent: minor
For the outcome walking ability (6MWT), there was a statistically significant result in favour of elosulfase alfa with unclear clinical relevance.	
Data on the category health-related quality of life were not recorded, and no usable data were available on the outcome infusion-related reactions.	
6MWT: 6-minute walk test; AE: adverse event; SAE: serious adverse event	

Compared with the ACT, negative effects of elosulfase alfa were shown for the overall rate of SAEs and a subcategory of SAEs at SOC level. The extent of the effect was minor in each case. For the outcome 6MWT, there was a statistically significant advantage in favour of elosulfase alfa, but the clinical relevance of this effect was unclear. In the given data situation, the positive and negative effects were therefore assessed as balanced. No data were recorded for the category health-related quality of life, and no suitable data were available for the outcome infusion-related reactions.

No suitable data were available for children aged < 5 years.

In the overall assessment of the available data, there is no proof of an added benefit of elosulfase alfa versus the ACT for patients with mucopolysaccharidosis type IVA.

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

Table 16: Elosulfase alfa – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients of all ages with mucopolysaccharidosis type IVA (Morquio A Syndrome, MPS IVA)	Best supportive care[b, c]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a considerable added benefit from the joint consideration of the direct, randomized comparison and the indirect, non-randomized comparison.

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 result of the G-BA's assessment conducted in the context of the market launch in 2014 and of the reassessment in 2018. In both cases, the G-BA had determined a minor added benefit of elosulfase alfa.

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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