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Risdiplam (spinal muscular atrophy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Risdiplam (spinale Muskelatrophie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 July 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
$AUC_{0\text{-}24h,ss}$	area under the curve at steady state (within 24 hours)
BSC	best supportive care
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MFM-32	Motor Function Measure – 32 items
RCT	randomized controlled trial
RULM	Revised Upper Limb Module
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMA	spinal muscular atrophy
SMN	survival motor neuron
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 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 risdiplam. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 April 2021.

Research question

The aim of the present report is the assessment of the added benefit of risdiplam in comparison with the appropriate comparator therapy (ACT) in patients with 5q spinal muscular atrophy (SMA), 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to 4 survival motor neuron (SMN)2 copies.

SMA is a disease with a heterogeneous phenotype ranging from mild to very severe. The classic classification by type is based on age at symptom onset and clinical presentation. In addition, with the introduction of newborn screening for 5q SMA, the group of patients with pre-symptomatic diagnosis represents an increasingly important patient population. Thus, the ACT specified by the G-BA resulted in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of risdiplam

Research question	Subindication	ACT[a]
	Patients with 5q SMA, 2 months of age and older, with	
1	SMA type 1	Nusinersen
2	SMA type 2	
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b, c]
4	Pre-symptomatic patients with 5q SMA, 2 months of age and older, with	
4a	1 to 3 SMN2 gene copies	Nusinersen
4b	4 SMN2 gene copies	Treatment of physician's choice choosing from nusinersen or BSC[b, c]

a. Presentation of the ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for patients with this ACT.
c. 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. Various measures, including e.g. physiotherapy according to the catalogue of remedies (catalogue of prescribable remedies according to §92 (6) SGB V as the second part of the guideline on the prescription of remedies in contracted doctor care), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary. Furthermore, it is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. In pre-symptomatic patients 2 months of age and older with 5q SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: patients with SMA type 1
- Research question 2: patients with SMA type 2
- Research question 3: patients with SMA type 3
- Research question 4: pre-symptomatic patients

For research question 1 and research question 2, the company followed the specification of the G-BA.

For research question 3, the company deviated from the G-BA's specification and named only best supportive care (BSC) as ACT. This does not concur with the current ACT specified by the G-BA.

Although pre-symptomatic patients are covered by the approval of risdiplam, the company did not investigate research question 4 in its dossier and did not name an ACT, either. Overall, however, the company's lack of consideration of research question 4 has no consequences, as no results from clinical studies are currently available for this patient population.

For all research questions, the present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit.

Research question 1: patients with SMA type 1

Comparison of individual arms of different studies

There are no randomized controlled trials (RCTs) of direct comparison between risdiplam and the ACT nusinersen or a corresponding indirect comparison based on RCTs for patients with SMA type 1. The company therefore presented a comparison of individual arms from different studies. For patients with SMA type 1, the company included the single-arm study BP39056 (hereinafter referred to as "FIREFISH study") on the side of risdiplam, and the nusinersen arm of the RCT CS3B (hereinafter referred to as "ENDEAR study") on the comparison of nusinersen and a sham intervention on the side of nusinersen.

Based on individual arms of different studies, the company presented, on the one hand, a matching-adjusted indirect comparison (MAIC) analysis without a common comparator and, on the other hand, an unadjusted comparison in the framework of a sensitivity analysis, referred to by the company as "naive" comparison. The company did not use the "naive" comparison for the derivation of the added benefit, however.

Study FIREFISH

The FIREFISH study is a single-arm study on the treatment of SMA patients with risdiplam. The study included patients with genetic documentation of 5q SMA, ≤ 7 months of age at enrolment, symptom onset between 28 days and ≤ 3 months of age, and 2 SMN2 gene copies. The included patient population thus only includes the subpopulation with 2 SMN2 gene copies of patients with SMA type 1. In addition to oral treatment with risdiplam, the patients received supportive measures that can be regarded as sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA.

The study consists of 2 parts, of which part 1 is divided into 2 cohorts. Part 1 cohort 1 is an exploratory dose-finding study (n = 4) and is not relevant for the benefit assessment because the dosage deviated considerably from the Summary of Product Characteristics (SPC). The present assessment considers patients from part 1 cohort 2 (n = 17) and part 2 (n = 41).

Study ENDEAR

The ENDEAR study is a double-blind RCT. In the study, patients were either treated with nusinersen or received a sham intervention, each in addition to supportive measures, which correspond to a BSC. The study included patients with genetic documentation of 5q SMA, ≤ 7 months of age at study start, symptom onset at ≤ 6 months of age, as well as 2 SMN2 gene copies.

Only the nusinersen arm (N = 81) is relevant for the comparison presented by the company. Treatment with nusinersen was by intrathecal bolus injection.

Similarity of study populations partly not assessable

Although various available patient characteristics of the considered populations of the studies FIREFISH and ENDEAR, such as age at first dose, disease duration or motor function at baseline, are sufficiently comparable, a comparison of the patient populations is not possible for other characteristics due to missing data. This applies in particular to information on ventilation and respiratory symptoms. The missing data are critical against the background of the clearly different exclusion criteria regarding ventilation and respiratory symptoms. Overall, based on the exclusion criteria of the studies FIREFISH and ENDEAR, it can be assumed that the study population of the ENDEAR study had a less favourable prognosis with regard to respiratory events. This had a particular influence on the interpretation of the outcomes on ventilation in the comparison of individual arms of different studies presented by the company.

Results

Only the results of the “naive” comparison presented by the company were considered for the outcomes for which there were clear effects under the assumption of comparable operationalizations.

Individual aspects of bias for the 2 studies or the outcomes presented are not assessed, as the available data involve the use of individual arms of different studies. No more than hints can be derived on the basis of the data presented.

Mortality

Overall survival

Based on the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR, there was no statistically significant difference between the treatment arms with regard to the outcome "overall survival".

Morbidity

Death or permanent ventilation and individual component of permanent ventilation

Based on the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR, there was a clear statistically significant difference in favour of risdiplam in comparison with nusinersen for the composite outcome "death or permanent ventilation" as well as for the individual component "permanent ventilation". The consideration of the results of the composite outcome and its individual components shows that the effect was mainly caused by the outcome "permanent ventilation".

Research question 2: patients with SMA type 2

As no study of direct comparison with patients with SMA type 2 is available, the company investigated the possibility of an adjusted indirect comparison.

Based on the SUNFISH study with risdiplam, the company searched for studies with patients with SMA type 2 who were treated with nusinersen in order to check the feasibility of an indirect comparison using the common comparator BSC (or placebo). The company identified the studies CHERISH and EMBRACE using the search in trial registries. In both studies, however, the population included in each case is not comparable with the population in the SUNFISH study with risdiplam – particularly due to age – so that an adjusted indirect comparison of risdiplam against nusinersen for patients with SMA type 2 is not possible based on the identified studies.

Research question 3: patients with SMA type 3

In its dossier, the company used the randomized controlled double-blind SUNFISH study on the comparison of risdiplam with placebo. Patients in both arms additionally received supportive measures. Non-ambulatory patients with type 2 or 3 SMA aged 2 to 25 years at screening were included. The subpopulation with SMA type 3 is relevant for research question 3. These were 36 patients in the risdiplam arm and 16 patients in the placebo arm.

The SUNFISH study is not suitable for deriving conclusions on the added benefit of risdiplam in comparison with the ACT of treatment of physician's choice choosing from nusinersen or BSC, as the ACT specified by the G-BA was not implemented in the study.

The supportive drug and non-drug measures used in the study were considered to be a sufficient implementation of the ACT BSC. In the present case, however, a single-comparator study does not represent the ACT of the G-BA, as it can be assumed that nusinersen would have been an approved and thus fundamentally suitable therapy option for a relevant proportion of the patients included in the study (or the relevant subpopulation).

Nevertheless, the results of the primary analysis after 12 months of randomized treatment of the SUNFISH study for the subpopulation with SMA type 3 are presented as supplementary information. A conclusion on the added benefit based on these data is not derived, however.

Risk of bias

The risk of bias across outcomes for the SUNFISH study was rated as low. The risk of bias for the results on the following outcomes was rated as low: overall survival, health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS], gross and fine motor skills (Motor Function Measure – 32 items [MFM-32], motor function of the upper extremities (Revised Upper Limb Module [RULM]), motor functioning (Hammersmith Functional Motor Scale Expanded [HFMSE]), discontinuation due to adverse events (AEs), as well as the specific AE "skin and subcutaneous tissue disorders" (System Organ Class [SOC], AEs). Events that are symptoms of the underlying disease or events that can be both side effects and symptoms of the underlying disease were also included to a large extent in the recording of serious AEs (SAEs). Therefore, the results are not interpretable and the risk of bias was not assessed.

Results

Mortality

Overall survival

In the subpopulation with SMA type 3, no deaths occurred until month 12.

Morbidity

Gross and fine motor skills (MFM-32) and motor functioning (HFMSE)

In the subpopulation with SMA type 3, there was no statistically significant difference between the treatment groups at month 12 for the mean change of the outcome "gross and fine motor skills", measured by the MFM-32 instrument, and for motor functioning, measured by the HFMSE.

Motor function of the upper extremities (RULM)

For the mean change in the outcome "motor function of the upper extremities" measured by the RULM instrument, there was a statistically significant difference at month 12 in favour of risdiplam + BSC against placebo + BSC in the subpopulation with SMA type 3. The standardized mean difference in the form of Hedges' g was considered to assess the relevance of the results. The 95% confidence interval was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect.

Health status (EQ-5D VAS)

The VAS was only completed by patients ≥ 12 years of age. In the subpopulation with SMA type 3, there was no statistically significant difference between the treatment groups at month 12 for the mean change of the outcome "health status" measured by the EQ-5D VAS.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the SUNFISH study.

Side effects

The results on SAEs cannot be interpreted because events that are symptoms of the underlying disease or events that can be both side effects and symptoms of the underlying disease were also included in the recording of SAEs.

Discontinuation due to AEs

In the subpopulation with SMA type 3, no discontinuations due to AEs occurred until month 12.

Skin and subcutaneous tissue disorders (SOC, AEs)

For the specific AE "skin and subcutaneous tissue disorders" (SOC, AEs), there was a statistically significant difference at month 12 to the disadvantage of risdiplam + BSC against placebo + BSC in the subpopulation with SMA type 3.

Research question 4: pre-symptomatic patients

The company did not consider the research question of pre-symptomatic SMA patients with one to 4 SMN2 gene copies in its dossier.

As there are currently no results for pre-symptomatic patients from a clinical study, the company's lack of consideration of this research question 4 has no consequences for the benefit assessment.

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

Based on the results presented, probability and extent of the added benefit of the drug risdiplam in comparison with the ACT are assessed as follows:

[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].

Research question 1: patients with SMA type 1

Based on the "naive" comparison of individual arms of different studies comparing risdiplam and nusinersen presented by the company, a clear statistically significant effect in favour of risdiplam was shown for the outcome "death or permanent ventilation" as well as for the individual component "permanent ventilation". The effect is mainly caused by the events of permanent ventilation. In the present situation, using individual arms of different studies, it cannot be ruled out with certainty that these effects were solely due to a systematic bias caused by confounding variables. This is due in particular to the fact that the exclusion criteria of the FIREFISH study with regard to ventilation at baseline and the medical history of respiratory symptoms (e.g. pneumonia) excluded patients with unfavourable prognosis more comprehensively than the exclusion criteria of the ENDEAR study. Thus, it can be assumed that the study population of the ENDEAR study had a less favourable prognosis with regard to respiratory events. The present patient characteristics cannot eliminate this uncertainty.

The data presented are difficult to interpret for the reasons described. However, the observed differences for the time to permanent ventilation or the composite outcome of time to death or time to permanent ventilation suggest that risdiplam is at least not inferior to nusinersen.

In addition, in the present situation, the oral administration of risdiplam is considered to have a noticeable advantage for the patient compared with the intrathecal administration of nusinersen. Risdiplam is given orally every day, whereas nusinersen must be administered intrathecally at regular intervals several times a year. The advantage of oral administration of risdiplam is thus justified by the high probability of morbidity associated with intrathecal administration of nusinersen.

In the overall picture, therefore, taking particular account of the severity of the disease and the present data constellation, there is a hint of a non-quantifiable added benefit of risdiplam compared with nusinersen for patients with SMA type 1.

Research question 2: patients with SMA type 2

As the company did not provide any relevant data for the assessment of the added benefit of risdiplam in comparison with the ACT in patients with SMA type 2, an added benefit of risdiplam for these patients is not proven.

Research question 3: patients with SMA type 3

As the company did not provide any relevant data for the assessment of the added benefit of risdiplam in comparison with the ACT in patients with SMA type 3, an added benefit of risdiplam for these patients is not proven.

Research question 4: pre-symptomatic patients

As the company did not provide any data for the assessment of the added benefit of risdiplam in comparison with the ACT in patients with pre-symptomatic SMA, an added benefit of risdiplam for these patients is not proven.

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

Table 3: Risdiplam – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
	Patients with 5q SMA, 2 months of age and older, with		
1	SMA type 1	Nusinersen	Hint of non-quantifiable added benefit[b]
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA, 2 months of age and older, with		
4a	1 to 3 SMN2 gene copies	Nusinersen	Added benefit not proven
4b	4 SMN2 gene copies	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. The results of the comparison presented using individual arms of different studies suggest that risdiplam is at least not inferior to nusinersen. The added benefit of risdiplam in the present situation results from its oral form of administration and a high probability of morbidity associated with intrathecal administration of nusinersen. Only data on patients with 2 SMN2 gene copies are available.
c. According to the G-BA's note, a single-comparator study is generally not sufficient for patients with this ACT.
d. 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. Various measures, including e.g. physiotherapy according to the catalogue of remedies (catalogue of prescribable remedies according to §92 (6) SGB V as the second part of the guideline on the prescription of remedies in contracted doctor care), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary. Furthermore, it is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. In pre-symptomatic patients 2 months of age and older with 5q SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of risdiplam in comparison with the ACT in patients with 5q SMA, 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to 4 SMN2 copies.

SMA is a disease with a heterogeneous phenotype ranging from mild to very severe. The classic classification by type is based on age at symptom onset and clinical presentation [3-5]. In addition, with the introduction of newborn screening for 5q SMA, the group of patients with pre-symptomatic diagnosis represents an increasingly important patient population [6-9]. Thus, the ACT specified by the G-BA resulted in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of risdiplam

Research question	Subindication	ACT[a]
	Patients with 5q SMA, 2 months of age and older, with	
1	SMA type 1	Nusinersen
2	SMA type 2	
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b, c]
4	Pre-symptomatic patients with 5q SMA, 2 months of age and older, with	
4a	1 to 3 SMN2 gene copies	Nusinersen
4b	4 SMN2 gene copies	Treatment of physician's choice choosing from nusinersen or BSC[b, c]

a. Presentation of the ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for patients with this ACT.
c. 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. Various measures, including e.g. physiotherapy according to the catalogue of remedies (catalogue of prescribable remedies according to §92 (6) SGB V as the second part of the guideline on the prescription of remedies in contracted doctor care [10]), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary. Furthermore, it is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. In pre-symptomatic patients 2 months of age and older with 5q SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: patients with SMA type 1
- Research question 2: patients with SMA type 2
- Research question 3: patients with SMA type 3
- Research question 4: pre-symptomatic patients

For research question 1 and research question 2, the company followed the specification of the G-BA.

For research question 3, the company deviated from the G-BA's specification and named only BSC as ACT. This does not concur with the current ACT specified by the G-BA. This was updated on 27 April 2021 and includes treatment of physician's choice choosing from nusinersen or BSC [11].

Although pre-symptomatic patients are covered by the approval of risdiplam, the company did not investigate research question 4 in its dossier and did not name an ACT, either. The ACT for this research question was specified shortly before the start of the dossier assessment (on 27 April 2021 [11]). Overall, however, the company's lack of consideration of research

question 4 has no consequences, as no results from clinical studies are currently available for this patient population (see Section 2.6).

For all research questions, the present benefit assessment was conducted in comparison with the ACT specified by the G-BA [11].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit. This deviates from the company, which did not define a minimum study duration.

2.3 Research question 1: patients with SMA type 1

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risdiplam (status: 15 February 2021)
- bibliographical literature search on risdiplam (last search on 15 February 2021)
- search in trial registries/trial results databases for studies on risdiplam (last search on 26 February 2021)
- search on the G-BA website for risdiplam (last search on 26 February 2021)
- bibliographical literature search on the ACT (last search on 15 February 2021)
- search in trial registries/trial results databases for the ACT (last search on 26 February 2021)
- search on the G-BA website for the ACT (last search on 26 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on risdiplam (last search on 4 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 12 May 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no relevant RCTs enabling a direct comparison or an adjusted indirect comparison with the ACT via a common comparator were identified from the check of the study pool. The company therefore presented a comparison of individual arms from different studies. For patients with SMA type 1, the company included the single-arm study BP39056 (hereinafter referred to as “FIREFISH study”) on the side of risdiplam, and the RCT CS3B (hereinafter referred to as “ENDEAR study”) on the comparison of nusinersen and a sham intervention on the side of nusinersen. The ENDEAR study is already known from the

benefit assessment of nusinersen [12]. The extension study ISIS 396443-CS11 (hereinafter referred to as "SHINE study") [13,14] to the ENDEAR study (SHINE-ENDEAR) was not considered by the company in its assessment (see below).

Studies in patients with SMA type 1 not considered

In addition to the studies FIREFISH and ENDEAR, for patients with SMA type 1, the company's search also identified the RCT 232SM202 (hereinafter referred to as "EMBRACE study") [15,16] comparing nusinersen with a sham intervention, and the single-arm study CS3A [17-19] for nusinersen, and the single-arm study BP39054 (hereinafter referred to as "JEWELFISH study") [20-22] for risdiplam. However, the company did not consider these studies when comparing individual arms of different studies. The approach of the company is appropriate and is justified below.

Study EMBRACE

The company excluded the EMBRACE study (for a detailed description of the study, see the benefit assessment of nusinersen [12]) on the nusinersen side because the population did not match the population of the FIREFISH study. The FIREFISH study included patients with 2 SMN2 gene copies, ≤ 7 months of age at enrolment, and symptom onset at ≤ 3 months of age (see Section 2.3.2). The EMBRACE study investigated patients with 2 or 3 SMN2 gene copies. Patients with 2 SMN2 gene copies had to be either > 7 months of age at study start if they were ≤ 6 months of age at symptom onset, or > 6 months of age at symptom onset. Thus, the subpopulation of the EMBRACE study with 2 SMN2 gene copies is not comparable to the population of the FIREFISH study due to the older age at study start or symptom onset. The exclusion of the study for the comparison of individual arms is appropriate.

Study CS3A

The reason given by the company for the exclusion of the CS3A study on the nusinersen side was that the dosing regimen did not comply with that in the SPC of nusinersen [23]. The study included 21 patients ≤ 7 months of age at study start and an age at symptom onset between 3 weeks and 6 months. 20 patients were treated with nusinersen. The study population thus represents patients with SMA type 1. All patients received 3 loading doses on days 1, 15 and 85, followed by one maintenance dose on day 253 (i.e. 5.5 months after the last dose) and then subsequent maintenance doses at 4-month intervals. According to the SPC, however, 4 loading doses should be given on days 0, 14, 28 and 63, followed by maintenance doses at 4-month intervals. Due to the dosing regimen at the beginning of treatment, which deviated from the SPC, it is comprehensible that the study was not considered for the comparison of individual arms. Beyond the argumentation of the company regarding the deviation of the dosing regimen from the SPC, in 4 patients, the loading dose administered also deviated from the SPC (6 mg instead of 12 mg). Overall, however, the deviation from the SPC was not so serious that a consideration of the CS3A study would not have been comprehensible in the present situation.

Study JEWELFISH

The JEWELFISH study is a single-arm study of risdiplam that included patients with SMA type 1, 2 or 3 who had been previously treated with a splicing modifier, nusinersen, olesoxime or onasemnogene abeparvovec. The company excluded the JEWELFISH study for the comparison of individual arms, as this study included only pretreated patients, whereas the ENDEAR study on the comparator side included only treatment-naive patients. The exclusion of the study is appropriate.

The results on harm outcomes presented as supplementary information by the company in the dossier were not taken into account, as no comparative data for this pretreated patient population were available.

Study SHINE

The SHINE study is an open-label, long-term study with patients who had previously participated in a nusinersen study (ENDEAR, CS3A, CHERISH, CS12 or EMBRACE). All included patients were treated with nusinersen. The patients were assigned to one of 5 groups depending on which study they had previously participated in. Only the group of the SHINE study in which patients from the ENDEAR study were included (SHINE-ENDEAR) is relevant for the present research question 1, as this part of the study provides long-term data of the patients treated with nusinersen in the ENDEAR study. The long-term data of the SHINE-ENDEAR study were published as part of the benefit assessment procedure for nusinersen (dossier Module 4 A.4) on 1 March 2021 [24]. Thus, long-term data on nusinersen have been published but were not considered in the present dossier. However, the last search conducted by the company in the present procedure on risdiplam took place on 15 February 2021 and thus before publication of the dossier on nusinersen from 2020. For its benefit assessment, the company used the dossier of the first assessment of nusinersen from 2017 [25], in which no results were available for the SHINE study. In accordance with the legal requirements, the last search conducted by the company did not take place more than 3 months before the relevant time point for the submission of the dossier, so the lack of consideration remains without consequence.

2.3.2 Comparison of individual arms of different studies

Table 5 shows the study pool of the comparison of individual arms of different studies presented by the company.

Table 5: Study pool of the company – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study with risdiplam						
BP39056 (FIREFISH[d])	Yes	Yes	No	Yes [26]	Yes [27,28]	Yes [29,30]
Study with nusinersen						
CS3B (ENDEAR[d])	No	No	Yes	No	Yes [31,32]	Yes [12,24,33,34]

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

CSR: clinical study report; G-BA: Federal Joint Committee; SMA: spinal muscular atrophy

The company presented a comparison of individual arms from the FIREFISH study with risdiplam, and the nusinersen arm of the ENDEAR study for research question 1.

Based on individual arms of different studies, the company presented, on the one hand, a MAIC analysis without a common comparator and, on the other hand, an unadjusted comparison in the framework of a sensitivity analysis, referred to by the company as “naive” comparison. The company did not use the “naive” comparison for the derivation of the added benefit, however.

The MAIC analysis presented by the company without a common comparator is generally not an adequate option for confounder adjustment [1]. Furthermore, in the case of non-randomized comparisons without a common comparator, as a rule only those approaches that, in contrast to the MAIC analysis, use individual patient data are meaningful for the confounder adjustment [35]. The MAIC analysis takes confounding into account on the basis of aggregate data. Regardless of this, the company did not provide sufficient justification for the selection of variables in its MAIC analysis, so that selective reporting cannot be ruled out.

In the present data situation, the “naive” comparison is considered. The results using the MAIC method are presented as supplementary information in Appendix B.1 of the full dossier assessment.

Table 6 and Table 7 describe the studies FIREFISH and ENDEAR.

Table 6: Characteristics of the studies FIREFISH and ENDEAR – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with risdiplam						
FIREFISH	Open-label, single-arm (part 1: dose finding, part 2: efficacy and tolerability)[b]	Patients with genetic documentation of 5q SMA and ▪ onset of clinical signs or symptoms between 28 days and ≤ 3 months of age[c] ▪ between 1 month (28 days) and ≤ 7 months (210 days) of age at enrolment ▪ 2 SMN2 gene copies	Part 1: ▪ risdiplam + BSC (N = 21) ▫ cohort 1 (N = 4)[d] ▫ cohort 2 (N = 17) Part 2: ▪ risdiplam + BSC (N = 41) Population used for the comparison of individual arms of different studies: part 1 cohort 2 + part 2 (n = 58)	Screening: 30 days Treatment: 24 months, followed by an open-label extension phase of 3 years maximum[e] Follow-up: 30 days	Part 1: 7 centres in: Belgium, France, Italy, Switzerland and USA 12/2016–ongoing[f] Data cut-offs (planned analyses): ▪ 27 February 2019 (1 year[g]) ▪ 14 November 2019 (safety) ▪ 3 March 2020 (2 years[g]) Part 2: 14 centres in: Brazil, China, Croatia, France, Italy, Japan, Poland, Russia, Turkey, Ukraine and USA 3/2018–ongoing[f] Data cut-offs (planned interim analyses): ▪ 14 November 2019 (1 year[g]) ▪ 12 November 2020 (2 years[g])	Part 1: safety, pharmacokinetics and pharmacodynamics and dose-finding for part 2 of the study Part 2[h]: Primary: BSID-III responders after 12 months (“sitting without support”) Secondary: overall survival, morbidity, AEs

Table 6: Characteristics of the studies FIREFISH and ENDEAR – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with nusinersen						
ENDEAR	RCT, double-blind, parallel	Patients with genetic documentation of 5q SMA and: ▪ age ≤ 7 months (210 days) at study start ▪ symptom onset at age ≤ 6 months[i] ▪ 2 SMN2 gene copies	Nusinersen + BSC (N = 81[j]) Sham intervention + BSC (N = 41)[k]	Start of study: ≤ 21 days Treatment: planned for 10 months (until day 302)[l] Follow-up: planned for 3 months (until day 394)[l, m, n]	31 centres in Australia, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, UK, USA Planned: 7/2014–7/2017[l] Interim analysis: 15 Jun 2016 Final data cut-off: 16 Dec 2016	Primary: ▪ proportion of HINE Section 2 responders ▪ time to death or permanent ventilation Secondary: overall survival, morbidity, AEs

Table 6: Characteristics of the studies FIREFISH and ENDEAR – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on relevant available outcomes from the information provided by the company in Module 4 A of the dossier.
b. This is a 2-part study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam. The study consists of an exploratory dose-finding part with increasing dosage (part 1) and a confirmatory part (part 2), which starts after selection of the dose in part 1. Patients from part 1 did not cross over into part 2 of the study.
c. Signs or symptoms (i.e. hypotension, absent deep tendon reflexes and/or tongue fasciculation) with onset after the age of 28 days, but prior to the age of ≤ 3 months, and inability to sit independently at the time of screening.
d. Cohort 1 is not relevant for the assessment and is no longer presented in the following tables.
e. After completion of the 3-year open-label extension phase, patients could continue treatment until the end of the study (until commercial availability of risdiplam in the respective member country).
f. Planned end of study 11/2023.
g. After inclusion of the last patient.
h. The listed outcomes or outcome categories were also recorded in part 1 of the study.
i. Patients with clinical signs or symptoms of SMA present at birth or within the first week after birth were excluded.
j. One patient did not receive study medication due to withdrawal of informed consent.
k. The arm is not relevant for the assessment and is no longer presented in the following tables.
l. The study was terminated early due to the proof of efficacy achieved in the prespecified interim analysis. This resulted in a patient-specific treatment duration and observation period. The median observation period is 280 days for the nusinersen arm and 187 days for the sham intervention arm.
m. Follow-up observation started after the last dose of nusinersen or the sham intervention on day 302 or the early termination of the study.
n. After the last study visit or in case of early termination of the study based on the data of the planned interim analysis, patients could participate in the open-label long-term SHINE study.

AE: adverse event; BSC: best supportive care; BSID-III: Bayley Scales of Infant and Toddler Development-Third Edition; HINE: Hammersmith Infant Neurological Examination; n: relevant subpopulation; N: number of randomized or included patients; RCT: randomized controlled trial; SMA: spinal muscular atrophy; SMN: survival motor neuron

Table 7: Characteristics of the interventions – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

<table>
<tr><th>Study</th><th>Intervention/comparator therapy</th></tr>
<tr><td colspan="2">Study with risdiplam</td></tr>
<tr><td>FIREFISH</td><td>Risdiplam, once/day orally[a] + BSC

<u>Part 1 cohort 1</u> (exploratory dose finding with increasing dosage):
▪ target $AUC_{0\text{-}24h,ss}$ 700 ng*h/mL: starting with 0.00106 mg/kg
<u>Part 1 cohort 2, part 2:</u>
▪ starting dose based on part 1 cohort 1 with target $AUC_{0\text{-}24h,ss}$ 2000 ng*h/mL[b]:
▫ infants > 1 month and < 3 months of age at enrolment: 0.04 mg/kg
▫ infants ≥ 3 months and < 5 months of age at enrolment: 0.08 mg/kg
▫ infants ≥ 5 months of age at enrolment: 0.2 mg/kg</td></tr>
<tr><td></td><td>Dose adjustments under consideration of the target exposure of $AUC_{0\text{-}24h,ss}$ 700 ng*h/mL or $AUC_{0\text{-}24h,ss}$ ≤ 2000 ng*h/mL were allowed.</td></tr>
<tr><td></td><td>Pretreatment[c]
▪ Supportive measures:
▫ medical care meets, in the opinion of the investigator, local accepted standard of care
▫ adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the investigator
Permitted concomitant treatment
▪ any medication, e.g. vaccines, prescription and over-the-counter drugs[d], herbal remedies, dietary supplements and any non-drug interventions (e.g. individual psychotherapy, cognitive behavioural therapy, physiotherapy and rehabilitative therapy), used by a patient within 30 days of screening until the follow-up visit
▪ physiotherapy, occupational therapy and other forms of exercise therapy were encouraged but the frequency had to remain the same during the study
▪ for any treatment of chronic diseases, patients had to be on stable regimen for 6 weeks prior to screening and remain on stable regimen throughout the study
Prohibited prior and concomitant treatment
▪ concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier (e.g. nusinersen) or gene therapy and any history of cell therapy
▪ treatment with oral beta2-adrenergic agonist (e.g. salbutamol) initiated within 6 weeks prior to enrolment
▪ during the study and within at least 90 days prior to randomization: use of medications for the treatment of SMA, e.g. growth hormones, anabolic steroids, creatine, riluzole, carnitine, sodium phenylbutyrate, valproic acid, hydroxyurea, and other agents anticipated to increase muscle strength, or medications with potential retinal toxicity [amiodarone, phenothiazines and chronic use of minocycline])</td></tr>
<tr><td colspan="2">Study with nusinersen</td></tr>
<tr><td>ENDEAR</td><td>Nusinersen, age-adjusted dose (according to schedule below) as intrathecal bolus injection on study days 1, 15, 29 and 64, 183 and 302
+
BSC</td></tr>
<tr><td></td><td>Age-adjusted dosing regimen:
<table>
<tr><th>Age (months)</th><th>Estimated CSF volume (mL)</th><th>Injection volume (mL)</th><th>Dose (mg)</th></tr>
<tr><td>0–3</td><td>120</td><td>4.0</td><td>9.6</td></tr>
<tr><td>3–6</td><td>130</td><td>4.3</td><td>10.3</td></tr>
</table></td></tr>
</table>

Table 7: Characteristics of the interventions – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study	Intervention/comparator therapy

6–12	135	4.5	10.8
12–24	140	4.7	11.3
> 24	150	5.0	12.0

Dose adjustments were not allowed.

Dosing delay by up to 8 weeks allowed

Pretreatment[c]

- Supportive measures:
  - medical care meets international standards of care regarding respiratory and gastrointestinal measures in the opinion of the investigator
  - adequate nutrition and hydration (with or without gastrostomy) in the opinion of the investigator
  - appropriate medical care, e.g. routine immunizations (including influenza, pneumococcal and pneumovirus prophylaxis, if available)

Permitted concomitant treatment

- drug or non-drug therapy at the investigator's discretion to treat side effects and ensure adequate supportive care

Prohibited prior and concomitant treatment

- investigational drugs not approved for the treatment of SMA (e.g. oral salbutamol/salmeterol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agents, or medical devices within 30 days before enrolment
- any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation

a. Patients unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ received the study medication via the tube.
b. The dose was increased to 0.2 mg/kg for all patients during the course of the study. For further information on dose increase, see running text.
c. These are respective inclusion criteria of the FIREFISH study and the ENDEAR study.
d. The study protocol lists the following drugs, among others, as permitted:
- inhaled corticosteroids
- other systemic inhaled drugs for the treatment of an obstructive airways disease (e.g. anticholinergics or anti-allergic agents, leukotriene receptor antagonists)
- laxatives and other drugs for the treatment of functional gastrointestinal disorders
- occasional use of analgesics, including opioids (e.g. codeine)
- any antibiotic treatment
- antihistamines
- proton pump inhibitors
- vaccines

$AUC_{0\text{-}24h,ss}$: area under the curve at steady state (within 24 hours); BSC: best supportive care; CSF: cerebrospinal fluid; SMA: spinal muscular atrophy; SMN: survival motor neuron;

Study FIREFISH

The FIREFISH study is a single-arm study on the treatment of SMA patients with risdiplam. The study included patients with genetic documentation of 5q SMA, ≤ 7 months of age at enrolment, as well as symptom onset between 28 days and ≤ 3 months of age. According to the inclusion criteria, participation in the study was restricted to patients with 2 SMN2 gene copies.

The included patient population thus only includes the subpopulation with 2 SMN2 gene copies of patients with SMA type 1.

In addition to the oral treatment with risdiplam, the patients received supportive measures (see below).

The study consists of 2 parts, of which part 1 is divided into 2 cohorts. Part 1 cohort 1 is an exploratory dose-finding study (n = 4). The patients from part 1 cohort 1 are not relevant for the benefit assessment (see below). Part 1 cohort 2 included 17 patients and part 2 included 41 patients.

The primary outcome of the study was the proportion of patients who were able to sit without support after 12 months of treatment. Other patient-relevant outcomes were overall survival, other morbidity outcomes and AEs.

The study design included a planned treatment duration of 24 months, followed by an open-label extension phase of a maximum of 3 years.

Treatment with the study medication

In line with the approach of the company, the exploratory dose-finding study (part 1 cohort 1 of the FIREFISH study) is not considered further in the present benefit assessment, as the patients received a dosage starting at 0.00106 mg/kg, which is well below the recommendations of the SPC [36], with the dosage then increasing to a low target area under the curve at steady state ($AUC_{0\text{-}24h,ss}$) of 700 ng*h/mL. 17 patients in part 1 cohort 2, and 41 patients in part 2 were treated with a target $AUC_{0\text{-}24h,ss}$ of 2000 ng*h/mL. These patients started with the following oral dose of risdiplam according to their age at baseline:

- infants > 1 month and < 3 months of age: 0.04 mg/kg
- infants ≥ 3 months and < 5 months of age: 0.08 mg/kg
- infants ≥ 5 months of age: 0.2 mg/kg

Dose levels were adjusted based on individual data on pharmacokinetics according to the target AUC.

The majority (57%) of patients from part 1 cohort 2 (n = 11) and part 2 of the study (n = 22) were already > 5 months of age at baseline and thus already received a starting dose of 0.2 mg/kg risdiplam daily according to the study protocol. For patients < 2 years of age, this corresponds to the recommendations of the SPC [36]. The dose of the remaining patients was increased to 0.2 mg/kg during the course of the study. The majority of patients received the dose increase within the first months after the start of the study [29]. The deviation from the SPC in the patients from part 1 cohort 2 and part 2 of the study has no overall influence on the present assessment and is not considered further.

Supportive measures

According to the G-BA's note on the ACT, BSC in the context of an RCT is necessary both in the control group and in the intervention group. (for the definition of BSC, see Section 2.5.1.2). This means that even in a single-arm study, it is assumed that patients receive additional supportive measures in the sense of a BSC when active therapy is administered.

According to the inclusion criteria in the FIREFISH study, medical care of the patients had to meet, in the opinion of the investigator, local accepted standards. At the time of screening, patients had to receive adequate nutrition and hydration (with or without gastrostomy) in the opinion of the investigator. Baseline data are available on patients with ventilatory support and feeding tubes (see Table 8). The study protocol explicitly mentioned drugs that are generally recommended as suitable supportive therapies in the therapeutic indication [37], such as inhaled drugs like anticholinergics, antibiotic treatments and laxatives. Furthermore, the study did not explicitly exclude any drugs that could call into question the implementation of a BSC. Physiotherapy, occupational therapy and other forms of exercise therapy were encouraged but according to the study protocol, the frequency had to remain the same during the study. To what extent the requirement of the study protocol of not changing the frequency of physiotherapeutic measures during the study was actually implemented in the study, and whether this limited optimal patient-specific care, cannot be inferred from the available documents. Information on physiotherapeutic measures at baseline is not available.

In summary, the concomitant drug and non-drug measures used in the study are considered a sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA [37,38].

The company did not comment on supportive measures in the dossier and therefore did not comment on whether the supportive measures in the FIREFISH study corresponded to a BSC.

Study ENDEAR

The ENDEAR study is a double-blind RCT. Patients in the study were either treated with nusinersen or received a sham intervention, each in addition to supportive measures, which correspond to a BSC (for a detailed description, see benefit assessment of nusinersen [12]). The study included patients with genetic documentation of 5q SMA and ≤ 7 months of age at study start as well as symptom onset at ≤ 6 months of age. According to the inclusion criteria, participation in the study was restricted to patients with 2 SMN2 gene copies. The included patient population thus only includes the subpopulation with 2 SMN2 gene copies of patients with SMA type 1.

A total of 122 patients were randomly allocated in a 2:1 ratio to treatment either with nusinersen (N = 81) or with a sham intervention (N = 41). Only the nusinersen arm is relevant for the comparison presented by the company. The BSC arm is therefore not considered further. Co-primary outcomes of the study were the composite outcome of time to death or permanent ventilation and the proportion of patients who achieved motor milestones assessed using

Hammersmith Infant Neurological Examination (HINE) Section 2. Other patient-relevant outcomes were overall survival, other morbidity outcomes and AEs.

Treatment with nusinersen was given as an intrathecal bolus injection on study days 1, 15, 29, 64 (loading) and 183 and 302 (maintenance). In deviation from the recommendations in the SPC [23], dosing was age-adjusted in accordance with the regimen described in Table 7. The deviation from the SPC had no overall influence on the present assessment and is not considered further (for information on the deviating dosage, see benefit assessment of nusinersen [12]).

The study design included a planned study duration of approximately 14 months in total. The study was terminated early due to the proof of efficacy of nusinersen based on positive effects for the outcome "motor milestone achievement". The median observation period at the final data cut-off on 16 December 2016 was 280 days in the nusinersen arm. After the last study visit, patients had the opportunity to participate in the open-label long-term SHINE study (see Section 2.3.1).

Study populations of the comparison presented

For the comparison of individual arms of different studies, the company used the pooled population from part 1 cohort 2 and part 2 of the FIREFISH study (n = 58) on the risdiplam side, and the data from the nusinersen arm of the ENDEAR study (n = 80) on the nusinersen side. The approach of the company to conduct a joint analysis of the patients from part 1 cohort 2 and part 2 of the FIREFISH study is comprehensible (see above).

Similarity of study populations partly not assessable

The studies used by the company correspond to the research question. To assess the similarity of the study populations of the studies FIREFISH and ENDEAR, the characteristics of the included patients were compared. Where necessary, the inclusion and exclusion criteria of the studies were additionally used.

Table 8 shows the available patient characteristics of the patient populations of the studies FIREFISH and ENDEAR included by the company for the comparison of individual arms.

Table 8: Characteristics of the study populations – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study / **Characteristic** / **Category**	**FIREFISH (part 1 cohort 2 + part 2)**	**ENDEAR**
	Risdiplam	**Nusinersen**
	N[a] = 58	**N[a] = 80**
Age at screening [weeks], mean (SD)	20.0[b] (ND)	21.0 (6.7)[b]
Age at first dose [weeks], mean (SD)	23.2[b] (ND)	23.3 (7.1)[b]
Age at symptom onset [weeks], mean (SD)	7.2 (3.0)[b]	7.9 (4.0)
Age at SMA diagnosis [weeks], mean (SD)	12.7 (6.0[b])	12.6 (6.6)
Disease duration: time from symptom onset to screening [weeks], mean (SD)	13.0[b] (ND)	13.2 (5.4)
Disease duration: time from symptom onset to first dose [weeks], mean (SD)	16.1 (5.8)[b]	15.4[c] (ND)
Sex [F/M], %	57/43	54/46
Geographical region, n (%)		
North America	4[d] (7)	38 (48)
Europe	38[d] (66)	30 (38)
Rest of the world[e]	16[d] (28)	12 (15)
Patients with impairment, n (%)		
Hypotension	ND	80 (100)
Delayed motor development	ND	71 (89)
Paradoxical breathing	ND	71 (89)
Pneumonia or respiratory symptoms	ND	28 (35)
Weakness of the extremities	ND	79 (99)
Swallowing/feeding difficulties	ND	41 (51)
Other	ND	20 (25)
Swallowing ability, n (%)	55 (95)	ND
Nutrition, n (%)		
Oral	39 (67)	ND
Via feeding tube	4 (7)	7 (9)
Combination of oral nutrition and tube	2 (3)	ND
Missing	13 (22)	ND
CHOP INTEND (total score), mean (SD)	22.5 (6.8)	26.6 (8.1)
HINE Section 2 (total score), mean (SD)	0.9 (1.0)	1.3 (1.1)
Patients with ventilatory support (excluded according to exclusion criteria: awake non-invasive ventilation, invasive ventilation and tracheostomy), n (%)	17[d] (29)	-
Patients with ventilatory support, n (%)	-	21 (26)
Type of ventilatory support, n (%)		
BiPAP < 16 hours per day	13 (22)	ND
BiPAP support ≥ 16 hours per day	0 (0)	ND
BiPAP support ≥ 16 hours per day for > 21 consecutive days	0 (0)	ND
Cough assistance – daily	5 (9)[d]	ND

Table 8: Characteristics of the study populations – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1) (multipage table)

Study Characteristic Category	FIREFISH (part 1 cohort 2 + part 2) Risdiplam N[a] = 58	ENDEAR Nusinersen N[a] = 80
Intubation for > 21 consecutive days	0 (0)	ND
Tracheostomy, n (%)	1 (2)	ND
Any prophylactic ventilation, n (%)	15 (26)	ND
Supportive ventilation during the day	0 (0)	ND
Supportive ventilation at night	13 (22)	ND
Midday nap with supportive ventilation	2 (3)	ND
> 16 hours of supportive ventilation	0 (0)	ND
Clearing the airways with cough assistants	3 (5)	ND
Physiotherapy, n (%)	ND	ND
Treatment discontinuation, n (%)	6 (10[d])[f, g]	47 (59)[h]
Study discontinuation, n (%)	5 (9)[i]	15 (19)[j]

a. Number of randomized or included patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation from data in days or months.
c. Institute's calculation from age at symptom onset and age at first dose.
d. Institute's calculation.
e. Specified in the ENDEAR study by Asia-Pacific region.
f. Treatment discontinuation at month 12 affected 4 (6.9%) patients.
g. Related to the following data cut-offs: part 1 cohort 2: 3 March 2020; part 2: 12 November 2020. At these data cut-offs, all patients had been observed for at least 24 months.
h. The study was terminated early due to the premature proof of efficacy of nusinersen. Patients who terminated the study early due to the premature proof of efficacy were counted as treatment discontinuations. This affected 39 (49%) patients in the nusinersen arm.
i. Study discontinuation due to death affected 3 (5.2%) patients.
j. Study discontinuation due to death affected 13 (16%) patients.

BiPAP: biphasic positive airway pressure; CHOP INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; F: female; HINE: Hammersmith Infant Neurological Examination; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; SD: standard deviation; SMA: spinal muscular atrophy

The patient characteristics of the considered populations in the studies FIREFISH and ENDEAR are comparable with regard to age at screening, age at first dose, age at symptom onset, age at SMA diagnosis, and disease duration, as well as the number of SMN2 gene copies (only patients with 2 SMN2 gene copies in both studies). Only minor differences between the study populations were shown at baseline also regarding motor function measured using the HINE Section 2 and the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND).

Clear differences between the studies were shown regarding geographical region. Whereas almost 50% of the patients in the ENDEAR study were enrolled in study centres in North

America (USA and Canada), this number was only 7% in the FIREFISH study (USA only). The FIREFISH study included a higher proportion of patients outside Europe and North America (rest of the world) (n = 16 [28%] versus n = 12 [15%]). In the FIREFISH study, this included 11 patients from China, 3 from Brazil, one from Japan, and one from Turkey. In the ENDEAR study, there were study centres outside Europe and North America in Australia, Japan, Korea and Turkey. However, no information is available on the number of patients included in the respective countries. The country distribution of the European centres also differs (FIREFISH: Belgium, Croatia, France, Italy, Poland, Russia, Switzerland, Turkey, Ukraine; ENDEAR: Belgium, France, Germany, Great Britain, Italy, Spain, Sweden, Turkey; see Table 6). For the assessment of the relevance of these differences, it must also be taken into account that the inclusion criteria differed with regard to medical care. Whereas in the ENDEAR study, medical care in the opinion of the investigator had to meet international standards of care [6,39], in the FIREFISH study, it had to meet local standards of care. There is no information on the proportion of patients with physiotherapy for either of the 2 studies. Due to a lack of data on patient care, the influence of the fact that the 2 studies were conducted in different countries remains unclear.

Information on further symptoms at baseline, such as hypotension, pneumonia or respiratory symptoms, is only available for the ENDEAR study. For the FIREFISH study, there is only information on the initial symptoms (presumably at the time of symptom onset). A comparison of the patients with regard to these characteristics is therefore not possible.

The data are insufficient for an assessment of the similarity of the 2 populations also with regard to the ventilation situation at baseline. The proportions of patients with ventilatory support at baseline in the FIREFISH and ENDEAR studies are of the same magnitude (n = 17 [29%] versus n = 21 [26%]). However, the aggregate data are not comparable between the studies due to notably different exclusion criteria regarding ventilation and respiratory symptoms (see Table 9). For example, the FIREFISH study excluded patients with awake non-invasive ventilation, invasive ventilation or tracheostomy, whereas there were no restrictions regarding ventilation for inclusion in the ENDEAR study. Data on ventilation subdivided according to type and duration of ventilation are only available for the FIREFISH study.

Table 9: Exclusion criteria regarding respiratory symptoms and ventilation situation of the studies FIREFISH and ENDEAR

Study FIREFISH (risdiplam)	Study ENDEAR (nusinersen)
▪ Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening	▪ Not explicitly excluded
▪ History of respiratory failure or severe pneumonia, and pulmonary function not fully recovered at the time of screening	
▪ Requiring awake non-invasive ventilation	
▪ Invasive ventilation or tracheostomy	
▪ Hypoxaemia defined as oxygen saturation awake < 95% with or without ventilatory support	▪ Hypoxaemia defined as oxygen saturation awake < 96% or oxygen saturation asleep < 96%, without ventilatory support

In addition to the non-permitted awake non-invasive ventilation, invasive ventilation or tracheostomy at baseline already mentioned for the FIREFISH study, there were also stricter exclusion criteria in comparison with the ENDEAR study with regard to respiratory symptoms. For example, patients with hospitalization for pulmonary event within the last 2 months, or planned at the time of screening, as well as those with a history of respiratory failure or severe pneumonia, and pulmonary function not fully recovered at the time of screening, were excluded. No corresponding exclusion criteria can be found in the study protocol of the ENDEAR study.

Furthermore, the definition regarding the exclusion criterion of hypoxaemia differs between the 2 studies. The relevance of the different definition (here tending towards a stricter exclusion criterion in the ENDEAR study) is unclear.

Overall, based on the exclusion criteria of the studies FIREFISH and ENDEAR, it can be assumed that the study population of the ENDEAR study had a less favourable prognosis with regard to respiratory events. This had a particular influence on the interpretation of the outcomes on ventilation in the comparison of individual arms of different studies presented by the company (see Section 2.3.4).

Transferability of the study results to the German health care context

The company assessed the transferability of the study results separately for the studies FIREFISH and ENDEAR.

According to the company, the patients' age at baseline in the FIREFISH study corresponded to the German health care context. In addition, the majority of patients were enrolled in Europe and were of Caucasian family origin. The company stated that the population of the FIREFISH study was overall very comparable to the patient population in the German health care context and the results were transferable to this context. With regard to the ENDEAR study, the company described that the majority of patients were included in North America and Europe and were of Caucasian family origin, thus corresponding to the German health care context.

According to the company, the selection of patients based on the time of onset of SMA-typical symptoms corresponded to the internationally recognized consensus and also was a sufficient reflection of the reality of treatment in Germany. In the overall view of the company, the study results of the ENDEAR study were also transferable to the German health care context.

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

2.3.3 Results on added benefit

2.3.3.1 Considered outcomes

The following patient-relevant outcomes were considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - death or permanent ventilation
  - motor functioning, measured by CHOP INTEND
  - motor milestone achievement, measured by HINE Section 2
  - serious respiratory events
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

Table 10 shows which of the outcomes for which the company presented comparative analyses of the studies FIREFISH and ENDEAR can be considered in the benefit assessment. Further outcomes considered as patient-relevant are additionally included in the matrix.

Table 10: Matrix of outcomes – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1)

	Outcomes								
	Overall survival	**Death or permanent ventilation[a]**	**Motor functioning (CHOP INTEND)**	**Motor milestone achievement (HINE Section 2)**	**Serious respiratory events**	**Hospitalization**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**
Comparison of individual arms of the studies FIREFISH and ENDEAR	Con-sidered	Con-sidered	Not considered[b, c]	Not considered[b, c]	No[d]	Not con-sidered[e]	No[f]	Not con-sidered[g]	Not con-sidered[g]

a. Composite outcome consisting of the individual components "death" and "permanent ventilation" (defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy); see running text for comparability of the operationalizations used in the studies FIREFISH and ENDEAR.
b. No statistically significant group difference or no sufficiently large effect that could not be based on systematic bias alone.
c. The company stated that a modified data set of the FIREFISH study with a median observation period of 283 days (approximately 9 months) was used as an adjustment to the median observation period of the nusinersen arm of the ENDEAR study (280 days) for the analysis of the binary outcomes. According to the company, all events in the FIREFISH population that occurred in a period of 6 months before the primary data cut-off (1 year after inclusion of the last patient) were not included in the analysis. Based on this information, it is unclear how the observation periods were adjusted. Furthermore, it is unclear whether and how the observation periods for continuous data were adjusted.
d. no comparison presented.
e. According to the operationalization, both studies also include events that do not have to be associated with the disease (FIREFISH: any hospitalizations; ENDEAR: hospitalizations for monitoring for general observation, due to symptoms after dosing, due to SAEs or additional investigations [e.g. planned surgery such as placement of a gastric feeding tube for preventive reasons]).
f. Health-related quality of life was not recorded in either study.
g. In the ENDEAR study, high proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. SOC "respiratory, thoracic and mediastinal disorders"). In Appendix 4G, the company presented analyses for the FIREFISH study without consideration of disease-related events. It cannot be inferred from Module 4A of the dossier which events were excluded from the analyses. There is no comparison with the ENDEAR study without consideration of disease-related events.

AE: adverse event; CHOP INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; HINE: Hammersmith Infant Neurological Examination; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class

The following outcomes were not considered for the comparison of individual arms:

- Motor functioning (CHOP INTEND) and motor milestone achievement (HINE Section 2)

  There were no statistically significant group differences or sufficiently large effects that could not be based on systematic bias alone for either outcome. Furthermore, based on the information provided by the company, it is unclear how or whether the different observation periods of the 2 studies were adjusted for binary and continuous outcomes (see Table 10).

- Serious respiratory events

  Serious respiratory events are an important patient-relevant outcome in the present therapeutic indication. In the ENDEAR study, the outcome was operationalized as SAEs classified as primary or secondary SOC in the SOC "respiratory, thoracic and mediastinal disorders" (see also dossier assessment of nusinersen [12]). The company presented no comparison for this outcome.

- Hospitalization

  According to the operationalization, both studies also include events that do not have to be associated with the disease (see Table 10).

- Health-related quality of life

  Health-related quality of life was not recorded in either study.

- SAEs and discontinuation due to AEs

  In the ENDEAR study, there was a high proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. SOC "respiratory, thoracic and mediastinal disorders"). A comparison of SAEs and discontinuations due to AEs between the FIREFISH study and the ENDEAR study without consideration of disease-related events is not available.

Only the outcome "death or permanent ventilation" and its individual components "death" or "permanent ventilation" were considered for the benefit assessment (see Section 2.3.3.2).

Death or permanent ventilation

The outcome "death or permanent ventilation" is a composite outcome of the individual components "death" and "permanent ventilation". Both studies (FIREFISH and ENDEAR) defined permanent ventilation as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy. Acute reversible events in both studies included fever (in the ENDEAR study defined as body temperature ≥ 38.9°C), infections diagnosed by defined laboratory methods, and surgical procedures that occurred in the 7 days before or 7 days after the start of ventilation. Differences in operationalization existed in the concrete definition of ventilation, which was "≥ 16 hours of non-invasive ventilation per day or intubation" in the FIREFISH study, and "≥ 16 hours of ventilation" in the ENDEAR study. In addition, the start of permanent ventilation was counted at 7 days after the resolution of a reversible event in the FIREFISH study, and at 14 days in the ENDEAR study. Overall, the

outcome operationalizations of both studies are sufficiently comparable despite these differences.

A precondition for using a composite outcome is that the individual components are of sufficiently similar severity. Respiratory muscle weakness is a common consequence of SMA and occurs secondary to neuromuscular weakness in patients with early onset of disease (SMA type 1). Pulmonary diseases are the main cause of increased mortality and morbidity in the patients [6]. Therefore, the 2 components (permanent ventilation, death) are assessed as sufficiently similar in terms of severity.

Note on observation periods in the analyses presented

For the FIREFISH study, the company presented results for 2 data cut-offs (1 year and 2 years after inclusion of the last patient). For the comparison of individual arms of different studies, the company used the data cut-off of 1 year after inclusion of the last patient for the FIREFISH study. At this data cut-off, all patients had been observed for at least 365 months. For the ENDEAR study, the company used the data from the final data cut-off with a median observation period of 280 days in the nusinersen arm. The maximum observation period in the ENDEAR study was 14.5 months. The company's approach to use the first data cut-off of the FIREFISH study is therefore appropriate.

2.3.3.2 Results

For the assessment of the added benefit of risdiplam in comparison with nusinersen in patients with SMA type 1, the results of the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR presented by the company are shown below. Only the outcomes for which there were clear effects under the assumption of comparable operationalizations are considered.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves for the outcomes presented as well as results of the MAIC analyses used by the company are presented in Appendix B of the full dossier assessment.

Table 11: Results (mortality and morbidity, time to event) – comparison of individual arms of different studies (unadjusted): risdiplam vs. nusinersen (SMA type 1)

Outcome category Outcome	Risdiplam (study FIREFISH part 1, cohort 2 + part 2)[a]		Nusinersen (study ENDEAR)[b]		Risdiplam vs. nusinersen
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][c]; p-value
Mortality[d]					
Overall survival	58	NA 5 (8.6)	80	NA 13 (16.3)	0.44 [0.09; 1.02]; ND
Morbidity[d]					
Death or permanent ventilation[e]	58	NA 8 (13.8)	80	NA [8.64; NC] 31 (38.8)	0.24 [0.09; 0.46]; ND
Permanent ventilation	58	NA 3 (5.2)	80	NA 18 (22.5)	0.15 [0.00; 0.41], ND

a. Data cut-off 1 year after inclusion of the last patient.
b. Final data cut-off from 16 December 2016.
c. HR and CI based on unstratified Cox model.
d. Observation periods in the FIREFISH study were censored at month 13.
e. Composite outcome consisting of the individual components "death" and "permanent ventilation", which was defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy (see Section 2.3.3.1 for comparability of the operationalizations used in the studies FIREFISH and ENDEAR).

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; ND: no data; SMA: spinal muscular atrophy

Individual aspects of bias for the 2 studies or for the outcomes presented are not assessed, as the available data involve the use of individual arms of different studies. No more than hints can be derived on the basis of the data presented.

Mortality

Overall survival

Operationalization

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome "overall survival".

Result

Based on the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR, there was no statistically significant difference between the treatment arms with regard to the outcome "overall survival".

Based on the results of the MAIC analysis (see Appendix B.1 of the full dossier assessment), the company derived a hint of a major added benefit.

Morbidity

Death or permanent ventilation and individual component of permanent ventilation

Operationalization

Information on the operationalization of the composite outcome "death or permanent ventilation" can be found in Section 2.3.3.1. The results for time to death or permanent ventilation were used for the composite outcome.

Result

Based on the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR, there was a clear statistically significant difference in favour of risdiplam in comparison with nusinersen for the composite outcome "death or permanent ventilation" as well as for the individual component "permanent ventilation". The consideration of the results of the composite outcome and its individual components shows that the effect was mainly caused by the outcome "permanent ventilation".

Based on the results of the MAIC analysis (see Appendix B.1 of the full dossier assessment), the company derived a "major added benefit with dramatic effect" for the composite outcome as well as for the individual outcome "permanent ventilation".

2.3.3.3 Subgroups and other effect modifiers

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

- sex (male/female)
- disease severity (symptom onset at ≤ 12 weeks/> 12 weeks of age)
- disease duration (≤ 12 weeks/> 12 weeks)

No subgroup results are available for the comparison of individual arms of the studies FIREFISH and ENDEAR. Therefore no conclusions on effect modifications are possible. The lack of subgroup analyses is particularly relevant as age at symptom onset and disease duration were identified as important effect modifiers for nusinersen + BSC in comparison with a sham intervention + BSC in the ENDEAR study [12].

2.3.4 Probability and extent of added benefit

Based on the "naive" comparison of individual arms of different studies comparing risdiplam and nusinersen presented by the company, a clear statistically significant effect in favour of risdiplam was shown for the outcome "death or permanent ventilation" as well as for the individual component "permanent ventilation". The effect is mainly caused by the events of permanent ventilation. In the present situation, using individual arms of different studies, it

cannot be ruled out with certainty that these effects were solely due to a systematic bias caused by confounding variables. This is due in particular to the fact that the exclusion criteria of the FIREFISH study with regard to ventilation at baseline and the medical history of respiratory symptoms (e.g. pneumonia) excluded patients with unfavourable prognosis more comprehensively than the exclusion criteria of the ENDEAR study. Thus, it can be assumed that the study population of the ENDEAR study had a less favourable prognosis with regard to respiratory events. The present patient characteristics cannot eliminate this uncertainty. There is a lack of comparative characteristics – and thus information on confounders – on respiratory symptoms before and at study start as well as on the ventilation situation at study start according to type (invasive, non-invasive, during the day, at night) and duration of ventilation. For example, an analysis of the subpopulation of the ENDEAR study according to the inclusion criteria of the FIREFISH study would also be relevant for an appropriate comparative assessment.

The data presented are difficult to interpret for the reasons described. However, the observed differences for the time to permanent ventilation or the composite outcome of time to death or time to permanent ventilation suggest that risdiplam is at least not inferior to nusinersen.

In addition, in the present situation, the oral administration of risdiplam is considered to have a noticeable advantage for the patient compared with the intrathecal administration of nusinersen. Risdiplam is given orally every day, whereas nusinersen must be administered intrathecally at regular intervals several times a year. The advantage of oral administration of risdiplam is thus justified by the high probability of morbidity associated with intrathecal administration of nusinersen.

In the overall picture, therefore, taking particular account of the severity of the disease and the present data constellation, there is a hint of a non-quantifiable added benefit of risdiplam compared with nusinersen for patients with SMA type 1.

The assessment described above differs from that of the company, which derived a hint of a major added benefit for patients with SMA type 1 based on a MAIC analysis using individual arms of different studies.

2.4 Research question 2: patients with SMA type 2

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risdiplam (status: 15 February 2021)
- bibliographical literature search on risdiplam (last search on 15 February 2021)

- search in trial registries/trial results databases for studies on risdiplam (last search on 26 February 2021)
- search on the G-BA website for risdiplam (last search on 26 February 2021)
- bibliographical literature search on the ACT (last search on 15 February 2021)
- search in trial registries/trial results databases for the ACT (last search on 26 February 2021)
- search on the G-BA website for the ACT (last search on 26 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on risdiplam (last search on 4 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 12 May 2021); for search strategies, see Appendix A of the full dossier assessment

The check identified no additional potentially relevant study for a direct or indirect comparison.

Approach of the company

Since no study of direct comparison in patients with SMA type 2 was available, the company checked the possibility of an adjusted indirect comparison for the assessment of the added benefit of risdiplam in comparison with nusinersen as ACT.

Based on the SUNFISH study with risdiplam, the company searched for studies with patients with SMA type 2 who were treated with nusinersen in order to check the feasibility of an indirect comparison using the common comparator BSC (or placebo). The SUNFISH study included non-ambulatory patients with clinical symptoms of SMA type 2 or 3 (for a detailed study description, see Section 2.5.1.2). Thus, the subpopulation of the SUNFISH study with type 2 SMA would be relevant for an adjusted indirect comparison (risdiplam [N = 84] versus placebo [N = 44]; ≙ 71.1% of the total population).

In the trial registry search, the company identified the studies CHERISH [40-42] and EMBRACE [15,16]. Both studies are already known from the benefit assessment of nusinersen [12].

The CHERISH study is an RCT in which patients were treated with either nusinersen or a sham intervention. The study included patients with genetic documentation of 5q SMA who were 2 to 12 years of age at screening and with symptom onset at > 6 months of age. Patients had to be able to sit independently, but, beyond that, never had the ability to walk independently. In accordance with these criteria, only patients with SMA type 2 were included in the CHERISH study [3,12].

The company then examined the similarity of the studies SUNFISH and CHERISH. This examination identified important differences, particularly with regard to the included patients' age at the time of screening and their disease duration. The patients across all arms in the SUNFISH study had a median age of 8 years at study start, whereas the patients in the CHERISH study were notably younger, with a median age of 3 and 4 years (see Module 4 A, Table 4-68). Since the patients included in each case were of similar age at symptom onset, the median duration of the disease also differed notably between the 2 studies (92.6 and 90 months [SUNFISH] versus 39.9 and 34.8 months [CHERISH]). This may also be a reason why the patients in the SUNFISH study were more severely ill at study start than the patients in the CHERISH study. For example, 34% of patients with SMA type 2 in the SUNFISH study had severe scoliosis (Cobb angle > 40 degrees) compared with 0% in the CHERISH study, and motor functioning (as assessed by the HFSME) was worse overall than in the CHERISH study. The company therefore came to the overall conclusion that the comparability between the 2 studies was not given and therefore did not conduct an indirect comparison. This view is shared.

The RCT EMBRACE included patients with genetic documentation of 5q SMA, who received either nusinersen (N = 14) or a sham intervention (N = 7). Since the age of the patients at enrolment differed fundamentally between the studies SUNFISH and EMBRACE (EMBRACE: < 18 months, SUNFISH: 2 to 25 years), the company conducted no further examination of the similarity between the studies. This approach is appropriate.

Overall, based on the identified studies, an adjusted indirect comparison of risdiplam against nusinersen for patients with SMA type 2 is therefore not possible.

2.4.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of risdiplam compared with the ACT nusinersen in patients with SMA type 2. Hence, there is no hint of an added benefit of risdiplam in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of risdiplam compared with the ACT nusinersen in patients with SMA type 2. An added benefit is therefore not proven. This concurs with the company's assessment.

2.5 Research question 3: patients with SMA type 3

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risdiplam (status: 15 February 2021)

- bibliographical literature search on risdiplam (last search on 15 February 2021)
- search in trial registries/trial results databases for studies on risdiplam (last search on 26 February 2021)
- search on the G-BA website for risdiplam (last search on 26 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on risdiplam (last search on 4 May 2021); for search strategies, see Appendix A of the full dossier assessment

No relevant study was identified from the check.

2.5.1.1 Study included by the company

In its dossier, the company included the study listed in Table 12 in the benefit assessment.

Table 12: Study pool of the company – RCT, direct comparison: risdiplam vs. BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
BP39055 (SUNFISH[d])	Yes	Yes	No	Yes [43]	Yes [44,45]	Yes [29]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: European Public Assessment Report.
d. In the following tables, the study is referred to with this abbreviated form.

BSC: best supportive care; CSR: clinical study report; RCT: randomized controlled trial

The BP39055 study (hereinafter referred to as "SUNFISH study") used by the company is not suitable for deriving conclusions on the added benefit of risdiplam in comparison with the ACT of treatment of physician's choice choosing from nusinersen or BSC for patients with SMA type 3. This is due to the fact that the ACT specified by the G-BA was not implemented in the SUNFISH study (see text on the implementation of the ACT on p. 41).

Nevertheless, the results of the SUNFISH study for the subpopulation with SMA type 3 are presented as supplementary information. A conclusion on the added benefit based on these data is not derived, however.

2.5.1.2 Study characteristics of the study included by the company

Table 13 and Table 14 describe the study included by the company.

Table 13: Characteristics of the SUNFISH study included by the company – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SUNFISH	RCT[b], double-blind, parallel	Patients with genetically confirmed diagnosis of 5q SMA[c] and ▪ clinical symptoms attributable to SMA type 2 or type 3 (non-ambulatory[d]) ▪ 2 to 25 years of age at screening ▪ RULM ≥ 2 points on item A (Brooke score)[e] ▪ ability to sit independently[f]	▪ Risdiplam (N = 120) ▪ placebo (N = 60) Patients thereof analysed by the company (patients with SMA type 3): ▪ risdiplam (n = 36) ▪ placebo (n = 16)	Screening: 30 days Treatment: ▪ 12 months of randomized treatment[g], followed by ▪ 12 months of active treatment with risdiplam, followed by ▪ 3 years of open-label continued treatment with risdiplam[h] Follow-up: 30 days	42 study centres in: Belgium, Brazil, Canada, China, Croatia, France, Italy, Japan, Poland, Russia, Serbia, Spain, Turkey and the USA Study period: 10/2017–ongoing Data cut-offs (planned analyses): ▪ 6 Sep 2019: after 12 months[g] ▪ 30 Sep 2020: after 24 months	Primary: change in total MFM-32 score at month 12 Secondary: morbidity, AEs

Table 13: Characteristics of the SUNFISH study included by the company – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. The RCT has 2 parts. The confirmatory part 2 is relevant for the benefit assessment. Part 1 is an independent, exploratory dose-finding study with placebo comparison, with a randomized phase of a maximum of 12 weeks. The information in the benefit assessment therefore refers exclusively to part 2 of the study. Patients from part 1 of the study did not cross over into part 2. c. Main exclusion criteria of the study: patients requiring invasive ventilation or tracheostomy; surgery for scoliosis or hip fixation in the year preceding screening or planned within the next 18 months; unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases, as considered to be clinically significant by the investigator; any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to first dose administration. d. Defined as not having the ability to walk unassisted (i.e. without braces, assisted devices such as canes, crutches or calipers, or person/hand-held assistance) for 10 m or more. e. Can raise 1 or 2 hands to the mouth but cannot raise a 200 g weight to the mouth. f. Score ≥ 1 on item 9 of the MFM-32 (with support of one or both upper limbs maintains the seated position for 5 seconds). g. The results presented in the benefit assessment refer to this treatment period or this data cut-off. The company did not present results for month 24 in Module 4 A. h. After 12 months of randomized treatment (i.e. at their visit in week 52), all patients received (continued) blinded treatment with risdiplam, and the blinded treatment was continued until month 24. After 24 months, the patients were given the opportunity to enter the open-label phase, in which they were regularly monitored for safety, tolerability and efficacy (see Figure 1). AE: adverse event; BSC: best supportive care; MFM-32: Motor Function Measure – 32 items; n: subpopulation; N: number of randomized patients; RCT: randomized controlled trial; RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy						

Table 14: Characteristics of the intervention, SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study	Intervention	Comparison
SUNFISH	Risdiplam, once daily orally[a] (usually with breakfast) ▪ 5 mg risdiplam for a body weight of ≥ 20 kg ▪ 0.25 mg/kg risdiplam for a body weight of < 20 kg	Placebo, once daily orally[a] (usually with breakfast)
	Permitted concomitant treatment ▪ any medication, e.g. prescription and over-the-counter drugs[b], herbal remedies, dietary supplements and any non-drug interventions (e.g. individual psychotherapy, cognitive behavioural therapy, physiotherapy and rehabilitative therapy), used by a patient within 30 days of screening until the follow-up visit ▪ physiotherapy, occupational therapy and other forms of exercise therapy were encouraged in the study but the frequency had to remain the same during the study ▪ for any treatment of chronic diseases, patients had to be on stable regimen for 6 weeks prior to screening and remain on this stable regimen throughout the study **Prohibited prior and concomitant treatment** ▪ concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier (e.g. nusinersen) or gene therapy (e.g. onasemnogene abeparvovec) and any history of cell therapy ▪ treatment with oral beta2-adrenergic agonist initiated within 6 months prior to randomization ▪ other medications for the treatment of SMA, (e.g. growth hormones, anabolic steroids, creatine, and other agents anticipated to increase muscle strength), or with potential retinal toxicity during the study and within at least 90 days prior to randomization	

a. The patients received the medication as an oral solution to swallow, followed by rinsing of the mouth. Patients unable to swallow and who have a naso-gastric or gastrostomy tube in situ received the study medication via the tube.
b. The study protocol lists the following drugs, among others, as permitted:
- oral salbutamol or another beta2-adrenergic agonist (oral), as long as treatment had been introduced at least 6 months before randomization and was well tolerated
- inhaled beta2-adrenergic agonists (e.g. for the treatment of asthma)
- inhaled corticosteroids
- other systemic inhaled drugs for the treatment of an obstructive airways disease (e.g. anticholinergics or anti-allergic agents, leukotriene receptor antagonists)
- laxatives and other drugs for the treatment of functional gastrointestinal disorders
- occasional use of analgesics, including opioids (e.g. codeine).
- any antibiotic treatment
- antihistamines
- proton pump inhibitors

ACT: appropriate comparator therapy; BSC: best supportive care; RCT: randomized controlled trial; SMA: spinal muscular atrophy; SMN: survival motor neuron

Study SUNFISH

The SUNFISH study (part 2) is a randomized, controlled, double-blind study on the direct comparison of risdiplam with placebo. Patients in both arms additionally received supportive measures (see also text on the implementation of the ACT on p. 41). Patients with genetically confirmed diagnosis of 5q SMA and 2 to 25 years of age at screening were included. The patients included had to have clinical symptoms of SMA type 2 or 3 and be unable to walk. The study defined inability to walk as the patient's inability to walk unassisted (i.e. without braces,

assisted devices such as canes, crutches or calipers, or person/hand-held assistance) for 10 m or more. Due to the restriction to only non-ambulatory patients with SMA type 3, the SUNFISH study only partially represents the population of patients with SMA type 3, which is the one relevant for research question 3.

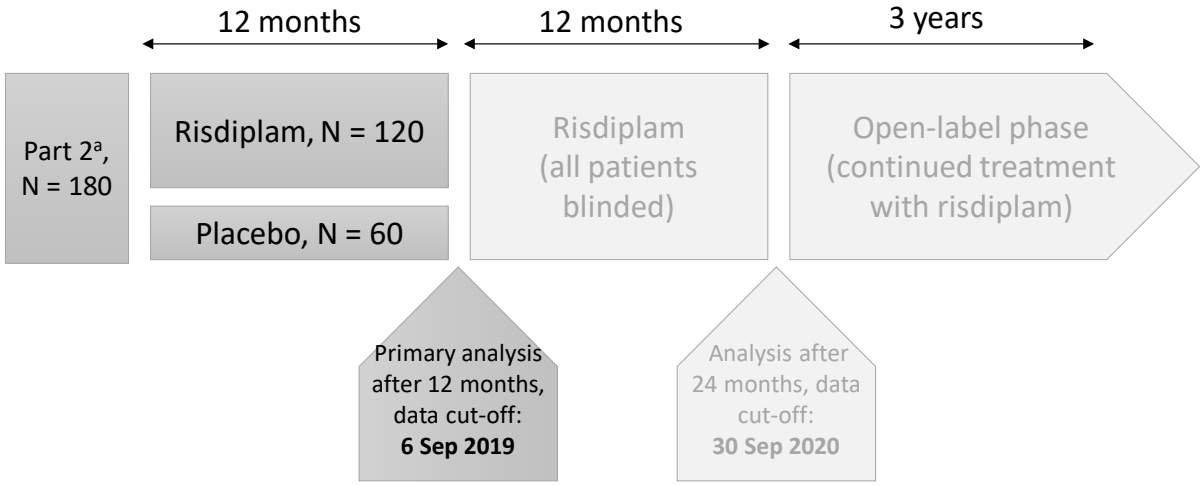
Patients should not have received any other drug therapy for the treatment of SMA (e.g. nusinersen or onasemnogene abeparvovec) before the start of the study. Patients with severe symptoms and clinically significant concomitant diseases were excluded from the study (e.g. invasive ventilation or tracheostomy, scoliosis surgery or hip surgery in the 1 year preceding screening or planned within the next 18 months).

A total of 180 patients were randomly allocated in a 2:1 ratio to treatment either with risdiplam (N = 120) or with placebo (N = 60). The stratification factor was age (2 to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years at randomization).

For the benefit assessment, the company considered the subpopulation of the SUNFISH study with a clinical diagnosis of SMA type 3 in order to answer research question 3. This approach is appropriate. This leaves 36 patients with SMA type 3 in the risdiplam arm and 16 in the placebo arm. All further information in the present assessment refers to this subpopulation.

Treatment with risdiplam was in compliance with the SPC [36]. Concomitant or previous administration of an SMN2-targeting antisense oligonucleotide (e.g. nusinersen), SMN2 splicing modifier or gene therapy (e.g. onasemnogene abeparvovec) and any history of cell therapy were not allowed.

Figure 1 presents a schematic diagram of the design of the SUNFISH study (part 2).



a. Part 1 of the study is an independent, exploratory dose-finding study with a randomized phase of a maximum of 12 weeks. The information in the benefit assessment therefore refers exclusively to part 2 of the study. Patients from part 1 of the study did not cross over into part 2.

Figure 1: Design of the SUNFISH study (part 2)

The SUNFISH study (part 2) started in October 2017. After 12 months of randomized treatment with risdiplam + BSC or placebo + BSC, all patients received blinded treatment with risdiplam + BSC until month 24. Afterwards, the patients were given the opportunity to receive unblinded treatment with risdiplam for a period of 3 years (open-label phase). The primary analysis was conducted after the last patient had been treated for 12 months or had terminated the study early (6 September 2019). Only data up to month 12 were included in the primary analysis for each individual patient. A further planned analysis took place after the last patient had been treated for 24 months (30 September 2020). The study with an open-label risdiplam treatment is currently ongoing. The company used the data cut-off from 6 September 2019 for its benefit assessment, as all patients with placebo treatment subsequently switched to risdiplam. This approach is appropriate.

The primary outcome of the study was to show the change in MFM-32 total score at month 12. Secondary outcomes were outcomes on morbidity and AEs. The SUNSHINE study recorded deaths as part of the AE recording.

Implementation of the appropriate comparator therapy

The G-BA determined treatment of physician's choice choosing from nusinersen or BSC as the ACT for patients with SMA type 3 (see Table 4). The benefit assessment subsequently examined 2 aspects regarding the implementation of the ACT in the SUNFISH study in order to decide on the study relevance.

- Do the concomitant drug and non-drug interventions used in the study correspond to a therapy in the sense of a BSC?
- Is the SUNFISH study, as a single-comparator study, suitable to represent the G-BA's ACT?

Implementation of BSC

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. In this therapeutic indication, various drug and non-drug interventions may be suitable for treating the symptoms of SMA and can be used on a patient-specific basis [37,38]. Generally, comprehensive and coordinated multidisciplinary treatment is required due to the complexity and severity of the disease [4,46]. Furthermore, BSC in the context of an RCT is necessary both in the control group and in the intervention group.

The study protocol explicitly mentioned drugs that are generally recommended as suitable supportive therapies in the therapeutic indication [37], such as inhaled beta2-adrenergic agonists, antibiotic treatments and laxatives (see Table 14). Furthermore, the study did not explicitly exclude any drugs that could call into question the implementation of a BSC. Physiotherapy, occupational therapy and other forms of exercise therapy were encouraged but according to the study protocol, the frequency had to remain the same during the study.

Referring to corresponding treatment recommendations [37,38], the company itself pointed out in Module 4 A that all patients were able to receive the best possible supportive and patient-individually optimized treatment to alleviate symptoms and improve the quality of life in accordance with the decision of the treating physician during the study.

Table 15 shows which concomitant therapies were administered in the total population during the course of the study. No data are available for the subpopulation with SMA type 3 presented by the company for research question 3. The data of the total population are therefore considered below as an approximation for the subpopulation with SMA type 3.

Table 15: Information on concomitant measures used in the SUNFISH study (≥ 10% of patients in at least one study arm) – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 2 and 3 [non-ambulatory])[a] (multipage table)

Study	**Patients with concomitant therapy n (%)**	
Drug class **Drug**	**Risdiplam + BSC** **N = 120**	**Placebo + BSC** **N = 60**
SUNFISH, data cut-off from 6 September 2019		
Concomitant drug interventions (total)	113 (94.2)	57 (95.0)
Sympathomimetics	12 (10.0)	8 (13.3)
Analgesics	49 (40.8)	27 (45.0)
Paracetamol	49 (40.8)	27 (45.0)
Antiemetics	9 (7.5)	7 (11.7)
Antihistamines	23 (19.2)	9 (15.0)
Antispasmodic/anticholinergic	35 (29.2)	17 (28.3)
Tropicamide	18 (15.0)	4 (6.7)
Cyclopentolate	8 (6.7)	6 (10.0)
Antiviral agents	9 (7.5)	6 (10.0)
Bronchodilators and antiasthmatics	19 (15.8)	18 (30.0)
Salbutamol	9 (7.5)	6 (10.0)
Fenoterol hydrobromide/ipratropium bromide	3 (2.5)	7 (11.7)
Cephalosporin antibiotics	24 (20.0)	7 (11.7)
Cough preparations	14 (11.7)	8 (13.3)
Dermatologics	13 (10.8)	4 (6.7)
Herbal, homeopathic and dietary supplements	33 (27.5)	16 (26.7)
Local anaesthetics	15 (12.5)	6 (10.0)
Macrolide antibiotics	16 (13.3)	8 (13.3)
Mucolytics	13 (10.8)	7 (11.7)
Nonsteroidal anti-inflammatory drugs	45 (37.5)	20 (33.3)
Ibuprofen	42 (35.0)	17 (28.3)
Penicillins	42 (35.0)	22 (36.7)
Amoxicillin	22 (18.3)	7 (11.7)
Amoxicillin/potassium clavulanate	17 (14.2)	10 (16.7)
Amoxicillin/clavulanic acid	9 (7.5)	7 (11.7)
Pharmacotherapeutic class unknown	12 (10.0)	2 (3.3)
Quinolone antibiotics	8 (6.7)	6 (10.0)
Steroids	31 (25.8)	18 (30.0)
Budesonide	11 (9.2)	10 (16.7)
Supplements	24 (20.0)	17 (28.3)
Sodium chloride	16 (13.3)	13 (21.7)
Vaccines, toxoids and serological agents	27 (22.5)	10 (16.7)
Influenza vaccines	21 (17.5)	7 (11.7)
Vitamins and minerals	24 (20.0)	8 (13.3)
Concomitant non-drug interventions[b]	85 (70.8)	36 (60.0)

Table 15: Information on concomitant measures used in the SUNFISH study (≥ 10% of patients in at least one study arm) – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 2 and 3 [non-ambulatory])[a] (multipage table)

Study	Patients with concomitant therapy n (%)	
Drug class Drug	Risdiplam + BSC N = 120	Placebo + BSC N = 60

a. No data available for the subpopulation with SMA type 3.
b. Documented measures within the framework of physiotherapy, occupational therapy or other exercise therapy. Since the measures carried out varied greatly from patient to patient (usually only one patient per specific measure), a detailed list of the individual measures is not provided.

BSC: best supportive care; n: number of patients with concomitant therapy; N: number of analysed patients; RCT: randomized controlled trial; SMA: spinal muscular atrophy

The available information based on the total population of the SUNFISH study shows that almost all patients in both study arms (approximately 95% in each arm) were treated with supportive drug therapies. Antibiotics, bronchodilators and anti-inflammatory drugs were used in particular. These appear adequate when compared with international treatment recommendations [37].

For about 2 thirds of the patients in both study arms, the implementation of concomitant non-drug interventions in accordance with the recommendations for the treatment of SMA [38] was also documented. These include physiotherapy, occupational therapy and other exercise therapies. To what extent the requirement of the study protocol of not changing the frequency of physiotherapeutic measures during the study was actually implemented in the study, and whether this limited optimal patient-specific care, cannot be inferred from the available documents.

In summary, the concomitant drug and non-drug measures used in the study are considered a sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA [37,38].

Single-comparator SUNFISH study does not represent the appropriate comparator therapy

A single-comparator study is generally not sufficient for the ACT of a treatment of physician's choice choosing from nusinersen or BSC as specified by the G-BA. For the implementation of the treatment of physician's choice in a study of direct comparison, the investigator should have a choice of several treatment options for the comparator arm at the beginning of the study (here: BSC and nusinersen [multi-comparator study]). A therapy decision regarding the comparator therapy should be made on an individual patient basis before group allocation (e.g. randomization).

A single-comparator study with BSC as the only treatment option in the comparator arm is only an adequate implementation of the ACT if treatment with nusinersen was not an option for the patients included. Therefore, it was examined in the benefit assessment whether treatment with BSC was the only treatment option for the patients in the SUNFISH study. The company did

not conduct such an examination. However, the current ACT of the G-BA for research question 3 was not available at the time of the dossier submission (see Section 2.2).

According to Section 4.2 of the SPC, the decision to treat with nusinersen *"should be based on an individualised expert evaluation of the expected benefits of treatment for that individual, balanced against the potential risk of treatment with Spinraza"* [23]. There are no explicit contraindications to the use of nusinersen beyond hypersensitivity to nusinersen or any other ingredient. However, it is noted that potential difficulties with the intrathecal administration may be seen in very young patients and those with scoliosis. Although approximately 2 thirds of the patients in the SUNFISH study had scoliosis (see Table 16), the administration of nusinersen is not excluded per se for these patients, which corresponds to the assessment of the company in Module 3 A, Section 3.2.2. In this case, intrathecal administration of nusinersen can be considered with the assistance of ultrasound or other imaging techniques. According to an investigation in adults with SMA, only in individual cases (e.g. with inserted implants) is it not possible to perform an intrathecal injection at all [47]. It can also be assumed that age does not in principle stand in the way of intrathecal administration. The SUNFISH study included patients aged 2 to 25 years.

The extent to which the occurrence of potential side effects associated with lumbar puncture (e.g. headache, back pain, vomiting) led to a decision against treatment with nusinersen cannot be answered retrospectively and is a matter for individual decision by the patients (or their parents) with the involvement of the treating physician.

Overall, there is no information that clearly indicates that nusinersen would not have been an option for the patients in the SUNFISH study. It can therefore be assumed that nusinersen would have been an approved and thus basically suitable therapy option for a relevant proportion of the patients included in the study (or subpopulation). Therefore, a single-comparator study is not sufficient to implement the ACT specified by the G-BA (treatment of physician's choice choosing from nusinersen or BSC).

Summary

The supportive drug and non-drug measures used in the study were considered to be a sufficient implementation of the ACT BSC. In the present case, however, a single-comparator study does not represent the ACT of the G-BA, as it can be assumed that nusinersen would have been an approved and thus fundamentally suitable therapy option for a relevant proportion of the patients included in the study (or the relevant subpopulation). Nevertheless, a complete description and assessment of the results of the SUNFISH study for the subpopulation of patients with SMA type 3 is provided.

Patient characteristics

Table 16 shows the characteristics of the subpopulation with SMA type 3 in the study included by the company.

Table 16: Characteristics of the study population, SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3) (multipage table)

Study **Characteristic** **Category**	**Risdiplam + BSC** **N = 36**	**Placebo + BSC** **N = 16**
SUNFISH		
Age at screening [years], median [min; max]	13.5 [2; 25]	12.0 [3; 24]
Sex [F/M],%	47/53	50/50
Geographical region[a], n (%)		
Europe	28 (77.8)	14 (87.5)
Rest of the world	8 (22.2)	2 (12.5)
Family origin, n (%)		
Caucasian	25 (69.4)	13 (81.3)
Asian	5 (13.9)	1 (6.3)
Other[b]	6 (16.7)[c]	2 (12.5)[c]
Number of SMN2 gene copies, n (%)		
2 copies	2 (5.6)	0 (0)
3 copies	24 (66.7)	10 (62.5)
4 copies	10 (27.8)	6 (37.5)
Age at symptom onset [months], median [min; max]	17 [0; 57]	18 [8; 135]
Disease duration[d] [months], median [min; max]	145 [19; 275]	110 [1; 243]
Standing ability, n (%)		
Able to stand	11 (30.6)	4 (25.0)
Unable to stand	25 (69.4)	12 (75.0)
Walking ability, n (%)		
Able to walk	3 (8.3)	1 (6.3)
Unable to walk	33 (91.7)	15 (93.8)
Highest motor milestone achieved, n (%)	ND	ND
Presence of scoliosis, n (%)		
Yes	24 (66.7)	11 (68.8)
No	12 (33.3)	5 (31.3)
Degree of curvature due to scoliosis, n (%)		
< 10	8 (22.2)	3 (18.8)
10–40	7 (19.4)	4 (25.0)
> 40	9 (25.0)	4 (25.0)
Unknown	12 (33.3)	5 (31.3)
Scoliosis surgery before screening, n (%)		
Yes	5 (13.9)	4 (25.0)
No	23 (63.9)	10 (62.5)
Unknown	8 (22.2)	2 (12.5)
Patients with wheelchair, n (%)	ND	ND
Patients with physiotherapy, n (%)	ND	ND
RULM total score, mean (SD)	25.6 (6.6)	25.3 (7.1)

Table 16: Characteristics of the study population, SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3) (multipage table)

Study **Characteristic** **Category**	**Risdiplam + BSC** **N = 36**	**Placebo + BSC** **N = 16**
MFM-32 total score, mean (SD)	54.4 (9.6)	55.1 (9.6)
HFSME total score, mean (SD)	25.5 (12.8)	24.8 (13.5)
Treatment discontinuation, n (%)	0 (0)	1 (6.3)[c]
Study discontinuation, n (%)	ND	ND

a. Information on the geographical region was taken from the subgroup analyses.
b. Black or African or unknown (designations by the company).
c. Institute's calculation.
d. Operationalized as the period between symptom onset and therapy initiation.

BSC: best supportive care; F: female; HFSME: Hammersmith Functional Motor Scale Expanded; M: male; max: maximum; MFM-32: Motor Function Measure – 32 items; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RULM: Revised Upper Limb Module; SD: standard deviation; SMA: spinal muscular atrophy; SMN: survival motor neuron

The demographic and disease-specific characteristics of the patients with SMA type 3 were largely comparable between the treatment arms.

The median age of the patients was about 13 years, about 50% were female, and most of them were from Europe. About 2 thirds of the included patients had 3 SMN2 gene copies. The median age at symptom onset in both treatment arms was approximately 18 months, which corresponds to the defined age of first manifestation in patients with SMA type 3 [48,49]. At baseline, about 71% of patients across arms were unable to stand. Contrary to the inclusion criteria, 4 patients were able to walk. About 2 thirds of the patients had scoliosis. The instruments used in the study to assess motor functions during the course of the study (MFM-32, RULM, HFSME) showed comparable values in both treatment arms at baseline.

Risk of bias across outcomes (study level)

Table 17 shows the risk of bias across outcomes (risk of bias at study level).

Table 17: Risk of bias across outcomes (study level), SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patients	**Treating staff**			
SUNFISH	Yes	Yes	Yes	Yes	Yes	Yes	Low

BSC: best supportive care; RCT: randomized controlled trial

The risk of bias across outcomes for the SUNFISH study was rated as low. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company stated that the results of the SUNFISH study presented for the subpopulation (patients with SMA type 3) were transferable to the German health care context for the following reasons: The population included patients aged 2 to 25 years, and there were no exclusion criteria regarding the severity of scoliosis. The majority of patients were included in North America and Europe and were of Caucasian family origin. The median age at symptom onset for patients with SMA type 3 was about 18 months, which corresponded to SMA type 3, which by definition has a disease onset around 18 months of age. Over 90% of the patient population had more than 2 SMN2 gene copies. Overall, the SMA type 3 population of the SUNFISH study was therefore very comparable to the patient population in the German health care context, according to the company.

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

It should be noted that although a large proportion of the patients with SMA type 3 included in the SUNFISH study were treated in Europe (approximately 80% across arms, see Table 16), a maximum of 4 patients came from Germany (data only available for the total population [45]). Particularly against the background that the standards of care also differ within European countries [50], it is not clearly proven by the explanations of the company that the health care context of the patients with SMA type 3 of the SUNFISH study can be transferred to the German health care context. However, with regard to the provision of supportive measures, it is assumed that the international treatment recommendations [37,38] were largely implemented in the participating study countries (see text on the implementation of the ACT on p. 41). The subgroup analyses presented by the company (see Module 4 A, p. 118 ff.) are also not suitable for an approximation to the question of the health care context due to the small number of patients in the investigated subpopulation. Due to the differences in the care of SMA patients within Europe (see above), the division of the subgroup characteristic "region" (Europe/rest of the world) presented by the company is not a suitable operationalization.

2.5.2 Results of the study included by the company

2.5.2.1 Patient-relevant outcomes

The following patient-relevant outcomes were to be presented for the SUNFISH study included by the company:

- Mortality
- Morbidity
  - gross and fine motor skills using the MFM-32 instrument

- motor function of the upper extremities using the RULM instrument
- motor functioning using the HFMSE instrument
- health status (EQ-5D VAS)

- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

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

Table 18 shows for which outcomes data are available.

Table 18: Matrix of outcomes, SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study	Outcomes								
	All-cause mortality[a]	**Gross and fine motor skills (MFM-32)**	**Motor function of the upper extremities (RULM)**	**Motor functioning (HFMSE)**	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Skin and subcutaneous tissue disorders (SOC, AEs)**
SUNFISH	Yes	Yes	Yes	Yes	Yes[b]	No[c]	No[d]	Yes	Yes

a. The SUNSHINE study recorded deaths as part of the AE recording.
b. Completed by patients ≥ 12 years of age.
c. Outcome not recorded.
d. Relevant proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. oxygen saturation decreased, sleep apnoea syndrome; see Table 28 of the full dossier assessment); the additional analyses submitted by the company excluding events attributable to the underlying diseases are not usable (see running text).

AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HFMSE: Hammersmith Functional Motor Scale Expanded; MFM-32: Motor Function Measure – 32 items; RCT: randomized controlled trial; RULM: Revised Upper Limb Module; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; VAS: visual analogue scale

Morbidity

Motor function

MFM-32 (gross and fine motor skills)

The MFM-32 examines motor function specifically in patients with neuromuscular diseases including SMA [51-53]. The instrument includes 32 test items that assess physical function in 3 domains (D1: standing, transfers, ambulation; D2: axial and proximal motor function; D3: distal motor function of the extremities). The test items are each rated on a 4-point Likert scale (0: The task cannot be initiated or the starting position cannot be maintained; 1: The task is partially performed; 2: The task is performed incompletely or incorrectly [with compensatory/uncontrolled movements or only very slowly]; 3: The task is performed completely and "normally"). The scores are summed and then transformed to a scale of 0 to 100, with higher scores indicating better motor skills. The recording in the SUNFISH study took place every 4 months in the first year and every six months in the second year.

In the dossier, the company presented results for the total score in the form of mean differences (referred to by the company as the main analysis) and responder analyses (patients with an improvement in the MFM-32-total score of ≥ 3 or ≥ 0 points; referred to by the company as supplementary analyses). The company presented no analyses for the individual domains. Their supplementary analysis might enable a more differentiated assessment, since some test items, especially of domain D1, require the ability to walk in order to be successfully completed [51] and the SUNFISH study only included non-ambulatory patients.

The benefit assessment presents the results for the total score in the form of the mean differences. The responder analyses presented by the company are not shown, as the response criteria chosen by the company are not face valid due to the high complexity of the instrument. In addition, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range) [1,54], which is not the case for the response criteria mentioned.

HFMSE (motor functioning)

The HFMSE can be used to assess motor skills in patients with SMA types 2 and 3 from the age of 2 years. The instrument includes 33 test items and operationalizes mainly gross motor functions (transitions relating to lying, crawling, standing up from kneeling, standing, walking and jumping) [55-58]. For this purpose, 13 test items were added to the original scale (HFMS) with 20 test items to enable the assessment of ambulatory SMA patients [58,59]. The test items are each scored on a 3-point scale (0: unable to perform, 1: performs with assistance, 2: performs without assistance), resulting in a maximum score of 66. Higher values mean better motor functioning. The recording in the SUNFISH study took place every 4 months in the first year and every six months in the second year.

In the dossier, the company presented results in the form of mean differences (referred to by the company as the main analysis) and responder analyses (patients with an improvement in the HFMSE total score of ≥ 2 or ≥ 0 points; referred to by the company as supplementary analyses).

The benefit assessment presents the results in the form of the mean differences. The responder analyses presented by the company are not shown, as the response criteria chosen by the company are not face valid due to the high complexity of the instrument and are not in line with the current methodological requirements (see above [1,54]).

RULM (motor function of the upper extremities)

The RULM is an instrument used to assess the motor function of the upper extremities in patients with SMA types 2 and 3 [60,61]. Validity and reliability have been shown. The instrument includes 19 items for testing proximal and distal motor functions of the arms and hands and an entry item for functional class identification. 18 of the 19 test items are scored on a 3-point scale (0: is unable to perform, 1: is able to perform [modified task], 2: is able to perform without difficulty), one test item is scored on a 2-point scale (0: is unable to perform, 1: is able to perform), resulting in a maximum score of 37. A higher total score corresponds to a better functional status. The RULM offers a useful addition to the instruments MFM-32 and HFMSE to specifically examine the functioning of the upper extremities. The recording in the SUNFISH study took place every 4 months in the first year and every six months in the second year.

In the dossier, the company presented results in the form of mean differences (referred to by the company as the main analysis) and responder analyses (referred to by the company as supplementary analyses).

The benefit assessment presents the results in the form of the mean differences. The responder analyses presented by the company (patients with an improvement in MFM-32 total score by ≥ 2 or ≥ 0 points) are not shown, as the response criteria chosen by the company are not face valid due to the high complexity of the instrument and are not in line with the current methodological requirements (see above [1,54]).

Function-related independence

SMA Independence Scale (SMAIS)

With the SMAIS, the company presented another instrument, which, according to its information, was developed specifically for use in patients with SMA types 2 and 3 in order to assess function-related independence. The SMAIS contains 29 test items, assessing the amount of assistance required from another person to perform daily activities (e.g. washing one's hair, putting on clothing, feeding) within the last 7 days. The company assigned the instrument to the outcome category of health-related quality of life.

The instrument is not presented in the benefit assessment. In contrast to what the company described, the SMAIS does not represent health-related quality of life. Scales for recording

health-related quality of life should consider the impact of the disease on mental, physical and social functioning or wellbeing and reflect at least these dimensions [62-64]. The aspects recorded with the SMAIS, however, predominantly ask about the patients' everyday practical skills, which are apparently to be assigned to morbidity. However, several validated instruments were used in the SUNFISH study to record morbidity, which are also presented in the benefit assessment (see above) and which also represent everyday practical skills (e.g. MFM-32 [65]). Furthermore, the company presented no validation in Module 4 A. The SMAIS is therefore not additionally considered.

Side effects

SAEs

Events that are symptoms of the underlying disease or events that can be both side effects and symptoms of the underlying disease were also included in the recording of SAEs (see Table 28 of the full dossier assessment, e.g. oxygen saturation decreased, sleep apnoea syndrome). However, analyses without events attributable to the underlying disease are relevant for the benefit assessment. In Appendix 4-G of the dossier, the company also presented rates excluding events attributable to the underlying diseases (0 versus 4 patients with at least one event excluding disease-related events with a narrow definition, or 0 versus 3 patients excluding disease-related events with a broad definition). However, since it is not clear from the available documents which events were taken into account or excluded in each case, these results cannot be interpreted either. The results on SAEs are therefore not presented.

2.5.2.2 Risk of bias

Table 19 describes the risk of bias for the results of the relevant outcomes.

Table 19: Risk of bias across outcomes and outcome-specific risk of bias, SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study	Study level	Outcomes								
		All-cause mortality	Gross and fine motor skills (MFM-32)	Motor function of the upper extremities (RULM)	Motor functioning (HFMSE)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Skin and subcutaneous tissue disorders (SOC, AEs)
SUNFISH	L	L	L	L	L	L	–[a]	–[b]	L	L

a. Outcome not recorded.
b. Relevant proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. oxygen saturation decreased, sleep apnoea syndrome) (see Table 28 of the full dossier assessment, as well as Section 2.5.2.1).

AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HFMSE: Hammersmith Functional Motor Scale Expanded; L: low; MFM-32: Motor Function Measure – 32 items; RCT: randomized controlled trial; RULM: Revised Upper Limb Module; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias was rated as low for the results of the following outcomes: overall survival, health status (EQ-5D VAS), fine and gross motor function skills (MFM-32), motor function of the upper extremities (RULM), motor functioning (HFMSE), discontinuation due to AEs and specific AE "skin and subcutaneous tissue disorders" (SOC, AEs). This deviates from the assessment of the company, which rated the risk of bias as low for all results in the outcome category of side effects in general.

Events that are symptoms of the underlying disease or events that can be both side effects and symptoms of the underlying disease were also included to a large extent in the recording of SAEs. Therefore, the results are not interpretable (see Section 2.5.2.1) and the risk of bias was not assessed.

2.5.2.3 Results

Table 20 and Table 21 summarize the results of the comparison of risdiplam + BSC with placebo + BSC in patients with SMA type 3. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables with common AEs, SAEs, as well as discontinuations due to AEs can be found in Appendix C.1 of the full dossier assessment.

Table 20: Results (mortality, side effects), SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study Outcome category Outcome	Risdiplam + BSC		Placebo + BSC		Risdiplam + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
SUNFISH (data cut-off 6 September 2019[a])					
Mortality					
All-cause mortality[b]	36	0 (0)	16	0 (0)	–
Side effects					
AEs (supplementary information)	36	33 (91.7)	16	15 (93.8)	–
SAEs	No usable data[c]				
Discontinuation due to AEs	36	0 (0)	16	0 (0)	–
Skin and subcutaneous tissue disorders (SOC, AEs)	36	8 (22.2)	16	0 (0)	–; 0.044[d]

a. The first 12 months of randomized treatment were included in the analysis for each patient.
b. Operationalized using the grade 5 AEs (AEs leading to death) that occurred in the study.
c. Relevant proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. oxygen saturation decreased, sleep apnoea syndrome; see Table 28 of the full dossier assessment, as well as Section 2.5.2.1).
d. Institute's calculation (unconditional exact test [CSZ method according to [66]]). No presentation of effect estimation and CIs, as these are not informative.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class

Table 21: Results (morbidity), SUNFISH study – RCT, direct comparison: risdiplam + BSC vs. placebo + BSC (SMA type 3)

Study Outcome category Outcome	Risdiplam + BSC			Placebo + BSC			Risdiplam + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SD)	MD [95% CI]; p-value[b]
SUNFISH (data cut-off 6 September 2019[c])							
Morbidity							
Gross and fine motor skills (MFM-32)[d, e]	35	54.4 (9.6)	0.9 (0.5)	14	55.1 (9.6)	-0.6 (0.7)	1.48 [-0.29; 3.24]; ND
Motor function of the upper extremities (RULM)[f]	34	25.6 (6.6)	1.7 (0.4)	15	25.3 (7.1)	-0.5 (0.6)	2.19 [0.71; 3.67]; ND Hedges' g: 0.91 [0.28; 1.53]
Motor functioning (HFMSE)[g]	34	25.5 (12.8)	0.2 (0.6)	15	24.8 (13.5)	-0.7 (0.9)	0.89 [-1.30; 3.07]; ND
Health status (EQ-5D VAS)[h, i]	21	74.5 (20.9)	4.3 (2.8)	8	72.5 (22.2)	2.1 (4.3)	2.17 [-8.33; 12.66]; ND
Health-related quality of life	Outcome not recorded						

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. MMRM with age (stratification variable), baseline value, visit as independent variables, and interaction between treatment and visit as well as baseline value and visit.
c. The first 12 months of randomized treatment were included in the analysis for each patient.
d. Higher values indicate better motor skills; positive effects (risdiplam minus placebo) indicate an advantage for risdiplam. Scale range: 0 to 100 points. The company presented no separate analyses for the individual domains D1, D2, D3 (see also Section 2.5.2.1).
e. Effect estimation according to "treatment policy estimand" (main analysis of the company): Analyses based on this estimand ignore the occurrence of intercurrent events, in this case the use of prohibited concomitant medication (affects 1 patient treated with nusinersen in the study [29]). The analysis excluding this patient ("hypothetical strategy estimand") does not differ from the main analysis of the company.
f. Higher values indicate better motor functioning; positive effects (risdiplam minus placebo) indicate an advantage for the intervention. Scale range: 0 to 37 points.
g. Higher values indicate better motor functioning; positive effects (risdiplam minus placebo) indicate an advantage for the intervention. Scale range: 0 to 66 points.
h. Completed by patients ≥ 12 years of age. Higher values indicate better health status; positive effects (risdiplam minus placebo) indicate an advantage for risdiplam. Scale range: 0 to 100 points.
i. The responder analyses on the EQ-5D VAS with a response criterion of 10 points provided by the company are presented as supplementary information in Appendix C.2 of the full dossier assessment.

BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HFMSE: Hammersmith Functional Motor Scale Expanded; MD: mean difference; MFM-32: Motor Function Measure – 32 items; MMRM: mixed-effects model with repeated measures; ND: no data; RCT: randomized controlled trial; RULM: Revised Upper Limb Module; SD: standard deviation; SMA: spinal muscular atrophy; VAS: visual analogue scale

The results of the SUNFISH study included by the company are presented below for the subpopulation with SMA type 3. There is a low risk of bias for all usable results (see Table 17).

Mortality

In the subpopulation with SMA type 3, no deaths occurred until month 12.

Morbidity

Gross and fine motor skills (MFM-32)

In the subpopulation with SMA type 3, there was no statistically significant difference between the treatment groups at month 12 for the mean change of the outcome "gross and fine motor skills" measured by the MFM-32 instrument.

Motor function of the upper extremities (RULM)

For the mean change in the outcome "motor function of the upper extremities" measured by the RULM instrument, there was a statistically significant difference at month 12 in favour of risdiplam + BSC against placebo + BSC in the subpopulation with SMA type 3. The standardized mean difference in the form of Hedges' g was considered to assess the relevance of the results. The 95% confidence interval was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect.

Motor functioning (HFMSE)

In the subpopulation with SMA type 3, there was no statistically significant difference between the treatment groups at month 12 for the mean change of the outcome "motor functioning" measured by the HFMSE instrument.

Health status (EQ-5D VAS)

The VAS was only completed by patients ≥ 12 years of age. In the subpopulation with SMA type 3, there was no statistically significant difference between the treatment groups at month 12 for the mean change of the outcome "health status" measured by the EQ-5D VAS.

Health-related quality of life

Health-related quality of life outcomes were not recorded in the SUNFISH study (see Section 2.5.2.1).

Side effects

SAEs

The results on SAEs cannot be interpreted because events that are symptoms of the underlying disease or events that can be both side effects and symptoms of the underlying disease were also included in the recording of SAEs (see Section 2.5.2.1).

Discontinuation due to AEs

In the subpopulation with SMA type 3, no discontinuations due to AEs occurred until month 12.

Skin and subcutaneous tissue disorders (SOC, AEs)

For the specific AE "skin and subcutaneous tissue disorders" (SOC, AEs), there was a statistically significant difference at month 12 to the disadvantage of risdiplam + BSC against placebo + BSC in the subpopulation with SMA type 3.

2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were to be considered for the presentation of the results of the SUNFISH study:

- age of patients at screening (2 to 5 years/6 to 11 years/12 to 17 years/18 to 25 years)
- sex (female/male)
- history of scoliosis surgery or hip surgery (yes/no)
- SMN2 gene copy number (1/2/3/4 gene copies)

The results for the subgroup characteristics of age and SMN2 gene copy number are not usable overall, as not all subgroups contain > 10 patients. With regard to the subgroup characteristic of age, pooling also does not appear meaningful due to the age-dependent high variability of the clinical manifestations. This is also the opinion of the company. Irrespective of this, it is also not possible to pool subgroups within the framework of the benefit assessment, as results were not available for all subgroups.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

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

The company presented subgroup analyses and interaction tests for all relevant outcomes with the exception of the outcome "EQ-5D VAS". For this outcome, the company did not present any subgroup analyses for the operationalization presented in the present benefit assessment (mean change at week 52).

In accordance with the methods described, no relevant effect modification was identified for the available outcomes.

2.5.2.5 Summary

The SUNFISH study presented by the company is unsuitable for the derivation of conclusions on the added benefit of risdiplam in comparison with the ACT for the subpopulation with SMA type 3. This is due to the fact that the ACT specified by the G-BA (treatment of physician's choice choosing from nusinersen or BSC) was not implemented in the SUNFISH study (see

text on the implementation of the ACT on p. 41). Nevertheless, the results of the SUNFISH study for the subpopulation with SMA type 3 are presented as supplementary information. A conclusion on the added benefit based on these data is not derived, however.

2.5.3 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of risdiplam compared with the ACT (treatment of physician's choice choosing from nusinersen or BSC) in patients with SMA type 3. An added benefit is therefore not proven. This deviates from the assessment of the company, which derived proof of a minor added benefit on the basis of the subpopulation of the SUNFISH study with SMA type 3.

2.6 Research question 4: pre-symptomatic patients

2.6.1 Information retrieval and study pool

The G-BA's specification of the ACT resulted in 2 different patient populations for the pre-symptomatic SMA patients 2 months of age and older, depending on the number of SMN2 gene copies present (see Table 4). These are described together below.

The company did not consider the research question of pre-symptomatic SMA patients with one to 4 SMN2 gene copies in its dossier. In Module 4 A, Section 4.2.1, referring to a publication by Calucho 2018 [67] it pointed out that the presence of one to 4 SMN2 gene copies usually has a clinical manifestation as SMA type 1, type 2 or type 3. This interpretation of the approved therapeutic indication of risdiplam is not followed. The current approval also covers patients 2 months of age and older with one to 4 SMN2 gene copies and a genetic diagnosis only, i.e. without clinical symptoms [29,36].

For the benefit assessment, the completeness of the study pool was checked using a trial registry search for risdiplam (last search on 4 May 2021, see Appendix A of the full dossier assessment for search strategies). One potentially relevant study was identified in the course of the trial registry search. This was the single-arm RAINBOWFISH study [29,68,69] in pre-symptomatic patients with genetically confirmed SMA who were < 6 weeks old at baseline (day 1 of treatment). The study is ongoing and the end of the study is planned for 2026, according to the company [44]. As there are currently no results for pre-symptomatic patients, the company's lack of consideration of this research question 4 has no consequences for the benefit assessment.

2.6.2 Results on added benefit

No data are available for the assessment of the added benefit of risdiplam in comparison with the ACT (depending on the number of SMN2 gene copies, nusinersen or treatment of physician's choice, see Table 4) in pre-symptomatic patients. Hence, there is no hint of an added benefit of risdiplam in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

No data are available for the assessment of the added benefit of risdiplam compared with the ACT nusinersen in pre-symptomatic patients. An added benefit is therefore not proven. This deviates from the assessment of the company insofar as the company did not consider pre-symptomatic patients in its assessment at all.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of risdiplam in comparison with the ACT is summarized in Table 22.

Table 22: Risdiplam – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
	Patients with 5q SMA, 2 months of age and older, with		
1	SMA type 1	Nusinersen	Hint of non-quantifiable added benefit[b]
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA, 2 months of age and older, with		
4a	1 to 3 SMN2 gene copies	Nusinersen	Added benefit not proven
4b	4 SMN2 gene copies	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. The results of the comparison presented using individual arms of different studies suggest that risdiplam is at least not inferior to nusinersen. The added benefit of risdiplam in the present situation results from its oral form of administration and a high probability of morbidity associated with intrathecal administration of nusinersen (see Section 2.3.4). Only data on patients with 2 SMN2 gene copies are available.
c. According to the G-BA's note, a single-comparator study is generally not sufficient for patients with this ACT.
d. 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. Various measures, including e.g. physiotherapy according to the catalogue of remedies (catalogue of prescribable remedies according to §92 (6) SGB V as the second part of the guideline on the prescription of remedies in contracted doctor care), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary. Furthermore, it is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. In pre-symptomatic patients 2 months of age and older with 5q SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

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

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Wirth B, Karakaya M, Kye MJ et al. Twenty-five years of spinal muscular atrophy research: From phenotype to genotype to therapy, and what comes next. Annu Rev Genomics Hum Genet 2020; 21. https://dx.doi.org/10.1146/annurev-genom-102319103602.

4. Chen TH. New and Developing Therapies in Spinal Muscular Atrophy: From Genotype to Phenotype to Treatment and Where Do We Stand? Int J Mol Sci 2020; 21(9): 3297. https://dx.doi.org/10.3390/ijms21093297.

5. Verhaart IEC, Robertson A, Wilson IJ et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis 2017; 12(1): 124. https://dx.doi.org/10.1186/s13023-017-0671-8.

6. Wang CH, Finkel RS, Bertini ES et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 2007; 22(8): 1027-1049. https://dx.doi.org/10.1177/0883073807305788.

7. Glascock J, Sampson J, Connolly AM et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis 2020; 7(2): 97-100. https://dx.doi.org/10.3233/JND-190468.

8. Glascock J, Sampson J, Haidet-Phillips A et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis 2018; 5(2): 145-158. https://dx.doi.org/10.3233/JND-180304.

9. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Kinder-Richtlinie: Neugeborenen-Screening auf 5q-assoziierte spinale Muskelatrophie (SMA) [online]. 2020 [Accessed: 28.06.2021]. URL: https://www.g-ba.de/downloads/40-268-7155/2020-12-17_Kinder-RL_SMA_TrG.pdf.

10. Gemeinsamer Bundesausschuss. Heilmittel-Richtlinie - Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (HeilM-RL) [online]. 2021 [Accessed: 15.02.2021]. URL: https://www.g-ba.de/downloads/62-492-2324/HeilM-RL_2020-10-15_iK-2021-01-01.pdf.

11. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Risdiplam (5q-assoziierte spinale Muskelatrophie (SMA)); zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/680/#zweckmaessige-vergleichstherapie].

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nusinersen (spinale Muskelatrophie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-114_nusinersen_nutzenbewertung-35a-sgb-v_v1-0.pdf.

13. Biogen Idec Research. An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443 [online]. [Accessed: 25.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001870-16.

14. Biogen. A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies [online]. 2020 [Accessed: 25.01.2021]. URL: https://ClinicalTrials.gov/show/NCT02594124.

15. Biogen. A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA). (EMBRACE) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02462759.

16. Acsadi G, Crawford TO, Muller-Felber W et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. Muscle Nerve 2021; 63(5): 668-677. https://dx.doi.org/10.1002/mus.27187.

17. Biogen. A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT01839656.

18. Ionis Pharmaceuticals. A Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Patients With Infantile-Onset Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000621-12.

19. Finkel RS, Chiriboga CA, Vajsar J et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen. Lancet 2016; 388(10063): 3017-3026. https://dx.doi.org/10.1016/S0140-6736(16)31408-8.

20. Sergott RC, Amorelli GM, Baranello G et al. Risdiplam treatment has not led to retinal toxicity in patients with spinal muscular atrophy. Ann Clin Transl Neurol 2021; 8(1): 54-65. https://dx.doi.org/10.1002/acn3.51239.

21. Hoffmann-La Roche. A Study of Risdiplam (RO7034067) in Adult and Pediatric Participants With Spinal Muscular Atrophy (Jewelfish) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT03032172.

22. F. Hoffmann-La Roche. An Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of RO7034067 in Adult and Pediatric Patients with Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004184-39.

23. Biogen. Spinraza 12 mg Injektionslösung [online]. 2021 [Accessed: 09.06.2021]. URL: https://www.fachinfo.de.

24. Biogen. Nusinersen (Spinraza); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 16.03.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/625/#dossier.

25. Biogen. Nusinersen (Spinraza): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2017 [Accessed: 27.10.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/298/#tab/dossier.

26. Roche. A Two Part Seamless, Open-label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Infants With Type 1 Spinal Muscular Atrophy; Report No. 1100385; study BP39056 (FIREFISH); Primary Clinical Study Report [unpublished]. 2020.

27. Hoffmann-La Roche. Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type1 Spinal Muscular Atrophy (FIREFISH) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02913482.

28. F. Hoffmann-La Roche. A Two Part Seamless, Open-Label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Infants with Type1 Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000778-40.

29. European Medicines Agency. Evrysdi; Assessment report [online]. 2021 [Accessed: 06.05.2021]. URL: https://www.ema.europa.eu/documents/assessment-report/evrysdi-epar-public-assessment-report_en.pdf.

30. Baranello G, Darras BT, Day JW et al. Risdiplam in Type 1 Spinal Muscular Atrophy. N Engl J Med 2021; 384(10): 915-923. https://dx.doi.org/10.1056/NEJMoa2009965.

31. Biogen. A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02193074.

32. Isis Pharmaceuticals. A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004422-29.

33. Finkel RS, Mercuri E, Darras BT et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med 2017; 377(18): 1723-1732. https://dx.doi.org/10.1056/NEJMoa1702752.

34. Food and Drug Administration. Evrysdi; Clinical Review(s) [online]. 2020 [Accessed: 11.05.2021]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000MedR.pdf.

35. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

36. Roche. Evrysdi 0,75 mg/ml Pulver zur Herstellung einer Lösung zum Einnehmen [online]. 2021 [Accessed: 03.05.2021]. URL: https://www.fachinfo.de.

37. Finkel RS, Mercuri E, Meyer OH et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord 2018; 28(3): 197-207. https://dx.doi.org/10.1016/j.nmd.2017.11.004.

38. Mercuri E, Finkel RS, Muntoni F et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018; 28(2): 103-115. https://dx.doi.org/10.1016/j.nmd.2017.11.005.

39. Bertini E, Burghes AH, Bushby K et al. 134th ENMC International Workshop: Outcome Measures and Treatment of Spinal Muscular Atrophy, 11–13 February 2005, Naarden, The Netherlands. Neuromuscul Disord 2005; 15(11): 802-816. https://dx.doi.org/10.1016/j.nmd.2005.07.005

40. Biogen. A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) (CHERISH) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02292537.

41. Mercuri E, Darras BT, Chiriboga CA et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018; 378(7): 625-635. https://dx.doi.org/10.1056/NEJMoa1710504.

42. Ionis Pharmaceuticals. A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Later-onset Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001947-18.

43. Roche. A Two-Part Seamless, Multi-center Randomized, Placebo-controlled, Double-blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Type 2 and 3 Spinal Muscular Atrophy Patients; Report No. 1099250; study BP39055 (SUNFISH); Primary Clinical Study Report [unpublished]. 2020.

44. Hoffmann-La Roche. A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal

Muscular Atrophy (SMA) Participants (SUNFISH) [online]. 2020 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02908685.

45. F. Hoffmann-La Roche. A two-part seamless, multi-center randomized, placebo-controlled, double blind study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in type 2 and 3 spinal muscular atrophy patients [online]. [Accessed: 28.05,2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000750-35.

46. Walter MC, Schoser B. Neue Therapien der spinalen Muskelatrophie. Aktuelle Neurologie 2018; 45(08): 617-624. https://dx.doi.org/10.1055/a-0642-1775.

47. Stolte B, Totzeck A, Kizina K et al. Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy. Ther Adv Neurol Disord 2018; 11: 1756286418803246. https://dx.doi.org/10.1177/1756286418803246.

48. Walter MC, Stauber AJ. Spinale Muskelatrophien: Klinik und Therapie. Fortschr Neurol Psychiatr 2018; 86(9): 543-550. https://dx.doi.org/10.1055/a-0621-9139.

49. D'Amico A, Mercuri E, Tiziano FD et al. Spinal muscular atrophy. Orphanet J Rare Dis 2011; 6: 71. https://dx.doi.org/10.1186/1750-1172-6-71.

50. Bladen CL, Thompson R, Jackson JM et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol 2014; 261(1): 152-163. https://dx.doi.org/10.1007/s00415-013-7154-1.

51. Bérard C, Payan C, Hodgkinson I et al. A motor function measure for neuromuscular diseases. Construction and validation study. Neuromuscul Disord 2005; 15(7): 463-470. https://dx.doi.org/10.1016/j.nmd.2005.03.004.

52. Trundell D, Le Scouiller S, Gorni K et al. Validity and Reliability of the 32-Item Motor Function Measure in 2- to 5-Year-Olds with Neuromuscular Disorders and 2- to 25-Year-Olds with Spinal Muscular Atrophy. Neurol Ther 2020; 9(2): 575-584. https://dx.doi.org/10.1007/s40120-020-00206-3.

53. Trundell D, Le Scouiller S, Le Goff L et al. Assessment of the validity and reliability of the 32-item Motor Function Measure in individuals with Type 2 or non-ambulant Type 3 spinal muscular atrophy. PLoS One 2020; 15(9): e0238786. https://dx.doi.org/10.1371/journal.pone.0238786.

54. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

55. Finkel R, Bertini E, Muntoni F et al. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord 2015; 25(7): 593-602. https://dx.doi.org/10.1016/j.nmd.2015.04.009.

56. Glanzman AM, O'Hagen JM, McDermott MP et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol 2011; 26(12): 1499-1507. https://dx.doi.org/10.1177/0883073811420294.

57. Mazzone E, Sanctis R, Fanelli L et al. Hammersmith Functional Motor Scale and Motor Function Measure-20 in non ambulant SMA patients. Neuromuscul Disord 2014; 24(4): 347-352. https://dx.doi.org/10.1016/j.nmd.2014.01.003.

58. O'Hagen JM, Glanzman AM, McDermott MP et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord 2007; 17(9-10): 693-697. https://dx.doi.org/10.1016/j.nmd.2007.05.009.

59. Cano SJ, Mayhew A, Glanzman AM et al. Rasch analysis of clinical outcome measures in spinal muscular atrophy. Muscle Nerve 2014; 49(3): 422-430. https://dx.doi.org/10.1002/mus.23937.

60. Mazzone ES, Mayhew A, Montes J et al. Revised upper limb module for spinal muscular atrophy. Muscle Nerve 2017; 55(6): 869-874. https://dx.doi.org/10.1002/mus.25430.

61. Mazzone E, Bianco F, Martinelli D et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. Neuromuscul Disord 2011; 21(6): 406-412. https://dx.doi.org/10.1016/j.nmd.2011.02.014.

62. European Medicines Agency. Reflection paper on the regulatory guidance for the use of Health Related Quality of Life (HRQL) measures in the evaluation of medicinal products [online]. 2005 [Accessed: 20.11.2019]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf.

63. Food and Drug Administration. Guidance for industry; patient-reported outcome measures: use in medical product development to support labeling claims [online]. 2009 [Accessed: 20.11.2019]. URL: https://www.fda.gov/media/77832/download.

64. World Health Organization. Constitution [online]. 2021 [Accessed: 01.07.2021]. URL: https://www.who.int/about/governance/constitution.

65. Duong T, Braid J, Staunton H et al. Understanding the relationship between the 32-item motor function measure and daily activities from an individual with spinal muscular atrophy and their caregivers' perspective: a two-part study. BMC Neurol 2021; 21(1): 143. https://dx.doi.org/10.1186/s12883-021-02166-z.

66. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

67. Calucho M, Bernal S, Alias L et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord 2018; 28(3): 208-215. https://dx.doi.org/10.1016/j.nmd.2018.01.003.

68. F. Hoffmann-La Roche. An Open-Label Study of Risdiplam in Infants with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy [online]. [Accessed: 28.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002087-12.

69. Hoffmann-La Roche. A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (Rainbowfish) [online]. 2021 [Accessed: 28.05.2021]. URL: https://ClinicalTrials.gov/show/NCT03779334.

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