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Nusinersen (spinal muscular atrophy) –

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

Extract

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Table of contents

Page

List of tables ..... **v**
List of abbreviations ..... **vii**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **13**
2.3 Research question 1: patients with early onset of disease (SMA type 1) **15**
2.3.1 Information retrieval and study pool 15
2.3.1.1 Studies included 16
2.3.1.2 Study characteristics 19
2.3.2 Results on added benefit 27
2.3.2.1 Outcomes included 27
2.3.2.2 Risk of bias 31
2.3.2.3 Results 32
2.3.2.4 Subgroups and other effect modifiers 37
2.3.3 Probability and extent of added benefit 41
2.3.3.1 Assessment of the added benefit at outcome level 41
2.3.3.2 Overall conclusion on added benefit 44
2.4 Research question 2: patients with later onset of disease (SMA type 2, type 3, type 4) **45**
2.4.1 Information retrieval and study pool 45
2.4.1.1 Indirect comparison based on RCTs 46
2.4.1.1.1 Study CHERISH 47
2.4.1.1.2 Meta-analyses of the studies CHERISH and EMBRACE 49
2.4.1.1.3 Study EMBRACE 50
2.4.1.2 Further investigations 50
2.4.1.2.1 Registry analysis (SMA type 3 and type 4) 50
2.4.1.2.2 Comparison of individual arms of different studies 56
2.4.2 Results on added benefit 56
2.4.3 Probability and extent of added benefit 57
2.5 Research question 3: pre-symptomatic patients **57**
2.5.1 Information retrieval and study pool 57
2.5.1.1 Studies included 58
2.5.2 Results on added benefit 62

2.5.3 Probability and extent of added benefit 64
2.6 Probability and extent of added benefit – summary 65
References for English extract 66

List of tables[2]

Page

Table 2: Research questions of the benefit assessment of nusinersen 1
Table 3: Overview of the data presented by the company 2
Table 4: Nusinersen – probability and extent of added benefit..... 12
Table 5: Research questions of the benefit assessment of nusinersen 13
Table 6: Overview of the data presented by the company 14
Table 7: Study pool – RCT, direct comparison: nusinersen vs. BSC, patients with early onset of disease (SMA type 1)..... 16
Table 8: Characteristics of the included ENDEAR study – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 20
Table 9: Characteristics of the intervention, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 21
Table 10: Characteristics of the study population, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 25
Table 11: Risk of bias across outcomes (study level), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 27
Table 12: Matrix of outcomes, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) ... 28
Table 13: Risk of bias across outcomes and outcome-specific risk of bias, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 31
Table 14: Results (mortality, morbidity, side effects, time to event), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)..... 33
Table 15: Results (morbidity, dichotomous), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 34
Table 16: Subgroups (mortality, morbidity, side effects), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) 38
Table 17: Extent of added benefit at outcome level, study ENDEAR: nusinersen + BSC vs. sham intervention + BSC 42
Table 18: Positive and negative effects from the assessment of nusinersen in comparison with BSC; study ENDEAR..... 44

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

Table 19: Characteristics of the populations included by the company – registry data: nusinersen vs. comparator group without treatment with SMA drug therapy – patients with SMA type 3 53
Table 20: Characteristics of the NURTURE study 59
Table 21: Characteristics of the intervention in the NURTURE study 60
Table 22: Characteristics of the study population – comparison: nusinersen + BSC, study NURTURE (pre-symptomatic) vs. nusinersen + BSC, study ENDEAR (early symptomatic start of therapy) in patients with 2 SMN2 copies 62
Table 23: Results (outcome categories, time to event) – comparison: nusinersen + BSC, study NURTURE (pre-symptomatic) vs. nusinersen + BSC, study ENDEAR (early symptomatic start of therapy [disease duration ≤ 12 weeks]) in patients with 2 SMN2 gene copies 63
Table 24: Nusinersen – probability and extent of added benefit 65

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CSF	cerebrospinal fluid
ECG	electrocardiogram
EMA	European Medicines Agency
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)
iSMAC	international SMA consortium
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
WHO	World Health Organization

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 nusinersen. 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 2 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of nusinersen in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with 5q spinal muscular atrophy (SMA).

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. However, overlaps between different types are observed in the context of improved supportive interventions as well as the development of specific treatment options. The different types of SMA should therefore be seen as a continuum rather than as clearly distinguishable types. In the therapeutic indication, patients with early onset of disease (infantile SMA, SMA type 1) can nonetheless be clearly distinguished from those with later onset of disease (SMA types 2, 3 and 4). Early onset of disease is defined as symptom onset at < 6 months of age. The group of patients with pre-symptomatic diagnosis during newborn screening for 5q SMA represents an additional important patient population. For the benefit assessment, this results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of nusinersen

Research question	Subindication	ACT[a]
1	Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	BSC[b]
2	Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)	
3	Pre-symptomatic patients with 5q SMA	

a. Presentation of the ACT specified by the G-BA.
b. 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. In addition, it is assumed that BSC is implemented in both study arms. In patients with pre-symptomatic SMA, BSC also includes watchful waiting.

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

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 early onset of disease (SMA type 1)
- Research question 2: patients with later onset of disease (SMA type 2, type 3 and type 4)
- Research question 3: pre-symptomatic patients

The company followed the G-BA in the specification of the ACT.

In its dossier, the company also differentiated between the patient populations according to research questions 1 to 3 in Table 2. In the present benefit assessment, a differentiation within research question 2 (patients with later onset of disease) is made, as far as possible, between SMA type 2, type 3 and type 4.

Table 3 shows an overview of the data presented by the company for the 3 research questions.

Table 3: Overview of the data presented by the company (multipage table)

Research question	**Subindication**	**Data presented by the company[a]**
1	Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	▪ RCT: nusinersen vs. BSC ▫ study ENDEAR ▫ study EMBRACE[b] ▫ meta-analysis of the studies ENDEAR and EMBRACE[c]
2	Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)	▪ RCT: nusinersen vs. BSC ▫ study CHERISH ▫ study EMBRACE[b] ▫ meta-analysis of the studies CHERISH and EMBRACE[c]
		▪ Registry analysis: nusinersen vs. no SMA drug therapy ▫ nusinersen: registries SMArtCARE, ISMAR (part Italy) and CuidAME ▫ no SMA drug therapy: registries ISMAR (part Italy) and CuidAME
		▪ Comparison of individual arms from different studies: nusinersen vs. “natural history cohort” ▫ nusinersen: Study CS12 ▫ “natural history cohort”: study Montes 2018
3	Pre-symptomatic patients with 5q SMA	▪ NURTURE (single-arm, nusinersen)
		▪ Comparison of individual arms from different studies ▫ nusinersen: study NURTURE ▫ BSC: study ENDEAR

Table 3: Overview of the data presented by the company (multipage table)

Research question	Subindication	Data presented by the company[a]
a. The company presented data from the ongoing long-term SHINE study in the context of an additional research question investigated by the company to compare "early vs. late" administration of nusinersen. In the SHINE study, patients who were previously treated in the studies ENDEAR, CHERISH, EMBRACE, CS12 and CS3A receive continued treatment with nusinersen (early nusinersen administration) or first-time treatment with nusinersen (late nusinersen administration). The comparison is not relevant for the benefit assessment. b. Subpopulation potentially relevant, no adequate analysis available. c. For individual outcomes. BSC: best supportive care; RCT: randomized controlled trial; SMA: spinal muscular atrophy		

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum treatment period of 12 months is required.

Results for research question 1: patients with early onset of disease (SMA type 1)

Study pool

The study pool for the benefit assessment of nusinersen in patients with early onset of disease (SMA type 1) consists of the ISIS 396443-CS3B study (hereinafter referred to as "ENDEAR" study) and the 232SM202 study (hereinafter referred to as "EMBRACE" study).

For research question 1, however, only the ENDEAR study is used to derive the added benefit. For the EMBRACE study, no suitable data are available for the benefit assessment.

No suitable data for the EMBRACE study

The EMBRACE study is a randomized, double-blind phase 2 study that included patients with genetic documentation of 5q SMA. The patients were randomly assigned in a 2:1 ratio to treatment with nusinersen (N = 14) or treatment with a sham intervention (N = 7). Overall, it is assumed that the patients in both study arms received treatment in accordance with BSC.

According to the inclusion criteria, the EMBRACE study included both patients with early onset of disease (SMA type 1, symptom onset at ≤ 6 months of age) and patients with later onset of disease (age at symptom onset > 6 and ≤ 18 months).

Primary outcomes of the study were side effect outcomes, change from baseline in laboratory parameters, electrocardiogram (ECG), and vital signs, as well as in neurological examination outcomes.

The company presented results of the total population of the EMBRACE study and, in addition, meta-analyses of subpopulations of the EMBRACE study with the total population of the ENDEAR study.

The total population is neither relevant for research question 1 nor for research question 2 of the benefit assessment because, using the criterion of age at symptom onset, the EMBRACE

study included both patients with early onset of disease (SMA type 1) and patients with later onset of disease.

The subpopulation of patients with early onset of disease (SMA type 1), which is in principle relevant for research question 1, comprises 9 children in the nusinersen arm and 4 children in the sham intervention arm. The company presented no analyses for this subpopulation.

The 2 meta-analyses of the ENDEAR study and individual patients of the EMBRACE study with SMA type 1 presented by the company are not relevant for the present benefit assessment, as the patients of the EMBRACE study considered by the company in both meta-analyses differ notably from patients of the ENDEAR study with regard to age at baseline. A meta-analytical summary of these patients is therefore not meaningful.

Study characteristics of the included ENDEAR study

The ENDEAR study is a randomized, double-blind, parallel-group study in which patients with genetic documentation of 5q SMA were either treated with nusinersen or received a sham intervention, in each case in addition to supportive measures (see below). The age of the included patients was ≤ 7 months at baseline and ≤ 6 months at symptom onset. According to the inclusion criteria, participation in the study was restricted to patients with 2 survival motor neuron (SMN)2 gene copies.

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 Section 2 of the Hammersmith Infant Neurological Examination (HINE). Other patient-relevant outcomes were overall survival, serious respiratory events and adverse event (AE) outcomes.

Patients in the comparator arm received a sham procedure in the form of a needle prick on the lower back (and no lumbar puncture) at the corresponding time points. The implementation of the ACT BSC was ensured by concrete requirements in the inclusion and exclusion criteria of the study as well as by the possibility to use supportive measures in both study arms at the discretion of the physician.

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low. The risk of bias was rated as low for the results of the following outcomes: overall survival, death or permanent ventilation, motor milestone achievement measured by HINE Section 2, and serious respiratory events. The risk of bias of the outcomes “serious AEs (SAEs)” and “discontinuation due to AEs” was not assessed due to lack of suitability of the data. Based on the available data, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Results

Due to the different observation periods between the treatment arms, analyses of the time to first event were used for the present benefit assessment, unless otherwise stated.

Mortality

- Overall survival

A statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC was shown for the outcome "overall survival". However, there was an effect modification by the characteristic "age at symptom onset" for this outcome. For patients with symptom onset at ≤ 12 weeks of age, there was a statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "overall survival". For patients with symptom onset at > 12 weeks of age, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for these patients for the outcome "overall survival"; an added benefit is therefore not proven.

Morbidity

- Death or permanent ventilation

A statistically significant difference in favour of nusinersen + BSC was shown between the treatment arms for the composite outcome "death or permanent ventilation". However, there were effect modifications by the characteristics of sex and disease duration for this outcome. Both effect modifications in the composite outcome were due to the effect modifications in the included outcome "permanent ventilation". Against this background, no meaningful interpretation of the subgroup results for the composite outcome is possible. Therefore, the components included in the composite outcome (overall survival and permanent ventilation) are considered separately in the derivation of the added benefit.

Permanent ventilation

There was no statistically significant difference between the treatment groups for the outcome "permanent ventilation". In the present data constellation, the effect modification by the characteristic of disease duration was considered for the outcome "permanent ventilation".

For patients with a disease duration of ≤ 12 weeks, there was a statistically significant difference between the treatment groups in favour of nusinersen + BSC in comparison with sham intervention + BSC. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "permanent ventilation". For patients with a disease duration of > 12 weeks, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for these patients for the outcome "permanent ventilation"; an added benefit is therefore not proven.

- Motor milestone achievement (HINE Section 2)

A statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC was shown for the outcome "motor milestone achievement" measured by HINE Section 2. However, there was an effect modification by the characteristic "disease duration".

For patients with a disease duration of ≤ 12 weeks, there was a statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "motor milestone achievement". For patients with a disease duration of > 12 weeks, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "motor milestone achievement"; an added benefit is therefore not proven.

- Serious respiratory events

No statistically significant difference between the treatment arms was shown for the outcome "serious respiratory events". This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the ENDEAR study.

Side effects

- SAEs and discontinuation due to AEs

In the ENDEAR study, events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. System Organ Class [SOC] "respiratory, thoracic and mediastinal disorders") were also included in the recording of SAEs and discontinuations due to AEs. This means that the results on SAEs and discontinuations due to AEs are not usable. For the outcomes "SAEs" and "discontinuation due to AEs", there was therefore no hint of greater or lesser harm from nusinersen + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Results for research question 2: patients with later onset of disease (SMA type 2, type 3, type 4)

The company used 2 RCTs of direct comparison, a registry analysis from 3 different registries, and a comparison of 2 single-arm studies for research question 2 (patients with later onset of disease [SMA type 2, type 3, type 4]). The studies and analyses used by the company are unsuitable for deriving conclusions on the added benefit of nusinersen in comparison with the ACT for the present research question 2.

RCTs CHERISH and EMBRACE

The CHERISH study was not included in the present benefit assessment due to the lack of evidence of an adequate implementation of BSC in accordance with the health care standard in Germany. The nusinersen treatment of the patients, which was not in compliance with the approval and limits the interpretability of the results on AEs, is another limitation of the study.

The EMBRACE study is basically relevant for research question 2, as it investigated a relevant subpopulation, and treatment with nusinersen or BSC was each appropriate in this study. The company's dossier contained no adequate preparation of the results for the relevant subpopulation, however.

Registry analysis (SMA type 3 and type 4)

The company presented a registry analysis from the 3 registries SMArtCARE (German-speaking region), ISMAR (Italy, UK, USA) and CuidAME (Spain). From the ISMAR registry, the company did not use data from UK and the USA, and justified this with a lack of data availability (UK) or an unsuitable health care context (USA). The registry analysis includes 382 patients treated with nusinersen (375 with SMA type 3, 7 with SMA type 4), and 37 patients not treated with SMA drug therapy (34 with SMA type 3, 3 with SMA type 4). This registry analysis is unsuitable for the benefit assessment for several reasons:

- The comparator group had a major disadvantage in terms of demonstrating an improvement in motor skills. This is due, on the one hand, to a clearly different baseline status with regard to the motor skills of the 2 groups and, on the other hand, to the notably shorter observation period of the comparator group.
- The relevant confounders identified by the company were not fully considered in the analysis, while other confounders (not identified as relevant) were added to the analysis.
- For the patient-relevant outcomes used by the company to assess motor function (Hammersmith Functional Motor Scale Expanded [HFMSE], Revised Upper Limb Module [RULM] and 6-minute walking test), there was a high proportion of missing values already at baseline.
- For a suitable registry study, it is necessary to describe basic requirements for the care of SMA patients, derived from the existing health care standard in Germany. The company did not explain what constitutes a different health care standard in the individual countries and what differences arise in each case in comparison with Germany. It therefore remains unclear why the company used the registry data from Italy and Spain, but not those from the USA.
- Irrespective of the relevance of the data from UK for the German health care context, the company did not justify why the data from the ISMAR registry, which is financially supported by the company, cannot be available to the company at least in the form of an aggregated analysis (registry study).

Comparison of individual study arms of the studies CS12 and Montes 2018

Study CS12 is a single-arm study of nusinersen in later-onset SMA. The Montes 2018 study is a joint analysis of 3 prospective natural history studies in the USA, Italy and UK on patients with SMA type 3. This comparison is unsuitable for the benefit assessment for the following reasons in particular:

- The study population of the CS12 study is a selective population of patients who already tolerated nusinersen in preliminary studies and did not discontinue.
- The company only considered some of the confounders that it had identified as relevant confounders in the context of the registry analysis. Moreover, the chosen matching procedure is obviously unsuitable, since there were no sufficiently balanced groups despite matching by age (age of the patients with nusinersen treatment: median of 11 years; age of the comparator group: median of 4 years).
- The company did not take into account the different health care contexts in the countries; moreover, it included data from the USA, which was inconsistent with the registry analysis.

Results for research question 3: pre-symptomatic patients

There are no RCTs of direct comparison between nusinersen and the ACT BSC or a corresponding indirect comparison based on RCTs for pre-symptomatic patients with 5q SMA.

The company presented results of the single-arm NURTURE study with nusinersen in pre-symptomatic patients with 5q SMA for research question 3 of the present benefit assessment. In addition, the company presented a comparison using individual arms of the NURTURE study in pre-symptomatic patients with the sham intervention arm (hereinafter referred to as "BSC arm") of the ENDEAR study in patients with early onset of disease.

The NURTURE study is an ongoing, open-label, single-arm study on nusinersen treatment of patients with genetic documentation of 5q SMA who did not have clinical symptoms of the disease at enrolment (pre-symptomatic patients). Patients were not allowed to be older than 6 weeks at the first administration of nusinersen. 25 children were included. 15 children had 2 SMN2 gene copies and 10 children had 3 SMN2 gene copies.

Primary outcome of the study was the composite outcome "time to death or ventilation". Patient-relevant secondary outcomes were overall survival, outcomes on morbidity and AEs.

The results of the single-arm NURTURE study are not suitable for the assessment of the added benefit of nusinersen in comparison with the ACT, as the study did not include a comparison with BSC.

The company included the following patients for the comparison of individual arms of the NURTURE study in pre-symptomatic patients and the ENDEAR study in patients with early onset of disease:

- children with pre-symptomatic nusinersen therapy and 2 SMN2 gene copies (study NURTURE, n = 15) versus
- children with early symptomatic start of therapy (disease duration ≤ 12 weeks) with BSC and 2 SMN2 gene copies (BSC arm of the ENDEAR study, n = 18)

This comparison is not suitable for the research question for the assessment of the added benefit in pre-symptomatic patients with 5q SMA.

Transfer of the results of patients with early symptomatic start of therapy (disease duration ≤ 12 weeks) to pre-symptomatic patients

Under certain circumstances, evidence can be transferred from one population to another population for which no or only insufficient data are available.

In the present situation, the single-arm NURTURE study on nusinersen is available for pre-symptomatic patients with 5q SMA. In addition, results are available from a randomized controlled comparison of nusinersen + BSC versus sham intervention + BSC from the ENDEAR study in patients with early onset of disease (onset of SMA-typical symptoms at ≤ 6 months of age) and 2 SMN2 gene copies. Based on the ENDEAR study, an indication of major added benefit was derived for patients with early onset of disease (type 1) and 2 SMN2 gene copies in the present benefit assessment. In addition, effect modifications for morbidity outcomes were shown for the characteristic of disease duration, with statistically significant advantages of major extent for nusinersen + BSC compared with sham intervention + BSC only in patients with a disease duration of ≤ 12 weeks (early symptomatic start of therapy).

In order to investigate the added benefit of nusinersen in comparison with BSC in pre-symptomatic patients, it is examined below whether the added benefit from the comparison of nusinersen + BSC versus BSC in patients with early symptomatic start of therapy (disease duration ≤ 12 weeks) of the ENDEAR study can be transferred to pre-symptomatic patients. In order to achieve as close an approximation as possible of the populations of the 2 studies under consideration, only patients with 2 SMN2 gene copies are considered from the NURTURE study, as only patients with 2 SMN2 gene copies were included in the ENDEAR study.

Assuming that pre-symptomatic patients with 2 SMN2 gene copies in the NURTURE study develop an early onset of disease in the natural course of the disease, i.e. SMA type 1, corresponding to the patients in the ENDEAR study, basic comparability between the patient populations used is assumed in the present situation.

A transfer of evidence from the ENDEAR study to pre-symptomatic patients is possible in the present situation if the results of pre-symptomatic nusinersen administration are equal to or better than those of the early symptomatic start of therapy (disease duration ≤ 12 weeks). For this purpose, the results of the nusinersen arm in patients with early symptomatic start of therapy (ENDEAR study) are compared with the results of the nusinersen arm in pre-symptomatic

patients (NURTURE study). The outcomes of the ENDEAR study, which form the basis for the added benefit in research question 1, are used.

Results on added benefit

In the present data constellation, only those outcomes are considered that were used for the added benefit in the ENDEAR study and for which results are also available in the NURTURE study.

Consistently across all benefit outcomes considered (overall survival, death or permanent ventilation, motor milestone achievement [HINE Section 2]), there was a better result of pre-symptomatic start of therapy with nusinersen in comparison with early symptomatic start of therapy. No usable data are available for outcomes in the outcome category of side effects. However, this does not call into question the advantages in the benefit outcomes. The results thus support a transfer of the added benefit in patients with early symptomatic start of therapy and 2 SMN2 gene copies from the ENDEAR study to pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

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 nusinersen + BSC in comparison with BSC are assessed as follows:

Research question 1: patients with early onset of disease (SMA type 1)

Overall, based on the available data for patients with early onset of disease (SMA type 1) and 2 SMN2 gene copies, there are positive effects exclusively for subgroups. For patients with symptom onset at ≤ 12 weeks of age, there was an indication of major added benefit of nusinersen + BSC in comparison with BSC in overall survival. For patients with a disease duration ≤ 12 weeks, there was an indication of major added benefit for the outcomes "permanent ventilation" and "motor milestone achievement" measured by HINE Section 2. Due to the recording of events of the underlying disease, no usable data are available for the outcomes "SAEs" and "discontinuation due to AEs". However, this does not call into question the major effects of nusinersen in comparison with BSC. Outcomes of the outcome category "health-related quality of life" were not recorded in the ENDEAR study.

[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].

The added benefit was derived on the basis of the total population, taking into account the content of the subgroup results with regard to treatment with nusinersen.

In summary, there is an indication of major added benefit of nusinersen in comparison with the ACT BSC for patients with early onset of disease (SMA type 1) and 2 SMN2 gene copies. To achieve an advantage in overall survival, it is important that patients with type 1 SMA who have early onset of symptoms (age ≤ 12 weeks) are treated with nusinersen. In order to achieve an advantage in symptoms (motor milestone achievement and permanent ventilation), it is important that treatment with nusinersen is initiated early after symptom onset.

No data are available on patients with early onset of disease and a number of SMN2 gene copies other than 2, who are also comprised by research question 1.

Research question 2: patients with later onset of disease (SMA type 2, type 3, type 4)

As the company did not provide any relevant data for the assessment of the added benefit of nusinersen in comparison with the ACT in patients with later onset of disease (type 2, type 3 and type 4), an added benefit of nusinersen for these patients is not proven.

Research question 3: pre-symptomatic patients

The added benefit from the ENDEAR study (see research question 1) can be transferred to pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

Due to the uncertainty in transferring evidence from patients with early symptomatic start of therapy to pre-symptomatic patients, a hint of a non-quantifiable added benefit of nusinersen + BSC in comparison with BSC for pre-symptomatic patients with 2 SMN2 gene copies was derived for the present research question. No suitable data are available for patients with a different number of SMN2 gene copies.

Table 4 shows a summary of probability and extent of the added benefit of nusinersen.

Table 4: Nusinersen – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Patients with 5q SMA and early onset of disease (infantile form, type 1)	BSC[b]	Indication of major added benefit[c]
Patients with 5q SMA and later onset of disease (type 2, type 3 and type 4)		Added benefit not proven
Pre-symptomatic patients with 5q SMA		Hint of a non-quantifiable added benefit[d]

a. Presentation of the ACT specified by the G-BA.
b. 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. In addition, it is assumed that BSC is implemented in both study arms. In patients with pre-symptomatic SMA, BSC also includes watchful waiting.
c. Only patients with 2 SMN2 gene copies were included in the ENDEAR study. It remains unclear whether the observed effects can be transferred to patients with another number of SMN2 gene copies.
d. For patients with 2 SMN2 gene copies. No suitable data are available for patients with a different number of SMN2 gene copies.

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.

Supplementary note

The result of the assessment partly deviates from the result of the G-BA assessment in the framework of the market access in 2017. Separated by type of 5q SMA, the G-BA assessment had determined a major added benefit for patients with SMA type 1 corresponding to research question 1 of the present benefit assessment, a considerable added benefit for patients with SMA type 2, and a non-quantifiable added benefit both for patients with type 3 and for patients with type 4. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs. Pre-symptomatic patients (in accordance with research question 3 of the present benefit assessment) were not part of the G-BA assessment.

2.2 Research question

The aim of the present report is the assessment of the added benefit of nusinersen in comparison with BSC as ACT in patients with 5q SMA.

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. However, overlaps between different types are observed in the context of improved supportive interventions as well as the development of specific treatment options. The different types of SMA should therefore be seen as a continuum rather than as clearly distinguishable types [3-6]. In the therapeutic indication, patients with early onset of disease (infantile SMA, type 1) can nonetheless be clearly distinguished from those with later onset of disease (SMA types 2, 3 and 4). Early onset of disease is defined as symptom onset at < 6 months of age [4-6]. The group of patients with pre-symptomatic diagnosis during newborn screening for 5q SMA represents an additional important patient population. For the benefit assessment, this results in the research questions presented in Table 5.

Table 5: Research questions of the benefit assessment of nusinersen

Research question	Subindication	ACT[a]
1	Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	BSC[b]
2	Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)	
3	Pre-symptomatic patients with 5q SMA	

a. Presentation of the ACT specified by the G-BA.
b. 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 [7]), 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. In addition, it is assumed that BSC is implemented in both study arms. In patients with pre-symptomatic SMA, BSC also includes watchful waiting.

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

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 early onset of disease (SMA type 1)
- Research question 2: patients with later onset of disease (SMA type 2, type 3 and type 4)
- Research question 3: pre-symptomatic patients

The company followed the G-BA in the specification of the ACT, but did not specify that, in patients with pre-symptomatic SMA, the ACT BSC also includes watchful waiting.

In its dossier, the company also differentiated between the patient populations according to research questions 1 to 3 in Table 5. In the present benefit assessment, a differentiation within research question 2 (patients with later onset of disease) is made, as far as possible, between SMA type 2, type 3 and type 4.

Table 6 shows an overview of the data presented by the company for the 3 research questions.

Table 6: Overview of the data presented by the company

Research question	Subindication	Data presented by the company[a]
1	Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	▪ RCT: nusinersen vs. BSC ▫ study ENDEAR ▫ study EMBRACE[b] ▫ meta-analysis of the studies ENDEAR and EMBRACE[c]
2	Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)	▪ RCT: nusinersen vs. BSC ▫ study CHERISH ▫ study EMBRACE[b] ▫ meta-analysis of the studies CHERISH and EMBRACE[c]
		▪ Registry analysis: nusinersen vs. no SMA drug therapy ▫ nusinersen: registries SMArtCARE, ISMAR (part Italy) and CuidAME ▫ no SMA drug therapy: registries ISMAR (part Italy) and CuidAME
		▪ Comparison of individual arms from different studies: nusinersen vs. "natural history cohort" ▫ nusinersen: Study CS12 ▫ "Natural history cohort": study Montes 2018 [8]
3	Pre-symptomatic patients with 5q SMA	▪ NURTURE (single-arm, nusinersen)
		▪ Comparison of individual arms from different studies ▫ nusinersen: study NURTURE ▫ BSC: study ENDEAR

a. The company presented data from the ongoing long-term SHINE study in the context of an additional research question investigated by the company to compare "early vs. late" administration of nusinersen. In the SHINE study, patients who were previously treated in the studies ENDEAR, CHERISH, EMBRACE, CS12 and CS3A receive continued treatment with nusinersen (early nusinersen administration) or first-time treatment with nusinersen (late nusinersen administration).
b. Subpopulation potentially relevant, no adequate analysis available.
c. For individual outcomes.

BSC: best supportive care; RCT: randomized controlled trial; SMA: spinal muscular atrophy

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum treatment period of 12 months is required. For research question 1 (patients with early onset of disease [SMA type 1]) and research question 3 (pre-symptomatic patients), this corresponds to the company's approach. For research question 2 (patients with later onset of disease [SMA type 2, type 3 and type 4]), the company chose a minimum treatment duration of 12 months (randomized controlled trials [RCTs]) and 6 months (registry analysis), depending on the evidence used by the company. For

the comparison of individual arms from different studies, the company did not restrict the minimum treatment duration, but only described that it had to be sufficient for the recording of at least one patient-relevant outcome.

2.3 Research question 1: patients with early onset of disease (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 nusinersen (status: 15 September 2020)
- bibliographical literature search on nusinersen (last search on 15 September 2020)
- search in trial registries/trial results databases for studies on nusinersen (last search on 22 September 2020)
- search on the G-BA website for nusinersen (last search on 15 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on nusinersen (last search on 11 December 2020)

The check did not identify any additional relevant studies.

2.3.1.1 Studies included

The studies listed in the following Table 7 were included in the benefit assessment.

Table 7: Study pool – RCT, direct comparison: nusinersen vs. BSC, patients with early onset of disease (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])
ISIS 396443-CS3B (ENDEAR[d, e])	Yes	Yes	No	No[f]	Yes [9-11]	Yes [12-14]
232SM202 (EMBRACE[d])	No	Yes	No	No[f]	Yes [15,16]	No

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.
d. In the following tables, the study is referred to with this abbreviated form.
e. The follow-up observations of patients from the ENDEAR study within the SHINE study is additionally considered.
f. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; SMA: spinal muscular atrophy; vs.: versus

Concurring with the company, the study pool for the benefit assessment of nusinersen in patients with early onset of disease (SMA type 1) consists of the ISIS 396443-CS3B study (hereinafter referred to as "ENDEAR" study) and the 232SM202 study (hereinafter referred to as "EMBRACE" study).

For research question 1, however, only the ENDEAR study is used to derive the added benefit. For an assessment of the long-term efficacy of nusinersen, partial results of the SHINE study are additionally considered (see Section 2.3.1.2)

For the EMBRACE study, no suitable data are available for the benefit assessment. This is justified below.

No suitable data for the EMBRACE study

Study design

The EMBRACE study is a randomized, double-blind phase 2 study that was conducted in 7 centres in Germany and the USA. The study included patients with genetic documentation of 5q SMA who were not eligible to participate in the ENDEAR study (see Section 2.3.1.2) or the CHERISH study (see Section 2.4.1.1). A total of 21 patients were included and randomly allocated in a 2:1 ratio either to treatment with nusinersen (N = 14) or to treatment with a sham

intervention (N = 7). Stratification factor was the age at symptom onset (≤ 6 months versus > 6 months). With regard to group allocation, all patients, their parents and the treating study staff were blinded. Dedicated study staff administered the study medication or the sham intervention. This staff were not blinded. To ensure blinding, the treatment took place in a separate room in the absence of parents and the treating study staff.

Treatment with nusinersen was age-dependent, as in the ENDEAR study. Section 2.3.1.2 describes how this was dealt with. In addition, the patients in both study arms were to receive treatment in accordance with BSC. Thus, the included patients had to have received appropriate medical care in terms of routine immunizations (including influenza, pneumococcal and pneumovirus prophylaxis, if available). In addition, the medical care had to meet international standards of care regarding respiratory and gastrointestinal measures in the opinion of the investigator [17]. During the study, the participating physicians could basically use concomitant medications and treatments at their own discretion to ensure adequate supportive care. Overall, it is therefore assumed that the patients in both study arms received appropriate therapy in the sense of BSC during the study.

According to the inclusion criteria of the EMBRACE study, the patients had to have

- symptom onset at ≤ 6 months of age and documentation of 3 SMN2 gene copies
- symptom onset at ≤ 6 months of age, an age of > 7 months at baseline, and documentation of 2 SMN2 gene copies, or
- symptom onset at > 6 months of age, an age of ≤ 18 months at baseline, and documentation of 2 or 3 SMN2 gene copies.

According to these criteria, the EMBRACE study included both patients with early onset of disease (SMA type 1, symptom onset at ≤ 6 months of age) and patients with later onset of disease (age at symptom onset > 6 and ≤ 18 months).

Due to the proof of efficacy of nusinersen achieved in the studies ENDEAR and CHERISH, the double-blind treatment of the EMBRACE study was terminated early. Patients who terminated the double-blind phase of the study (as scheduled or early due to the proof of efficacy) could participate in an open-label extension phase of the study. In this phase, all patients were treated with nusinersen for up to 24 months or until commercial availability and were then followed up for 4 months. Following this open-label extension phase of the EMBRACE study (end of study: 24 September 2018), patients could participate in the open-label, long-term ISIS 396443-CS11 study (hereinafter referred to as the “SHINE” study) [18,19]. With the exception of one patient from the sham intervention arm, all included patients of the EMBRACE study transferred to the SHINE study. The SHINE study is described in Section 2.3.1.2.

Primary outcomes of the study were side effect outcomes, change from baseline in laboratory parameters, ECG, and vital signs, as well as in neurological examination outcomes.

Tables on further characteristics of the EMBRACE study can be found in Appendix A of the full dossier assessment.

Analyses of the EMBRACE study presented by the company

In Module 4 A.1 of the dossier, the company presented results of the total population of the EMBRACE study and, in addition, meta-analyses of subpopulations of the EMBRACE study with the total population of the ENDEAR study.

Analyses of the EMBRACE study presented by the company not suitable for the benefit assessment

Since, based on the criterion of age at symptom onset, the EMBRACE study included both patients with early onset of disease (SMA type 1) and patients with later onset of disease, the total population is relevant neither for research question 1 nor for research question 2 of the present benefit assessment. This concurs with the company's approach insofar as the company also did not use the results of the total population for the derivation of the added benefit and only presented them as supplementary information.

The subpopulation of patients with early onset of disease (SMA type 1), which is in principle relevant for research question 1, comprises 9 children in the nusinersen arm and 4 children in the sham intervention arm. Within this subpopulation, there are children with 2 or 3 SMN2 gene copies as well as those with early and later start of treatment (> 7 months), who may require separate consideration. The company did not delineate these patient groups within the subpopulation. Overall, no analyses are available for the basically relevant subpopulations with SMA type 1.

Meta-analyses of the studies ENDEAR and EMBRACE not suitable for the benefit assessment

The company presented 2 meta-analyses of the studies ENDEAR and EMBRACE in Module 4 A.1. Either of these included the total population of the ENDEAR study (see Section 2.3.1.2) as well as individual patients with early onset of disease (SMA type 1) from the EMBRACE study:

- Meta-analysis 1: patients from the EMBRACE study with 2 SMN2 gene copies and symptom onset at ≤ 6 months of age (N = 4 in the nusinersen arm and N = 3 in the sham intervention arm)
- Meta-analysis 2: patients from the EMBRACE study with ≤ 2 SMN2 gene copies (N = 3 in the nusinersen arm and N = 4 in the sham intervention arm)

The approach of the company was not followed. The EMBRACE study included patients with early onset of disease (SMA type 1, symptom onset at ≤ 6 months of age) who did not meet the inclusion criteria of the ENDEAR study. In the ENDEAR study, patients had to have 2 SMN2 gene copies and be ≤ 7 months of age at baseline to be eligible for participation in the study. In line with the different inclusion criteria of the studies with regard to age at baseline, the patients

of the EMBRACE study considered by the company in the 2 meta-analyses differ notably from the patients of the ENDEAR study (data on EMBRACE: Module 4 A.1 in the company's dossier, ENDEAR: Section 2.3.1.2). The patients in the subpopulations of the EMBRACE study formed by the company for the meta-analyses were about 3 times as old at the time of the first dose as those in the ENDEAR study. A meta-analytical summary of these patients is therefore not meaningful.

The meta-analytical summaries of the studies ENDEAR and EMBRACE presented by the company in Module 4 A.1 were therefore not used for the benefit assessment.

2.3.1.2 Study characteristics

Table 8 and Table 9 describe the ENDEAR study used for the benefit assessment.

Table 8: Characteristics of the included ENDEAR study – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

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

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. Patients with clinical signs or symptoms of SMA present at birth or within the first week after birth were excluded.
c. One patient did not receive study medication due to withdrawal of informed consent.
d. 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.
e. Follow-up observation started after the last dose of nusinersen or the sham intervention on day 302 or the early termination of the study.
f. 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 (see Section 2.3.1.2).
g. The outcome was subsequently defined as co-primary outcome of the study (protocol amendment 3 from 22 April 2016). Children who met the following criteria were rated as total score responders: (1) at least 2-point improvement or achievement of the maximal score (touching toes) in the category of ability to kick or at least 1-point improvement in the category of head control, rolling, sitting, crawling, standing, or walking, and ≥ 1-point improvement in the categories of head control, rolling, sitting, crawling, standing, or walking or ≥ 2-point improvement in the category of ability to kick and/or achievement of the maximal score in the category of ability to kick and (2) more categories with improvement than categories with worsening. For the category of ability to kick, similar to the definition of improvement, worsening was defined as at least a 2-point decrease or decrease to the lowest possible score (no kicking).

AE: adverse event; BSC: best supportive care; HINE: Hammersmith Infant Neurological Examination; N: number of randomized patients; RCT: randomized controlled trial; SMA: spinal muscular atrophy; SMN: survival motor neuron; vs.: versus

Table 9: Characteristics of the intervention, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></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
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>
<tr><td>6–12</td><td>135</td><td>4.5</td><td>10.8</td></tr>
<tr><td>12–24</td><td>140</td><td>4.7</td><td>11.3</td></tr>
<tr><td>> 24</td><td>150</td><td>5.0</td><td>12.0</td></tr>
</table>
Dose adjustments were not allowed.
Dosing delay by up to 8 weeks allowed.
Pretreatment[a]
▪ Supportive measures:
▫ medical care meets international standards of care regarding respiratory and gastrointestinal measures in the opinion of the investigator [17,20]
▫ 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 study start
▪ any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation</td><td>Sham intervention in the form of a needle prick on the lower back (no lumbar puncture) on study days 1, 15, 29 and 64, 183 and 302
+
BSC</td></tr>
</table>

a. These are inclusion criteria of the ENDEAR study.

BSC: best supportive care; CSF: cerebrospinal fluid; RCT: randomized controlled trial; SMA: spinal muscular atrophy

Study and intervention characteristics

The ENDEAR study is a randomized, double-blind, parallel-group study conducted in 31 centres in North America, Europe, Asia and Australia. In the study, patients were either treated with nusinersen or received a sham intervention, each in addition to supportive measures (see below). All patients, their parents and the study staff who looked after the children and

assessed the outcomes were blinded with regard to group allocation. Dedicated study staff administered the study medication or the sham intervention. This staff were not blinded. To ensure blinding, the treatment took place in a separate room in the absence of parents and the treating study staff. Study staff making decisions regarding the need for ventilation and performing efficacy evaluations were always blinded.

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 early onset of disease (SMA type 1).

A total of 122 patients were randomly allocated in a 2:1 ratio either to treatment with nusinersen (N = 81) or sham intervention (N = 41). Stratification factor was disease duration (≤ 12 weeks versus > 12 weeks), determined from the difference of the child's age at baseline and the child's age at symptom onset.

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 HINE Section 2. The latter was subsequently defined as co-primary outcome of the study (protocol amendment from 22 April 2016). The rationale for this protocol amendment was that phase 2 data suggested that a functional response could provide early evidence of efficacy and thus allow for an earlier interim analysis. Other patient-relevant outcomes were overall survival, serious respiratory events and AE outcomes.

The study design included a planned study duration of approximately 14 months in total (see Table 8). The study was terminated early due to the proof of efficacy of nusinersen based on positive effects for the outcome "motor milestone achievement" after a prespecified interim analysis (15 June 2016). The median observation period at the final data cut-off on 16 December 2016 was 280 days in the nusinersen arm and 187 days in the sham intervention arm. After the last study visit, patients had the opportunity to participate in the open-label long-term SHINE study (see below).

Treatment with the study medication

In the ENDEAR study, 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 Summary of Product Characteristics (SPC) [21], dosing was age-adjusted in accordance with the regimen described in Table 9. The volume of the injection was adjusted based on the cerebrospinal fluid (CSF) volume depending on the child's age on the day of dosing and was in compliance with the SPC from the age of 24 months (12 mg). Children < 2 years of age received age-dependent doses between 9.6 mg and 11.3 mg per application, so that the dose differences between fixed or age-adjusted dosing were ≤ 20%. In the dossier, the company justified the dosage, which deviated from the approval, by stating that, in consultation

with the European Medicines Agency (EMA), the different dosing regimens of the approval studies ENDEAR and CHERISH had been combined in a dosage in compliance with the SPC and that the data generated so far did not support the need for a dose adjustment based on age or CSF volume. According to the company, the area under the concentration-time curve was comparable for a fixed and an age-adjusted dose. The approval documents of nusinersen also show that the pharmacokinetic profile of nusinersen in CSF and plasma are similar across the studies and comparable between patients with later-onset SMA and children with SMA [22].

Irrespective of this, it can be seen from the approval documents that the fixed dose of 12 mg cited in the SPC is not yet conclusive with regard to the possible benefit to be achieved. It is not excluded that higher doses of nusinersen could not show greater efficacy [22]. This is currently being investigated in the ongoing clinical study DEVOTE [23]. The deviation from the SPC had no overall influence on the present assessment and is not considered further.

Patients in the comparator arm received a sham procedure in the form of a needle prick on the lower back (and no lumbar puncture) at the corresponding time points (see Table 9).

In addition, supportive measures could be used at the discretion of the physician in both study arms.

Implementation of the appropriate comparator therapy BSC

The G-BA defined BSC as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The G-BA mentioned measures such as physiotherapy according to the catalogue of remedies [7], and a corresponding ventilation of the patient, if necessary.

In the ENDEAR study, concrete measures for a BSC were already defined with the inclusion and exclusion criteria. For example, the medical care had to meet international standards of care in SMA regarding respiratory and gastrointestinal measures in the opinion of the investigator both at the start and in the course of the study [17,20]. At study entry, patients had to receive adequate nutrition and hydration (with or without gastrostomy) in the opinion of the investigator, had to have an age-appropriate body weight and have received appropriate medical care in terms of routine immunizations (including influenza, pneumococcal and pneumovirus prophylaxis, if available).

In addition, baseline data are available on patients with ventilatory support and gastric feeding tubes, but not on physiotherapeutic measures (see Table 10). During the study, however, the participating physicians could basically use concomitant medications and treatments at their own discretion to ensure adequate supportive care. This did not include the concomitant medications that were not allowed according to the study protocol (see Table 9). Overall, the available data are therefore considered sufficient for the implementation of the ACT BSC.

Long-term study SHINE

The SHINE study is an open-label, long-term study with patients who had previously participated in a nusinersen study of the company (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. For the present research question 1, only the group of the SHINE study, in which patients from the ENDEAR study were included (hereinafter referred to as "SHINE-ENDEAR"), is considered. All patients who had completed the ENDEAR study transitioned to the SHINE-ENDEAR study (24 children treated with a sham intervention in the ENDEAR study [group 1 A] and 65 children treated with nusinersen in the ENDEAR study [group 1 B]). The design of the study included a blinded loading phase (injections on days 1, 15, 29 and 64), after which patients from both groups received unblinded nusinersen as a maintenance dose every 4 months. Nusinersen treatment in both groups, 1 A and 1 B, was in compliance with the SPC [21]. The study is ongoing with a planned study duration of 5 years (from day 1 of the maintenance dose to day 1800) and a planned end of study in 2023.

The company presented the data from the SHINE study at the data cut-off on 27 August 2019 in Module 4 A.4 for the comparison of early versus late nusinersen administration (see Table 6). This analysis of the SHINE study is not taken into account for the present assessment, as no conclusions on the added benefit of nusinersen in comparison with the ACT BSC can be derived from the results. However, the results of the SHINE-ENDEAR analysis are considered as supplementary information to assess the long-term efficacy of nusinersen and are included in the overall conclusion on the added benefit (see Section 2.3.3.2). The results are presented as supplementary information in Appendix B.3 of the full dossier assessment.

Patient characteristics

Table 10 shows the characteristics of the patients in the included ENDEAR study.

Table 10: Characteristics of the study population, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) (multipage table)

Study **Characteristic** **Category**	**Nusinersen + BSC** **N[a] = 80**	**Sham intervention + BSC** **N[a] = 41**
ENDEAR		
Age at baseline [weeks], median [Q1; Q3]	21.6 [15.9; 27.1][b]	27.1 [18.7; 28.7][b]
Age category, n (%)		
< 12 weeks	10 (12)[c]	4 (10)[c]
≥ 12 weeks	70 (88)[c]	37 (90)[c]
Age at first dose [weeks], median [Q1; Q3]	23.5 [16.9; 29.8][b]	29.3 [20.4; 30.7][b]
Age category, n (%)		
< 12 weeks	6 (8)[c, d]	2 (5)[c, d]
≥ 12 weeks	74 (92)[c]	39 (95)[c]
Age at symptom onset [weeks], median [Q1; Q3]	6.5 [4.5; 11.0]	8.0 [6.0; 12.0]
Age category, n (%)		
< 12 weeks	72 (90)	32 (78)
≥ 12 weeks	8 (10)	9 (22)
Age at SMA diagnosis [weeks], median [Q1; Q3]	11.0 [8.0; 18.0]	20.0 [12.0; 22.0]
Disease duration [weeks], median [Q1; Q3]	13.1 [8.9; 17.7]	12.7 [10.1; 18.4]
Categories [n (%)]		
≤ 12 weeks	34 (43)	18 (44)
> 12 weeks	46 (58)	23 (56)
Sex [F/M], %	54/46	59/41
Geographical region, n (%)		
North America	38 (48)	22 (54)
Europe	30 (38)	17 (41)
Asia-Pacific region	12 (15)	2 (5)
Patients with impairment, n (%)		
Hypotension	80 (100)	41 (100)
Delayed motor development	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Weakness of the extremities	79 (99)	41 (100)
Swallowing/feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Patients with ventilatory support, n (%)	21 (26)	6 (15)
Patients with gastric feeding tubes, n (%)	7 (9)	5 (12)
Patients with physiotherapy, n (%)	ND	ND
HINE Section 2, total score, mean (SD)	1.3 (1.1)	1.5 (1.3)
Treatment discontinuation[e], n (%)	47 (59)	26 (63)
Study discontinuation[f], n (%)	15 (19)	17 (41)

Table 10: Characteristics of the study population, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) (multipage table)

Study Characteristic Category	Nusinersen + BSC N[a] = 80	Sham intervention + BSC N[a] = 41
a. Number of randomized patients. One additional patient in the nusinersen arm withdrew consent to participate in the study before the first dose of study medication. b. Institute's calculation from data in days. c. Institute's calculation. d. No patient was younger than 4 weeks. e. Patients who terminated the study early due to the premature proof of efficacy of nusinersen were counted as treatment discontinuations. These were 39 (49%) patients in the nusinersen arm and 13 (32%) patients in the sham intervention arm. f. Study discontinuation due to death affected 13 (16%) patients in the nusinersen arm and 16 (39%) patients in the sham intervention arm. BSC: best supportive care; F: female; HINE: Hammersmith Infant Neurological Examination; M: male; n: number of patients in the category; N: number of randomized patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; SMA: spinal muscular atrophy; vs.: versus		

The patient characteristics were sufficiently comparable between the treatment arms of the ENDEAR study. The median age of the patients at baseline was 22 weeks in the nusinersen arm and 27 weeks in the sham intervention arm. Slightly more girls than boys were included (54% in the nusinersen arm and 59% in the sham intervention arm). The majority of patients (90% in the nusinersen arm and 78% in the sham intervention arm) had an age of ≤ 12 weeks at symptom onset. The median disease duration in each of the groups was about 13 weeks. The patients included in the nusinersen arm had overall more severe impairment than those in the sham intervention arm (especially with regard to paradoxical breathing, pneumonia or respiratory symptoms, swallowing/feeding difficulties). This is potentially to the disadvantage of treatment with nusinersen.

In the course of the study, 59% of patients in the nusinersen arm and 63% of patients in the sham intervention arm discontinued therapy. Patients who terminated the study early due to the premature proof of efficacy of nusinersen (49% in the nusinersen arm and 32% in the sham intervention arm) were counted as treatment discontinuations. Due to the early termination of the study, there are different observation periods for individual patients. The median treatment duration was 280 days in the nusinersen arm and 187 days in the sham intervention arm (see above).

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

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			
ENDEAR	Yes	Yes	Yes	No[a]	Yes	Yes	Low

a. Administration of treatment was unblinded, assessment of outcomes was blinded.

BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes 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 study results are transferable to the German health care context. The company justified this by stating that the operationalization of the outcomes corresponds to the German health care context. In addition, the majority of patients were included in North America and Europe (50% and 39% respectively), and 86% were of Caucasian family origin. According to the company, the selection of patients based on the time of onset of SMA-typical symptoms corresponds to the internationally recognized consensus and also reflects 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.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - death or permanent ventilation
  - motor milestone achievement (HINE Section 2)
  - serious respiratory events
- 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.1).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

Study	Outcomes							
	Overall survival	Death or permanent ventilation[a]	Motor milestone achievement (HINE Section 2)	Serious respiratory events[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ENDEAR	Yes	Yes	Yes	Yes	No[c]	Yes[d]	Yes[d]	No[e]

a. Composite outcome consisting of the individual components "time to death" and "time to 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 definition of acute reversible events.
b. Summary of SAEs classified as primary SOC or secondary SOC in the SOC "respiratory, thoracic and mediastinal disorders".
c. Outcome not recorded.
d. 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") (see Section 2.3.2.2).
e. No specific AEs were identified.

AE: adverse event; BSC: best supportive care; HINE: Hammersmith Infant Neurological Examination; RCT: randomized controlled trial; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; vs.: versus

Morbidity

Death or permanent ventilation

In the ENDEAR study, both the composite outcome "death or permanent ventilation" and its component "permanent ventilation" as separate outcome were analysed. Permanent ventilation was defined as ≥ 16 hours ventilation/day continuously for > 21 days in the absence of acute reversible events or tracheostomy. Acute reversible events included fever ≥ 38.9°C (tympanic, rectal, axillary, skin, sublingual), infections diagnosed by defined laboratory methods, and

surgical procedures (operation and any procedure requiring regional or general anaesthesia). Each case was reviewed by a blinded, central and independent committee. For the present benefit assessment, the composite outcome "death or permanent ventilation" was primarily considered.

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 [17]. Therefore, the 2 components (permanent ventilation, death) are assessed as sufficiently similar in terms of severity.

Morbidity

Motor milestone achievement

For motor function, the company presented results for the HINE Section 2 and for the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND).

HINE

The HINE was developed for routine neurological examination of infants and children between the ages of 2 and 24 months. It consists of 3 sections: (1) neurological examinations (posture, cranial nerve function, reflexes, tone, movements), (2) assessment of motor development (voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing and walking), and (3) assessment of behaviour (state of consciousness, social orientation and emotional state).

No information on the validation of the instrument in children with SMA is available in the company's dossier. Due to the lack of data on the validation in patients with SMA, no conclusive assessment of the relevance of Sections 1 and 3 is therefore possible. However, Section 2 of the HINE reflects the developmental milestones (voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing and walking) in analogy to the World Health Organisation (WHO) milestones and is face valid in relation to motor milestone achievement. The HINE Section 2 was therefore used for the present benefit assessment. The company also only used the data of Section 2 for the derivation of the added benefit and did not present the results of Sections 1 and 3 in Module 4 A.1.

For Section 2, the company presented analyses in the form of responder analyses and mean differences. The responder analyses in the form of the time to first event were used for the present benefit assessment. The definition of total score responders in the ENDEAR study was based on 7 of the 8 milestone categories of the HINE Section 2, each measured using scales of 3 to 5 possible levels of development. Voluntary grasp was not taken into account in the analysis presented. According to the company, a total score of a maximum of 26 points was formed. The more motor milestones were achieved, the higher the total score. Further information on the interpretation of the total score is not available.

Children who met the following criteria were rated as total score responders:

- at least 2-point improvement or achievement of the maximal score (touching toes) in the category of ability to kick or at least 1-point improvement in the category of head control, rolling, sitting, crawling, standing, or walking

and

- more categories with improvement than categories with worsening. For the category of ability to kick, similar to the definition of improvement, worsening was defined as at least a 2-point decrease or decrease to the lowest possible score (no kicking).

Deceased children and patients who discontinued the study were rated as non-responders.

The prespecified response criterion is face valid given that any improvement in the form of motor milestone achievement is patient-relevant in children with early onset of disease (SMA type 1) and especially in the context of the low baseline values in the investigated patient population of the ENDEAR study. The company did not present the results of the responder analyses for the individual milestones in the dossier. However, the results of the total score responder analyses can be interpreted in combination with the publicly available results on the individual motor milestone categories [24]. These show that improvements in the individual motor milestones, with the exception of one child with sham treatment, are seen exclusively in children with nusinersen treatment. The mean differences presented by the company in the dossier also confirm the effects of the responder analyses (see Section 2.3.2.3).

CHOP INTEND

The CHOP INTEND is also an instrument for the assessment of motor functioning. It was developed for SMA type 1 patients and consists of 16 items, each rated with a score from 0 (non-functional) to 4 (fully functional). This results in a total score of 0 to 64 points, with higher scores corresponding to better motor functioning.

In the dossier, the company presented results in the form of responder analyses and mean differences. The predefined response criterion (improvement by ≥ 4 points) is not face valid due to the higher complexity of the CHOP INTEND scale compared with the HINE Section 2. The results are therefore not usable.

Approach in the benefit assessment

The results of HINE Section 2 were used for the present benefit assessment, as particularly motor development with regard to motor milestone achievement is an important therapeutic goal in the present therapeutic indication, and these are represented by HINE Section 2. The CHOP INTEND, on the other hand, represents motor functioning. The results of the mean differences of the CHOP INTEND are not presented, but they point in the same direction as the results of the HINE Section 2 used (see Section 2.3.2.3).

Side effects

SAEs and discontinuation due to AEs

Events that are symptoms 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") were also included to a large extent in the recording of SAEs and discontinuations due to AEs. However, analyses without events attributable to the underlying disease are relevant for the benefit assessment. The results on SAEs and discontinuations due to AEs are therefore not usable.

2.3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias, study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

Study	Study level	Outcomes							
		Overall survival	Death or permanent ventilation[a]	Motor milestone achievement (HINE Section 2)	Serious respiratory events[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ENDEAR	L	L	L	L	L	–[c]	–[d]	–[d]	–[e]

a. Composite outcome consisting of the individual components "time to death" and "time to permanent ventilation" (defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy); see Section 2.3.2.3 for definition of acute reversible events.
b. Summary of SAEs classified as primary SOC or secondary SOC in the SOC "respiratory, thoracic and mediastinal disorders".
c. Outcome not recorded.
d. 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").
e. No specific AEs were identified.

AE: adverse event; BSC: best supportive care; H: high; HINE: Hammersmith Infant Neurological Examination; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; vs.: versus

Concurring with the assessment of the company, the risk of bias was rated as low for the results of the following outcomes: overall survival, death or permanent ventilation, motor milestone achievement measured by HINE Section 2, and serious respiratory events.

Events that are symptoms of the underlying disease or that can be both side effects and symptoms of the underlying disease (e.g. SOC "respiratory, thoracic and mediastinal disorders") were also included to a large extent in the recording of SAEs and discontinuations due to AEs. However, analyses without events attributable to the underlying disease are relevant for the benefit assessment. The results on SAEs and discontinuations due to AEs are therefore not usable and the risk of bias was not assessed. The company assumed a low risk of bias for the results of both outcomes.

2.3.2.3 Results

Table 14 and Table 15 summarize the results on the comparison of nusinersen + BSC with sham intervention + BSC in patients with early onset of disease (SMA type 1). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. If available, Kaplan-Meier curves or cumulative distribution functions on the outcomes included are presented in Appendix B.1 of the full dossier assessment. Tables with common AEs, SAEs and discontinuations due to AEs can be found in Appendix B.2 of the full dossier assessment.

Due to the different observation periods between the treatment arms, analyses of the time to first event were used for the present benefit assessment, unless otherwise stated.

Table 14: Results (mortality, morbidity, side effects, time to event), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) (multipage table)

Study Outcome category Outcome	Nusinersen + BSC		Sham intervention + BSC		Nusinersen + BSC vs. sham intervention + BSC
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value
ENDEAR					
Mortality					
Overall survival	80	NA 13 (16)	41	NA [23.1; NC] 16 (39)	0.37 [0.18; 0.77]; 0.008
Morbidity					
Death or permanent ventilation[b]	80	NA [36.3; NC] 31 (39)	41	22.6 [13.6; 31.3] 28 (68)	0.53 [0.32; 0.89]; 0.017
Permanent ventilation	80	NA 18 (22)	41	NA [22.6; NC] 13 (32)	0.66 [0.32; 1.37]; 0.269
Motor milestone achievement (HINE Section 2)[c]	80	26.1 [25.1; 29.1] 49 (61)	41	NA 8 (20)	3.22 [1.50; 6.90]; 0.003
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	80	2.40 [1.3; 3.1] 77 (96)	41	1.6 [0.9; 3.1] 40 (98)	–
SAEs	No usable data[d]				
Discontinuation due to AEs	No usable data[d]				

a. Cox proportional hazards regression with treatment and disease duration at baseline as independent variables.
b. 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 running text for definition of acute reversible events.
c. Predefined response criterion based on 7 of the 8 milestone categories of HINE Section 2 without the category of voluntary grasp; defined as (1) at least 2-point improvement or achievement of the maximal score (touching toes) in the category of ability to kick or at least 1-point improvement in the category of head control, rolling, sitting, crawling, standing, or walking, and (2) more categories with improvement than categories with worsening. For the category of ability to kick, similar to the definition of improvement, worsening was defined as at least a 2-point decrease or decrease to the lowest possible score (no kicking).
d. 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") (see Section 2.3.2.2).

AE: adverse event; BSC: best supportive care; CI: confidence interval; HINE: Hammersmith Infant Neurological Examination; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity, dichotomous), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1)

Study Outcome category Outcome	Nusinersen + BSC		Sham intervention + BSC		Nusinersen + BSC vs. sham intervention + BSC
	N	Adjusted annual rate [95% CI] Number of events	N	Adjusted annual rate [95% CI] Number of events	Rate ratio [95% CI]; p-value[a]
ENDEAR					
Morbidity					
Serious respiratory events[b]	80	4.41 [3.43; 5.66] 238	41	5.43 [3.80; 7.77] 117	0.81 [0.53; 1.25]; 0.346

a. Negative binomial regression with treatment, age at symptom onset and disease duration at baseline as independent variables.
b. Summary of SAEs classified as primary SOC or secondary SOC in the SOC "respiratory, thoracic and mediastinal disorders".

BSC: best supportive care; CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SMA: spinal muscular atrophy; SOC: System Organ Class; vs.: versus

Based on the available data, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

In the derivation of the added benefit in the dossier, the company first described the added benefit separately for the results of the ENDEAR study and, in support of this, for the results of the 2 meta-analyses from the studies ENDEAR and EMBRACE (see Section 2.3.1). It then drew a summary conclusion on the added benefit, taking into account the entire data situation. The meta-analyses are not relevant for the present benefit assessment (see Section 2.3.1.1). The comparison with the data provided by the company is only carried out here for the results of the ENDEAR study.

Mortality

Overall survival

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome "overall survival". There was a statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC. However, there was an effect modification by the characteristic "age at symptom onset" for this outcome (see Section 2.3.2.4). For patients with symptom onset at ≤ 12 weeks of age, this resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC. For patients with symptom onset at > 12 weeks of age, there was no hint of an added benefit of nusinersen + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven for these patients.

This deviates from the assessment of the company, which did not consider the present effect modification in the derivation of the added benefit. Based on the event time analysis for the total population, the company derived a major added benefit for nusinersen. The company did not comment on the certainty of conclusions, but derived a low risk of bias for this outcome.

Morbidity

Death or permanent ventilation

Operationalization

Information on the operationalization of the composite outcome "death or permanent ventilation" can be found in Section 2.3.2.1. The results for time to death or permanent ventilation were used for the composite outcome.

Result

A statistically significant difference in favour of nusinersen + BSC was shown between the treatment arms for the composite outcome "death or permanent ventilation". However, there were effect modifications by the characteristics of sex and disease duration for this outcome. These cannot be meaningfully interpreted for the composite outcome (see Section 2.3.2.4). Therefore, only the components included in the composite outcome (overall survival and permanent ventilation) are considered separately in the derivation of the added benefit.

Permanent ventilation

There was no statistically significant difference between the treatment groups for the outcome "permanent ventilation". However, there were effect modifications by the characteristics of sex and disease duration. In the present data constellation, the effect modification by the characteristic of disease duration was considered for the outcome "permanent ventilation" (see Section 2.3.2.4). For patients with a disease duration of ≤ 12 weeks, this resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC. For patients with a disease duration of > 12 weeks, there was no hint of an added benefit of nusinersen + BSC in comparison with BSC; an added benefit is therefore not proven for these patients.

This deviates from the assessment of the company, which did not consider effect modifications in the derivation of the added benefit. The company derived an added benefit of nusinersen for the outcome category of morbidity (ventilation) for the total population using different operationalizations. The company claimed an indication of considerable added benefit for the composite outcome "time to death or permanent ventilation". The company did not derive an added benefit using the operationalization of time to permanent ventilation.

Motor milestone achievement (HINE Section 2)

Operationalization

Motor milestone achievement was recorded using HINE Section 2. The responder analyses in the form of the event time analyses (time to first event) described in Section 2.3.2.1 were used.

Result

A statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC was shown for the outcome "motor milestone achievement" measured by HINE Section 2. However, there was an effect modification by the characteristic "disease duration" for this outcome (see Section 2.3.2.4). For patients with a disease duration of ≤ 12 weeks, this resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC. For patients with a disease duration of > 12 weeks, there was no hint of an added benefit of nusinersen + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which did not consider effect modifications in the derivation of the added benefit and used further analyses for the derivation of an added benefit for the outcome category of morbidity (motor function). It derived a major added benefit on the basis of the responder analyses (time to first event) of HINE Section 2. The company did not comment on the certainty of conclusions, but derived a low risk of bias for this outcome.

Serious respiratory events

Operationalization

The ENDEAR study defined serious respiratory events as SAEs classified as primary SOC or secondary SOC in the SOC "respiratory, thoracic and mediastinal disorders". The adjusted event rate is used.

Result

No statistically significant difference between the treatment arms was shown for the outcome "serious respiratory events". This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the ENDEAR study.

Side effects

SAEs and discontinuation due to AEs

In the ENDEAR study, 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") were also included in the recording of SAEs and discontinuations due to AEs (see Section 2.3.2.2). This means that the results on SAEs and discontinuations due to AEs are not usable. For the outcomes "SAEs" and "discontinuation due to AEs", there was therefore no hint of greater or lesser harm from nusinersen + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This does not concur with the assessment of the company, which, on the basis of the ENDEAR study, derived an indication of a minor added benefit of nusinersen for the outcome "SAEs" and an indication of considerable added benefit for the outcome "discontinuation due to AEs".

2.3.2.4 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)

Subgroup analyses were available for all outcomes included.

The post hoc defined subgroup characteristic "age at first dose" was not considered in the present benefit assessment, as this characteristic represents an uninterpretable mixture of the already considered subgroup characteristics on disease severity and disease duration.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must 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.

Table 16: Subgroups (mortality, morbidity, side effects), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) (multipage table)

Study Outcome Characteristic Subgroup	Nusinersen + BSC N	Nusinersen + BSC Median time to event in weeks [95% CI] Patients with event n (%)	Sham intervention + BSC N	Sham intervention + BSC Median time to event in weeks [95% CI] Patients with event n (%)	Nusinersen + BSC vs. sham intervention + BSC HR [95% CI][a]	 p-value
ENDEAR						
Mortality						
Overall survival						
Age at symptom onset						
≤ 12 weeks	72	NA 10 (14)	32	NA [13.6; NC] 14 (44)	0.26 [0.12; 0.59]	0.001
> 12 weeks	8	30.6 [0.9; NC] 3 (38)	9	NA [23.1; NC] 2 (22)	3.28 [0.50; 21.37]	0.215
Total[b]					Interaction:	0.021
Morbidity						
Death or permanent ventilation						
Sex						
Male	37	36.3 [10.0; NC] 18 (49)	17	33.6 [13.1; NC] 9 (53)	0.98 [0.44; 2.18]	0.957
Female	43	NA [NC; 39.1] 13 (30)	24	19.0 [NC; 11.3] 19 (79)	0.31 [0.15; 0.64]	0.002
Total[b]					Interaction:	0.028
Disease duration						
≤ 12 weeks	34	NA 6 (18)	18	25.4 [13.1; 40.3] 12 (67)	0.16 [0.06; 0.44]	< 0.001
> 12 weeks	46	30.6 [12.0; NC] 25 (54)	23	19.1 [12.1; 27.1] 16 (70)	0.82 [0.43; 1.55]	0.535
Total[b]					Interaction:	0.003
Permanent ventilation						
Sex						
Male	37	NA [29.0; NC] 11 (30)	17	NA [25.4; NC] 2 (12)	2.62 [0.58; 11.89]	0.211
Female	43	NA 7 (16)	24	24.3 [15.1; NC] 11 (46)	0.23 [0.09; 0.63]	0.004
Total[b]					Interaction:	0.005

Table 16: Subgroups (mortality, morbidity, side effects), study ENDEAR – RCT, direct comparison: nusinersen + BSC vs. sham intervention + BSC, patients with early onset of disease (SMA type 1) (multipage table)

Study Outcome Characteristic Subgroup	Nusinersen + BSC N	Nusinersen + BSC Median time to event in weeks [95% CI] Patients with event n (%)	Sham intervention + BSC N	Sham intervention + BSC Median time to event in weeks [95% CI] Patients with event n (%)	Nusinersen + BSC vs. sham intervention + BSC HR [95% CI][a]	 p-value
Disease duration						
≤ 12 weeks	34	NA 3 (9)	18	NA [15.0; NC] 6 (33)	0.12 [0.03; 0.52]	0.005
> 12 weeks	46	NA [36.3; NC] 15 (33)	23	27.1 [19.1; NC] 7 (30)	1.17 [0.47; 2.89]	0.739
Total[b]					Interaction:	0.002
Motor milestone achievement (HINE Section 2)						
Disease duration						
≤ 12 weeks	34	25.3 [10.1; 27.0] 27 (79)	18	NA 2 (11)	9.03 [2.09; 39.04]	0.003
> 12 weeks	46	43.1 [25.1; 57.1] 22 (48)	23	NA [10.1; NC] 6 (26)	1.53 [0.62; 3.78]	0.362
Total[b]					Interaction:	0.004

a. Cox proportional hazards regression with treatment and disease duration at baseline as independent variables.
b. For event time analyses, the p-values for the interaction test were calculated with a Cox regression using the R package "survival" and the R functions "coxph" and "Surv".

BSC: best supportive care; CI: confidence interval; HINE: Hammersmith Infant Neurological Examination; HR: hazard ratio; n: number of patients with event; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SMA: spinal muscular atrophy; vs.: versus

Mortality

Overall survival

There was an effect modification by the characteristic "age at symptom onset" for the outcome "overall survival". For patients with symptom onset at ≤ 12 weeks of age, there was a statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "overall survival". For patients with symptom onset at > 12 weeks of age, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for these patients for the outcome "overall survival"; an added benefit is therefore not proven.

Morbidity

Death or permanent ventilation

There were effect modifications by the characteristics of sex and disease duration for the composite outcome "death or permanent ventilation" as well as for the outcome "permanent ventilation" included in the composite outcome.

Both effect modifications in the composite outcome were due to the effect modifications in the included outcome "permanent ventilation". Against this background, no meaningful interpretation of the subgroup results for the composite outcome is possible. Therefore, only the results of the component "permanent ventilation" were considered in the derivation of the added benefit (see Sections 2.3.2.3 and 2.3.3.1). The component "death" is covered by the outcome "overall survival".

Permanent ventilation

There were effect modifications by the characteristics of sex and disease duration for the outcome "permanent ventilation". The totality of effect modifications cannot be assessed without examining for cross-interactions.

SMA is characterized by progressive motor neuron degeneration, leading to muscular atrophy and muscle weakness. In the course of the disease, motor skills that have been achieved may therefore be lost again. The respiratory muscles also become more and more impaired as the disease progresses, so that patients with early onset of disease (SMA type 1) eventually require artificial ventilation [17,25]. The duration of the disease thus plays a decisive role in the course of the disease. An effect modification by disease duration also exists for the outcome "motor milestone achievement". The effect modification by sex, on the other hand, is only present for the outcome "permanent ventilation". Therefore, only the subgroup characteristic on disease duration is considered in the following (see Sections 2.3.2.3 and 2.3.3.1).

For patients with a disease duration of ≤ 12 weeks, there was a statistically significant difference between the treatment groups in favour of nusinersen + BSC in comparison with sham intervention + BSC. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "permanent ventilation". For patients with a disease duration of > 12 weeks, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for these patients for the outcome "permanent ventilation"; an added benefit is therefore not proven.

Motor milestone achievement (HINE Section 2)

There were effect modifications by the characteristic "disease duration" for the outcome "motor milestone achievement" measured by HINE Section 2.

For the characteristic "disease duration", there was a statistically significant difference in favour of nusinersen + BSC in comparison with sham intervention + BSC for patients with a disease

duration of ≤ 12 weeks. This resulted in an indication of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "motor milestone achievement". For patients with a disease duration of > 12 weeks, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of nusinersen + BSC in comparison with BSC for the outcome "motor milestone achievement"; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 17).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Motor milestone achievement (HINE Section 2)

The outcome "motor milestone achievement", measured by HINE Section 2, was assigned to the outcome category of serious/severe symptoms/late complications. This is due to the fact that the patient population with early-onset SMA (SMA type 1) comprised by research question 1 generally have severe impairments regarding motor development. This is also shown by the fact that, contrary to normal motor development, the patients included in the study had not yet reached nearly any motor milestones according to their age at study start (mean values of HINE Section 2 at baseline [without the item "voluntary grasp"]: 0.58 in the nusinersen arm versus 0.79 in the BSC arm). Based on this information on motor function at baseline, it can be assumed that the majority of the patients had a serious/severe impairment in terms of motor development at this time point.

Although the company did not explicitly comment on the assignment to an outcome category for the present outcome, it can be implicitly inferred from the derivation of a major added benefit by the company that the company also assigned the outcome "motor milestone achievement" to the outcome category of serious/severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level, study ENDEAR: nusinersen + BSC vs. sham intervention + BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nusinersen vs. BSC** **Median time to event (weeks) or event rate** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Age at symptom onset		
≤ 12 weeks	NA vs. NA HR: 0.26 [0.12; 0.59]; p = 0.001 probability: "indication"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "major"
> 12 weeks	30.6 vs. NA HR: 3.28 [0.50; 21.37]; p = 0.215	Lesser benefit/added benefit not proven
Morbidity		
Permanent ventilation		
Disease duration		
≤ 12 weeks	NA vs. NA HR: 0.12 [0.03; 0.52]; p = 0.005 probability: "indication"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"
> 12 weeks	NA vs. 27.1 months HR: 1.17 [0.47; 2.89]; p = 0.739	Lesser benefit/added benefit not proven
Motor milestone achievement (HINE Section 2)		
Disease duration		
≤ 12 weeks	25.3 months vs. NA HR: 9.03 [2.09; 39.04]; HR: 0.11 [0.03; 0.48][c] p = 0.003 probability: "indication"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"
> 12 weeks	43.1 months vs. NA HR: 1.53 [0.62; 3.78]; p = 0.362	Lesser benefit/added benefit not proven
Serious respiratory events	Rate: 4.41 vs. 5.43[d] rate ratio: 0.81 [0.53; 1.25]; p = 0.35	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes of this outcome category were not recorded		

Table 17: Extent of added benefit at outcome level, study ENDEAR: nusinersen + BSC vs. sham intervention + BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nusinersen vs. BSC** **Median time to event (weeks) or event rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	No usable data	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. Adjusted annual rate from a negative binomial regression with treatment, age at symptom onset and disease duration at baseline as independent variables.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; HINE: Hammersmith Infant Neurological Examination; HR: hazard ratio; NA: not achieved; SAE: serious adverse; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of nusinersen in comparison with BSC; study ENDEAR

Positive effects	Negative effects
Mortality ▪ Overall survival (mortality) ▫ Age at symptom onset (≤ 12 weeks) indication of an added benefit – extent: "major"	–
Morbidity: serious/severe symptoms/late complications ▪ Permanent ventilation ▫ Disease duration (≤ 12 weeks) indication of an added benefit – extent: "major" ▪ Motor milestone achievement (HINE Section 2) ▫ Disease duration (≤ 12 weeks) indication of an added benefit – extent: "major"	
Health-related quality of life ▪ Outcomes of this outcome category were not recorded	
Side effects ▪ No usable data on SAEs and discontinuations due to AEs available	
Data are only available for the subpopulation of patients with early onset of disease (SMA type 1) and 2 SMN2 gene copies.	
AE: adverse event; BSC: best supportive care; HINE: Hammersmith Infant Neurological Examination; SAE: serious adverse event; SMA: spinal muscular atrophy; SMN: survival motor neuron	

Overall, based on the available data for patients with early onset of disease (SMA type 1) and 2 SMN2 gene copies, there are positive effects exclusively for subgroups. For patients with symptom onset at ≤ 12 weeks of age, there was an indication of major added benefit of nusinersen + BSC in comparison with BSC in overall survival. For patients with a disease duration ≤ 12 weeks, there was an indication of major added benefit for the outcomes "permanent ventilation" and "motor milestone achievement" measured by HINE Section 2. No usable data are available for the outcomes "SAEs" and "discontinuation due to AEs" due to the recording 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") (see Section 2.3.2.1). However, a balancing of benefit and harm is possible based on the common AEs, common SAEs and common discontinuations due to AEs. This does not call into question the major effects of nusinersen in comparison with BSC. Outcomes of the outcome category "health-related quality of life" were not recorded in the ENDEAR study.

Due to a lack of data to investigate the possible dependencies between the subgroup characteristic of age at symptom onset for the outcome "overall survival" and the subgroup characteristic of disease duration for the outcomes "motor milestone achievement" and

"permanent ventilation", no conclusive interpretation of the subgroup results is possible. Overall, however, treatment with nusinersen shows a survival advantage regardless of disease duration, but only in patients with severe disease, i.e. those with early symptom onset (at ≤ 12 weeks of age; the earlier the onset of symptoms, the worse the prognosis [17,25,26]). In addition, there is an advantage in motor milestone achievement regardless of age at symptom onset (i.e. disease severity), but only when treatment with nusinersen is started early (disease duration ≤ 12 weeks). The added benefit was therefore derived on the basis of the total population, taking into account the content of the subgroup results with regard to treatment with nusinersen (see below).

There was an indication of an added benefit of nusinersen versus BSC for the outcome "motor milestone achievement" measured by HINE Section 2. Information on whether this is a permanent improvement was not provided by the company. This cannot be deduced from the data of the ENDEAR study either. However, taking into account the results of the long-term SHINE-ENDEAR study (see Section 2.3.1.2), it was shown that the improvement in the outcome "motor milestone achievement" was sustained until day 578 (about 1.5 years). No conclusion can be drawn regarding a longer period of time due to the low patient numbers at the later documentation time points. Overall, the long-term data from the SHINE-ENDEAR study do not call into question the results of the ENDEAR study in terms of efficacy (see Appendix B.3 of the full dossier assessment). No conclusion can be drawn regarding long-term safety of nusinersen on the basis of the results of the SHINE-ENDEAR study, as all patients were treated with nusinersen.

To achieve an advantage in overall survival, it is important that particularly patients with type 1 SMA with early symptom onset (age ≤ 12 weeks) are treated with nusinersen. In order to achieve an advantage in symptoms (motor milestone achievement and permanent ventilation), it is additionally important that treatment with nusinersen is initiated early after symptom onset.

In summary, there is an indication of major added benefit of nusinersen in comparison with the ACT BSC for patients with early onset of disease (SMA type 1) and 2 SMN2 gene copies. No data are available on patients with early onset of disease and a number of SMN2 gene copies other than 2, who are also comprised by research question 1.

This assessment basically concurs with that of the company, which also derived an indication of major added benefit for patients with early onset of disease (SMA type 1).

2.4 Research question 2: patients with later onset of disease (SMA type 2, type 3, type 4)

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 lists on nusinersen (status: 16 September 2020)
- bibliographical literature search on nusinersen (last search on 15 September 2020)
- search in trial registries/trial results databases for studies on nusinersen (last search on 22 September 2020)
- search on the G-BA website for nusinersen (last search on 15 September 2020)
- bibliographic search on registry studies/comparison of individual arms on SMA (last search on 16 September 2020)
- search in trial registries/trial results databases for registry studies on SMA (last search on 26 September 2020)
- search on the G-BA website for registry studies/comparison of individual arms on SMA (last search on 26 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on nusinersen (last search on 11 December 2020)

The completeness check did not identify any additional relevant study for the direct comparison, the comparison of individual arms from different studies, and the registry analysis on nusinersen.

With the steps of information retrieval mentioned, the company identified the 2 RCTs of direct comparison CHERISH and EMBRACE on the one hand, and the single-arm studies CS12 and Montes 2018 on the other. In addition, the company presented a registry analysis from 3 different registries (SMArtCARE, ISMAR, CuidAME) for research question 2.

The studies and analyses presented by the company are unsuitable for deriving conclusions on the added benefit of nusinersen in comparison with the ACT for the present research question 2. This also applies to the RCT EMBRACE, which is suitable in principle, as the analyses presented by the company for this study are unsuitable. This is justified in the following sections.

2.4.1.1 Indirect comparison based on RCTs

For patients with later onset of disease (SMA type 2, type 3 and type 4), the company included the 2 RCTs ISIS 396443-CS4 (hereinafter referred to as the “CHERISH” study) [27-29] and EMBRACE in its study pool. For the CHERISH study, it presented results both for the total population and for subpopulations that have SMA type 2 or type 3 in the opinion of the company. It additionally presented results of 3 meta-analyses, which include individual patients from the studies CHERISH and EMBRACE, depending on the operationalization of the patient population. Contrary to the assessment of the company, the CHERISH study, the meta-analyses including the CHERISH study and the analyses of the EMBRACE study presented by the company are not suitable for the benefit assessment. This is justified below.

2.4.1.1.1 Study CHERISH

The CHERISH study is a randomized, double-blind, parallel-group study conducted in 24 centres in Europe, Asia and North America. In the study, patients were either treated with nusinersen or received a sham intervention. With regard to group allocation, all patients, their parents and the treating study staff were blinded. Dedicated study staff administered the study medication. This staff were not blinded. To ensure blinding, the treatment took place in a separate room in the absence of parents and the treating study staff. Study staff making decisions regarding the need for ventilation and performing efficacy evaluations were always blinded. In addition to the study treatment, supportive measures were to be used at the discretion of the treating medical staff.

The study included patients with genetic documentation of 5q SMA who were 2 to 12 years of age at baseline and with symptom onset at > 6 months of age. Regarding motor function, patients had to have a baseline HFMSE score between 10 and 54. In addition, patients had to be able to sit independently, but never had the ability to walk independently. According to this criterion, only patients with type 2 SMA were included in the CHERISH study [3,4,30].

Patients with severe impairments such as respiratory insufficiency (defined by the medical necessity for invasive or non-invasive ventilation for > 6 hours during a 24 hour period), medical necessity for a gastric feeding tube (where the majority of feeds were given by this route), and severe contractures or severe scoliosis evident at baseline were excluded from participation in the study.

A total of 126 patients were randomly allocated in a 2:1 ratio either to treatment with nusinersen (N = 84) or sham intervention (N = 42). Stratification factor was age at baseline (< 6 years versus ≥ 6 years).

Primary outcome of the study was the change from baseline in motor function measured with the HFMSE. Further patient-relevant outcomes were further symptom outcomes, health-related quality of life and AE outcomes.

The planned study duration was approximately 15 months. The study was terminated early due to the proof of efficacy of nusinersen after a prespecified interim analysis (31 August 2016). The final data cut-off of the study was on 3 March 2017. After the last study visit (20 February 2017), patients had the opportunity to participate in the open-label long-term SHINE study (see Section 2.3.1.2). The company presented the data from the long-term SHINE study with patients who transitioned from the CHERISH study to the SHINE study (SHINE-CHERISH) in Module 4 A.4 for the comparison of early versus late administration of nusinersen (see Table 6). Since the CHERISH study was not used for the present research question (for justification, see below), the long-term data of SHINE-CHERISH are also not considered further.

Tables on further characteristics of the CHERISH study can be found in Appendix C of the full dossier assessment.

Implementation of the appropriate comparator therapy BSC not guaranteed

The G-BA defined BSC as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The G-BA mentioned measures such as physiotherapy according to the catalogue of remedies, and a corresponding ventilation of the patient, if necessary.

In contrast to the ENDEAR study, in which concrete requirements for a BSC were already defined by the inclusion and exclusion criteria of the study (see Section 2.3.1.2), the study documents of the CHERISH study do not contain any concrete requirements for the use of supportive therapies, e.g. regarding respiratory and gastrointestinal measures, immunizations, or physiotherapy. The company also did not provide any information in the dossier regarding the extent to which supportive therapies were provided in the CHERISH study and whether these were comparable in both treatment arms, although the recording of such data was planned in the study. According to the study protocol of the CHERISH study, the participating physicians could basically use concomitant medications and treatments at their own discretion to ensure adequate supportive care. However, this information is not sufficient to assume the best possible supportive therapy corresponding to the German health care context, especially against the background that the standards of care in Germany differ notably from those of other countries in the present therapeutic indication [31].

Treatment with nusinersen was not in compliance with the approval

In the CHERISH study, treatment was given as an intrathecal bolus injection at a dose of 12 mg of nusinersen per application, which is in compliance with the SPC [21]. However, deviating from the SPC, which specifies treatment with 4 loading doses (days 0, 14, 28 and 63) and subsequent maintenance doses every 4 months, patients in the CHERISH study were treated with nusinersen on study days 1, 29 and 85 (loading) and on day 274 (maintenance). Day 0 in the SPC corresponds to day 1 in the study. In the course of the study, the patients therefore received only 3 instead of 4 loading doses and only 1 maintenance dose after 6 months instead of 2 maintenance doses after 4 months each.

The company justified the deviation from the SPC in the dossier analogous to research question 1 (see Section 2.3.1.2). However, this argumentation of the company only refers to the dosage in the ENDEAR study, which deviated from the SPC, and not to the deviating dosing intervals in the CHERISH study. Patients in the CHERISH study received a total of only 4 doses of nusinersen instead of 6 doses. As a result, the side effects that occurred in the CHERISH study – in particular side effects caused by the intrathecal application – cannot be meaningfully interpreted in relation to an application that is in compliance with the approval.

Summary

The CHERISH study was not included in the present benefit assessment due to the lack of evidence of an adequate implementation of BSC in accordance with the health care standard in Germany. The nusinersen treatment of the patients, which was not in compliance with the approval and limits the interpretability of the results on AEs, is another limitation of the study.

The study characteristics and results of the CHERISH study are presented as supplementary information in Appendix C of the full dossier assessment.

2.4.1.1.2 Meta-analyses of the studies CHERISH and EMBRACE

In Module 4 A 2, the company presented a total of 3 meta-analyses of the studies CHERISH and EMBRACE in support of the results of the CHERISH study:

- Meta-analysis 1: total population of the CHERISH study (N = 126) + patients from the EMBRACE study with symptom onset at > 6 months of age and 3 or 2 SMN2 gene copies (N = 8); according to the company, this summary enables the highest possible homogeneity of the patient population
- Meta-analysis 2: patients with SMA type 2, as assessed by the company, from the CHERISH study (N = 106) + patients from the EMBRACE study with symptom onset at > 6 months of age and 3 or 2 SMN2 gene copies (N = 8)
- Meta-analysis 3: patients with ≥ 3 SMN2 gene copies from the CHERISH study (N = 114) and the EMBRACE study (N = 13)

As the CHERISH study is not suitable for the present benefit assessment on the basis of the available data (see above), the meta-analytical summaries of the studies CHERISH and EMBRACE presented by the company are consequently also not relevant.

Irrespective of this, in contrast to the assessment of the company, pooling the patient populations from the 2 studies CHERISH and EMBRACE would not be meaningful due to the differences in the patient populations. The CHERISH study included patients who were 2 to 12 years of age at baseline and with symptom onset at > 6 months of age. Patients had to be able to sit independently, but never had the ability to walk independently. The median disease duration in relation to diagnosis was 26.0 months (sham intervention arm) and 27.8 months (nusinersen arm). The EMBRACE study included patients who were ≤ 18 months of age at baseline and with symptom onset at > 6 months of age. Data on motor milestones achieved so far are not available for the study population. The median disease duration in relation to diagnosis for patients with type 2 SMA in the EMBRACE study was 13 months in both study arms.

The meta-analytical summaries of the studies CHERISH and EMBRACE presented by the company in Module 4 A.2 were therefore also not used for the benefit assessment of nusinersen.

2.4.1.1.3 Study EMBRACE

For the present research question, the EMBRACE study is, in principle, relevant both for research question 1 and for research question 2, as it investigated relevant subpopulations corresponding to the research questions, and treatment with nusinersen or BSC was each appropriate in this study. A description of the EMBRACE study can be found in Section 2.3.1.1. Tables on further characteristics of the study and the patient population are presented in Appendix A of the full dossier assessment.

The subpopulation of patients with later onset of disease of SMA type 2, which is in principle relevant for research question 2, comprises 5 patients in the nusinersen arm and 3 patients in the sham intervention arm. The company's dossier contained no adequate preparation of the results for this subpopulation, however. The results are available in Module 4 A 2 only in the context of the meta-analyses with the CHERISH study (see Section 2.4.1.1.2) and only in the form of forest plots. In addition, the reporting of results was selective and relevant results of the subpopulation were not presented (e.g. the outcome "permanent ventilation").

Overall, there are therefore no suitable data available from the EMBRACE study for the basically relevant subpopulation of patients with later onset of disease of SMA type 2.

2.4.1.2 Further investigations

As further investigations, the company presented a registry analysis of patients with SMA type 3 and type 4, and a comparison of individual arms of published studies. These further investigations are not suitable for the benefit assessment, which is justified below.

2.4.1.2.1 Registry analysis (SMA type 3 and type 4)

The company presented analyses from 3 registry sources for patients with SMA type 3 and type 4 as well as for adult patients regardless of SMA type. These are the SMArtCARE registry in German-speaking countries [32,33], the Spanish CuidAME registry (http://www.registro-cuidame.org; no public source information provided by the company) and the Italian part of the ISMAR registry, an international registry from Italy, the UK and the USA [34,35]. All 3 registries were or are financially supported by the company.

The SMArtCARE registry has emerged from a joint initiative of neurologists, neuropaediatricians and patient organizations in German-speaking countries. The aim of the SMArtCARE registry is a standardized collection of observational data of patients with SMA [32]. The SMArtCARE registry was founded in the course of the approval of nusinersen. Not only patients treated with nusinersen should be included, but also patients with SMA in general. There is no public registry protocol for the SMArtCARE registry. However, the registry was analysed in the course of the elaboration of a concept for an application-accompanying data collection for onasemnogene abeparvovec, and detailed information on the registry is therefore available in the corresponding rapid report A20-61 [36], among other sources.

ISMAR is an international registry resulting from an initiative of an international SMA consortium (iSMAC) in Italy, the UK and the USA. The aim of the ISMAR registry is the standardized collection of observational data of patients with SMA [34]. There is no public registry protocol for the ISMAR registry.

The company did not cite a public source for the CuidAME registry in Module 4. However, the registry protocol is publicly available on the website http://www.registro-cuidame.org [37]. According to the registry protocol, the registry serves as an online platform to collect longitudinal data on patients with SMA to better understand the natural history of the disease and patient outcomes. The CuidAME registry is part of the SMArtCARE platform, which is also used for the SMArtCARE registry.

The company presented a comparison of data on 382 patients treated with nusinersen (of which, according to the company, n = 375 with SMA type 3 and n = 7 with SMA type 4) on the one hand, and data on 37 patients not treated with SMA drug therapy (of which, according to the company, n = 34 with SMA type 3 and n = 3 with SMA type 4) on the other. These data are from the German part of the SMArtCARE registry, the Italian part of the ISMAR registry and the Spanish CuidAME registry. The data for the comparator group are exclusively from Italy and Spain. From the results presented for the outcomes of morbidity (HFMSE, RULM, 6-minute walking test) and side effects, the company claimed a hint of considerable added benefit for patients with SMA type 3 as well as for adult patients regardless of SMA type.

Irrespective of the suitability of the registries for conducting a meaningful registry study, the data presented by the company are not suitable for the assessment of the added benefit of nusinersen in comparison with BSC in patients with 5q SMA. This is justified below.

Health care context and transferability

The company did not include all available data from the 3 registries in its registry analysis. It justified this partly with the health care context in the respective survey country (US data of the ISMAR registry), partly with the data availability (data of the ISMAR registry from the UK, see below).

According to an international analysis, there are relevant differences in the care of SMA patients between the different countries [31]. This also applies to the comparison of countries with a more developed health care system. In the present therapeutic indication, these differences appear particularly relevant due to the severity of the disease and the associated multimodal therapy approaches. In particular, standards for and availability of non-drug interventions including the provision of remedies and aids, as well as different standards for ventilation (invasive versus non-invasive) should be mentioned here. In this respect, it is in principle reasonable and understandable if data from other countries are not taken into account due to lack of transferability to the German health care context. However, the company did not explain what constitutes a different health care standard in the individual countries and what differences arise in each case in comparison with Germany. It therefore remains unclear why the registry

data from Italy and Spain were used, but not those from the USA. Besides, the procedure of the company in this regard was inconsistent within its dossier, as it excluded the US data for its own registry analysis, but used a published analysis including the US data without comment (see Section 2.4.1.2.2 [8]).

For a suitable registry study, it is necessary to describe basic requirements for the care of SMA patients, derived from the existing health care standard in Germany. If there are significant differences between these requirements and the health care standard in another country, registry data from other countries should not be used; in the case of gradual differences, this could be decided on an outcome-specific basis if necessary.

Data availability

The company excluded data from the ISMAR registry from the UK “due to data availability”. Irrespective of their relevance for the German health care context, this lack of data availability was neither explained further nor is it comprehensible why the data from this registry, which is financially supported by the company, cannot be available to the company at least in the form of an aggregated analysis (registry study).

Populations on nusinersen and comparator treatment not sufficiently similar

Table 19 shows the characteristics of the patients with SMA type 3 included by the company in the registry analysis.

Table 19: Characteristics of the populations included by the company – registry data: nusinersen vs. comparator group without treatment with SMA drug therapy – patients with SMA type 3 (multipage table)

Study **Characteristic** **Category**	**Nusinersen** **N[a] = 375**	**Comparator group without treatment with SMA drug therapy** **N[a] = 34**
Registry data SMArtCARE, ISMAR, CuidAME		
Registry, n (%)		
SMArtCARE (Germany)	240 (64.0)	0 (0)
ISMAR (part Italy)	104 (27.7)	10 (29.4)
CuidAME (Spain)	31 (8.3)	24 (70.6)
Age at baseline[b] [years], median [min; max][c]	23 [1; 71][d]	16 [4; 69][d]
Age at last follow-up [years], median [min; max]	24 [3; 72][d]	16 [4; 70][d]
Sex [F/M], %	44/56	56/44
Number of SMN2 gene copies, n (%)		
1	2 (0.5)	0 (0)
2	30 (8.0)	4 (11.8)
3	125 (33.3)	15 (44.1)
4	146 (38.9)	11 (32.4)
> 4	9 (2.4)	0 (0)
Unknown	63 (16.8)	4 (11.8)
Age at diagnosis	ND	ND
Age at symptom onset [months], median [min; max]	33 [4; 278]	36 [12; 192]
Age at symptom onset, n (%)		
< 3 years	192 (51.9)	ND
≥ 3 years	178 (48.1)	ND
Disease duration [years], median [min; max]	17.3 [0.04; 67][d]	12.7 [1.6; 63.9][d]
Walking ability, n (%)		
Fully ambulant	216 (57.6)	25 (73.5)
Not fully ambulant	159 (42.4)	9 (26.5[d])
Wheelchair, n (%)		
Yes	204 (54.4[d])	6 (17.6[d])
No	159 (42.4[d])	10 (29.4[d])
Unknown	12 (3.2)[d]	18 (52.9)[d]
Ventilation; n (%)		
Non-invasive	24 (6.4)	2 (5.9)
Invasive	0 (0)	0 (0)
Scoliosis, n (%)[e]		
Yes	92 (24.5[d])	0 (0)

Table 19: Characteristics of the populations included by the company – registry data: nusinersen vs. comparator group without treatment with SMA drug therapy – patients with SMA type 3 (multipage table)

Study Characteristic Category	**Nusinersen N[a] = 375**	**Comparator group without treatment with SMA drug therapy N[a] = 34**
No	282 (75.2[d])	34 (100)
Unknown	1 (0.3)[d]	0 (0)
HFMSE score at baseline[b], median [min; max][f]	39 [0; 66]	58 [24; 66]
RULM score at baseline[b], median [min; max][g]	32 [0; 37]	37 [ND; ND]
6-minute walking test (in metres) at baseline[b], median [min; max][h]	311[i] [25; 697]	535 [280; 625]
Number of doses, mean (SD)	7.2 (2.7)	-
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Definition of baseline unclear.
c. Corresponds to age at first dose in nusinersen group.
d. Institute's calculation.
e. In the registries ISMAR and CuidAME, 40 patients (ISMAR: n = 36 and CuidAME: n = 4) among the patients in the comparator group were excluded from the analysis as "not treatable due to scoliosis".
f. Data related to the number of analysed patients (nusinersen: n = 281 [75%]; comparator group: n = 26 [76%]).
g. Data related to the number of analysed patients (nusinersen: n = 253 [67%]; comparator group: n = 25 [74%]).
h. Data related to the number of analysed patients (nusinersen: n = 115 [31%]; comparator group: n = 5 [15%]).
i. Corrected data; presumably incorrect data in the company's dossier.

F: female; HFMSE: Hammersmith Functional Motor Scale Expanded; M: male; n: number of patients in the category; N: number of patients included; ND: no data; RULM: Revised Upper Limb Module; SD: standard deviation; SMA: spinal muscular atrophy; SMN: survival motor neuron; vs.: versus

Patients with SMA type 3 were notably younger in the comparator group with corresponding notably shorter disease duration compared with patients treated with nusinersen (see Table 19). In addition, the comparator group showed a notably better motor status at baseline across all characteristics presented by the company (see Table 19). The patients in the comparator group were more often fully ambulatory, had a wheelchair less frequently, could walk markedly longer and had markedly better motor skills as measured by the HFMSE and RULM motor function scales. Due to the clearly different baseline status with regard to the motor skills of the 2 groups, the possibility of a potential improvement in the course of observation in the comparator group compared with the group of patients treated with nusinersen was very limited. Thus, there were strong ceiling effects in the comparator group for both the HFMSE and the RULM, the changes in which the company used as outcomes of motor function. With a maximum possible score on the HFMSE scale of 66 points, 50% of the patients in the

comparator group already had at least 58 points at baseline. In contrast, the median for patients treated with nusinersen was 39 points. With a maximum possible score on the RULM scale of 37 points, at least 50% of the patients in the comparator group already had achieved the maximum score at baseline. In contrast, the median for patients treated with nusinersen was 32 points (see Table 19).

Regardless of this, there was no comparison of patient characteristics including the treatment of patients by data source (SMArtCARE, ISMAR and CuidAME).

High proportion of missing values at baseline

For the patient-relevant outcomes used by the company to assess motor function (HFMSE, RULM and 6-minute walking test), there was a high proportion of missing values already at baseline. The proportion with data at baseline for the patients with nusinersen treatment was 75%, 67% and 31% for the HFMSE, RULM and 6-minute walk test, respectively, and 76%, 74% and 15% for the comparator group (see Table 19). The company did not give reasons for the missing values. Information on missing values in the course of the observation is completely missing.

Further comments on the registry analysis

Confounding

The company described that relevant confounders were selected in accordance with the literature and 2 independent experts. However, on the one hand, not all relevant confounders identified in this way were taken into account in the analysis, and on the other hand, a further confounder not identified a priori was added. Furthermore, there was no presentation of the impact of the consideration of confounders in the form of sensitivity analyses that check the robustness of the results. Corresponding analyses were described in the description of the registry analyses in Module 4 A.2, Appendix 4 E, but results were not presented. With only 34 patients in the comparator group, a meaningful adjustment for 8 variables must also be questioned.

Observation period

The company specified an observation period of at least 6 months. At least 12 months of observation are necessary for conclusions on the added benefit. Furthermore, there is no information on the mean observation period in the 2 comparator groups. The company estimated a mean observation period of 18 months from the difference between the mean age at last follow-up and age at baseline within the patients treated with nusinersen (n = 375, SMA type 3). With this procedure for calculating the observation period (analogous to the company), the mean observation period in the comparator group would be 8 months (n = 34, SMA type 3). Thus, the comparator group not only had a notable disadvantage regarding the possibility of potential improvement compared with patients treated with nusinersen (see above), but was also observed for a notably shorter period of time.

2.4.1.2.2 Comparison of individual arms of different studies

Besides the registry analysis, the company presented a comparison of individual arms of different studies. For this purpose, it used data from the single-arm CS12 study [25,38] on nusinersen and, on the comparator side, data from the Montes 2018 study [8]. Study CS12 is a single-arm study of nusinersen in later-onset SMA. The Montes 2018 study is a joint analysis of 3 prospective natural history studies in the USA, Italy and UK on patients with SMA type 3. Results are only available for one outcome (6-minute walking test).

From the results presented for the outcome "6-minute walking test", the company claimed a hint of considerable added benefit for patients with SMA type 3. The data presented are not suitable for assessing the added benefit of nusinersen over BSC in patients with 5q SMA. The reasons for this are as follows:

- Patients in study CS12 had to have completed satisfactorily all dosages of the single-arm studies CS2 (NCT01703988) or CS10 (NCT01780246) with an acceptable safety profile before study inclusion. Thus, the study population of the CS12 study is a selective population of patients who already tolerated nusinersen in the preliminary studies and did not discontinue.
- For the presented comparison of individual arms of different studies, only 3 confounders (sex, age at start of the observation, and score of the 6-minute walking test at start of the observation) were considered using propensity score matching. Consideration of confounders was insufficient. In the analysis of the registry data, the company itself described further confounders that are considered relevant in the therapeutic indication on the basis of experts and literature research.
- For the comparison presented by the company, the health care context (data from the USA, Italy and the UK were used in addition to the single-arm study CS12) was not addressed. In addition, the approach of the company is contradictory, as it assessed data from the USA as irrelevant in the presented registry analyses (see Section 2.4.1.2.1) due to lack of transferability, but as relevant in the analysis using individual arms of different studies.

Of the n = 47 patients in the CS12 study and n = 73 patients in the Montes 2018 study, only 13 pairs matched by propensity score (n = 26) were included in the analysis. However, the selected matching procedure was obviously unsuitable: Despite matching according to age at the start of the observation using the arithmetic mean, the median age of the patients treated with nusinersen included in the analyses was more than twice as high as that of patients in the natural history studies (median 11 versus 4 years).

2.4.2 Results on added benefit

The company did not provide any relevant data for the assessment of the added benefit of nusinersen compared with the ACT in patients with late onset of disease (SMA type 2, type 3

and type 4). This resulted in no hint of an added benefit of nusinersen in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

As the company did not provide any relevant data for the assessment of the added benefit of nusinersen in comparison with the ACT in patients with later onset of disease (SMA type 2, type 3 and type 4), an added benefit of nusinersen for these patients is not proven.

This deviates from the assessment of the company, which derived considerable added benefit for patients with later onset of disease. Depending on the available data, it distinguished between an indication (RCTs) or a hint (e.g. registry analysis, data from long-term study, comparison of individual arms from different studies) of considerable added benefit.

2.5 Research question 3: pre-symptomatic patients

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 nusinersen (status: 15 September 2020)
- bibliographical literature search on nusinersen (last search on 15 September 2020)
- search in trial registries/trial results databases for studies on nusinersen (last search on 22 September 2020)
- search on the G-BA website for nusinersen (last search on 15 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on nusinersen (last search on 11 December 2020)

Concurring with the company, the check did not identify any RCTs of direct comparison in pre-symptomatic patients with 5q SMA comparing nusinersen with the ACT BSC or a corresponding indirect comparison based on RCTs.

Due to the lack of directly comparative data, the company presented a comparison of individual arms from different studies in the section “Further investigations”.

The company limited its information retrieval for the present research question 3 to studies on nusinersen. The company conducted no information retrieval for further investigations on the ACT BSC. In its inclusion criteria for the information retrieval on nusinersen, the company stated that studies with pre-symptomatic as well as “early symptomatic” patients should be considered. Among the further investigations, it hereby identified the single-arm 232SM201 study (hereinafter referred to as the “NURTURE” study) [39-41] in pre-symptomatic patients,

and the RCT ENDEAR comparing nusinersen + BSC with sham intervention + BSC in patients with early onset of disease (see Section 2.3).

The company's approach in the information retrieval for research question 3 of the present benefit assessment is not adequate, as the company did not search for studies on the ACT for further investigations and, in addition, patients with early onset of disease are not part of the present research question. This had no consequence for the present benefit assessment, however (see below).

The company used data on patients with early onset of disease from the ENDEAR study for a comparison using individual arms of the studies NURTURE and ENDEAR (see the following Section 2.5.1.1).

2.5.1.1 Studies included

In the present data constellation, the results of a subpopulation of the RCT ENDEAR comparing nusinersen + BSC with sham intervention + BSC (see Section 2.3) were used to test whether these results can be transferred to the target population of pre-symptomatic patients. The relevant subpopulation of the ENDEAR study comprises patients with a disease duration ≤ 12 weeks and 2 SMN2 copies. The transferability was examined under consideration of the results of a subpopulation of the NURTURE study (pre-symptomatic patients with 2 SMN2 gene copies).

This deviates from the approach of the company in that the company also used the studies ENDEAR and NURTURE, but for a comparison of individual arms of different studies.

Data presented by the company

For research question 3 of the present benefit assessment, the company presented results of the single-arm NURTURE study with nusinersen in pre-symptomatic patients with 5q SMA and, in addition, a comparison of individual arms of the NURTURE study in pre-symptomatic patients with the sham intervention arm (hereinafter referred to as "BSC arm") of the ENDEAR study in patients with early onset of disease. The ENDEAR study is described in Section 2.3.1.2.

The NURTURE study and the comparison of individual arms of different studies presented by the company are not relevant for the present benefit assessment. This is justified below. First, the NURTURE study is described.

Study NURTURE

Table 20 and Table 21 describe the NURTURE study.

Table 20: Characteristics of the NURTURE study

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NURTURE	Open-label, single-arm	Patients with genetic documentation of 5q SMA and: ▪ no clinical signs or symptoms suggestive of SMA immediately before study start or first dose of study medication ▪ age ≤ 6 weeks at first dose of study medication ▪ 2 or 3 SMN2 gene copies ▪ ulnar CMAP ≥ 1 mV	Nusinersen + BSC[b] (N = 25) Thereof, subpopulation with 2 SMN2 gene copies used for transfer of evidence: nusinersen + BSC[b] (N = 15)	Start of study: 21 days Treatment: planned for 5 years Follow-up observation: planned for 3 months	15 study centres in Australia, Germany, Italy, Qatar, Taiwan, Turkey, USA 5/2015–ongoing Data cut-offs: 15 May 2018[c] 29 March 2019[d]	Primary: time to death or ventilation[e] Secondary: overall survival, morbidity, AEs

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. Data from IQWiG report S18-02 [24].
c. Data cut-off presented by the company for results of the NURTURE study.
d. Date taken from de Vivo et al. [41]; presumed data cut-off for the comparison of individual arms from the studies NURTURE and ENDEAR presented by the company. The company only states that the data were taken from a current interim data cut-off from 2019.
e. Invasive or non-invasive for ≥ 6 hours/day continuously for > 7 days or tracheostomy.

AE: adverse event; BSC: best supportive care; CMAP: compound muscle action potential; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); N: number of patients included; SMA: spinal muscular atrophy; SMN: survival motor neuron

Table 21: Characteristics of the intervention in the NURTURE study

Study	Intervention	Prior and concomitant treatment
NURTURE	Nusinersen as intrathecal injection on study days 1, 15, 29, 64, then every 4 months: ▪ until March 2017 (including protocol version 5): age-adjusted dose[a] (from 24 months: 12 mg) ▪ as of March 2017[b] (protocol version 6): 12 mg + BSC[c]	Not allowed: ▪ 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 study start or during the study ▪ any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation

a. The company does not provide information on the dosage according to age groups.
b. The last patient was enrolled in February 2017.
c. Data from IQWiG report S18-02 [24].

BSC: best supportive care; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); SMA: spinal muscular atrophy

The NURTURE study is an ongoing, open-label, single-arm study on nusinersen treatment of patients with genetic documentation of 5q SMA who did not have clinical symptoms of the disease at enrolment (pre-symptomatic patients). Patients were not allowed to be older than 6 weeks at the first administration of nusinersen. 25 children were included. 15 children had 2 SMN2 gene copies and 10 children had 3 SMN2 gene copies.

The children received nusinersen as an intrathecal bolus injection (loading) on each of study days 1, 15, 29 and 64. From study day 183, one maintenance dose was given every 4 months for a total of 5 years. The dosing was age-adjusted until March 2017, i.e. almost 2 years after the start of the study. The company did not provide information on the dosage according to age groups. Since March 2017, the dosage of nusinersen has been 12 mg in accordance with the SPC [21].

Primary outcome of the study was the composite outcome “time to death or ventilation”. Patient-relevant secondary outcomes were overall survival, outcomes on morbidity and AEs.

The results of the single-arm NURTURE study are not suitable for the assessment of the added benefit of nusinersen in comparison with the ACT. The company also did not use the results of the NURTURE study for the derivation of the added benefit.

Comparison of individual arms of different studies

The company included the following patients for the comparison of individual arms of the NURTURE study in pre-symptomatic patients and the ENDEAR study in patients with early onset of disease:

- children with pre-symptomatic nusinersen therapy and 2 SMN2 gene copies (study NURTURE, n = 15) versus

- children with early symptomatic start of therapy (disease duration ≤ 12 weeks) with BSC and 2 SMN2 gene copies (BSC arm of the ENDEAR study, n = 18)

In addition, the company presented a sensitivity analysis of all pre-symptomatic patients in the NURTURE study (2 or 3 SMN2 gene copies, n = 25) and the BSC arm of all patients with early onset of disease in the ENDEAR study (2 SMN2 gene copies, no restriction regarding disease duration, n = 41).

The company did not present any data for the comparison of nusinersen versus BSC in pre-symptomatic patients. The comparison of a pre-symptomatic patient population with a patient population with early symptomatic start of therapy presented by the company is not relevant to the research question for the assessment of the added benefit in pre-symptomatic patients with 5q SMA. The company did not conduct a further search for BSC in pre-symptomatic patients.

Transfer of the results of patients with early symptomatic start of therapy (disease duration ≤ 12 weeks) to pre-symptomatic patients

Under certain circumstances, evidence can be transferred from one population to another population for which no or only insufficient data are available.

In the present situation, the single-arm NURTURE study on nusinersen is available for pre-symptomatic patients with 5q SMA. However, this study does not allow a comparison with the ACT.

In addition, results are available from a randomized controlled comparison of nusinersen + BSC versus sham intervention + BSC from the ENDEAR study in patients with early onset of disease (onset of SMA-typical symptoms at ≤ 6 months of age) and 2 SMN2 gene copies. Based on the ENDEAR study, an indication of major added benefit was derived for patients with early onset of disease (type 1) and 2 SMN2 gene copies in the present benefit assessment (see Section 2.3.3.2). In addition, effect modifications for morbidity outcomes were shown for the characteristic of disease duration, with statistically significant advantages of major extent for nusinersen + BSC compared with sham intervention + BSC only in patients with a disease duration of ≤ 12 weeks (early symptomatic start of therapy) (see Section 2.3.2.4).

In order to investigate the added benefit of nusinersen in comparison with BSC in pre-symptomatic patients, it is examined below whether the added benefit from the comparison of nusinersen + BSC versus BSC in patients with early symptomatic start of therapy (disease duration ≤ 12 weeks) of the ENDEAR study can be transferred to pre-symptomatic patients. In order to achieve as close an approximation as possible of the populations of the 2 studies under consideration, only patients with 2 SMN2 gene copies are considered from the NURTURE study, as only patients with 2 SMN2 gene copies were included in the ENDEAR study.

Assuming that pre-symptomatic patients with 2 SMN2 gene copies in the NURTURE study develop an early onset of disease in the natural course of the disease, i.e. SMA type 1,

corresponding to the patients in the ENDEAR study, basic comparability between the patient populations used is assumed in the present situation.

Table 22 shows the characteristics of the considered patient populations.

Table 22: Characteristics of the study population – comparison: nusinersen + BSC, study NURTURE (pre-symptomatic) vs. nusinersen + BSC, study ENDEAR (early symptomatic start of therapy) in patients with 2 SMN2 copies

Characteristic	Nusinersen + BSC study NURTURE (pre-symptomatic) N[a] = 15	Nusinersen + BSC study ENDEAR (early symptomatic start of therapy, i.e. disease duration ≤ 12 weeks)[b] N[a] = 34
Sex [F/M], %	47/53	53/47
Age at symptom onset [weeks], median [min; max]	Not applicable	6 [3; 18]
Age at diagnosis [weeks], mean (SD)	2 (1)[c]	11 (5)
Disease duration [weeks], median [min; max]	Not applicable	8 [0; 12]
Age at first dose [weeks], median [min; max]	3 [1; 6][d]	16 [7; 34]

a. Number of analysed patients.
b. Data on the ENDEAR study from IQWiG report S18-02 [24].
c. Institute's calculation from data in months.
d. Institute's calculation from data in days.

BSC: best supportive care; F: female; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); M: male; max: maximum; min: minimum; SD: standard deviation; SMN: survival motor neuron; vs.: versus

As expected, pre-symptomatic patients were younger at diagnosis compared with patients with early symptomatic start of therapy (mean of 9 weeks). Whereas therapy in pre-symptomatic patients started immediately after diagnosis, start of therapy in patients with early symptomatic start of therapy was defined by a maximum disease duration of 12 weeks. Correspondingly, pre-symptomatic patients were younger also at the first dose compared with patients with early symptomatic start of therapy (median of 13 weeks).

A transfer of evidence from the ENDEAR study to pre-symptomatic patients is possible in the present situation if the results of pre-symptomatic nusinersen administration are equal to or better than those of the early symptomatic start of therapy (disease duration ≤ 12 weeks). For this purpose, the results of the nusinersen arm in patients with early symptomatic start of therapy (ENDEAR study) are compared with the results of the nusinersen arm in pre-symptomatic patients (NURTURE study). The outcomes of the ENDEAR study, which form the basis for the added benefit in research question 1, are used (see Section 2.3.3.2).

2.5.2 Results on added benefit

In the present data constellation, only those outcomes are presented that were used for the added benefit in the ENDEAR study and for which results are also available in the NURTURE study.

Table 23 shows a comparison of the results of nusinersen in pre-symptomatic patients versus nusinersen in patients with early symptomatic start of therapy.

Table 23: Results (outcome categories, time to event) – comparison: nusinersen + BSC, study NURTURE (pre-symptomatic) vs. nusinersen + BSC, study ENDEAR (early symptomatic start of therapy [disease duration ≤ 12 weeks]) in patients with 2 SMN2 gene copies

Outcome category **Outcome**	**Nusinersen + BSC study NURTURE (pre-symptomatic)**		**Nusinersen + BSC study ENDEAR (early symptomatic start of therapy [disease duration ≤ 12 weeks])**	
	N[a]	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**
Mortality				
Overall survival	15	– 0 (0)	34	NA 3 (9)
Morbidity				
Death or permanent ventilation[b]	15	– 0 (0)	34	NA 6 (18)
Permanent ventilation	15	– 0 (0)	34	NA 3 (9)
Motor milestone achievement (HINE Section 2)[c]	15	ND[d] 15 (100)	34	25.3 [10.1; 27.0] 27 (79)
Side effects				
SAEs	No usable data[e]			
Discontinuation due to AEs	No usable data[e]			

a. Number of patients in the analysis.
b. 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.
c. Predefined response criterion based on 7 of the 8 milestone categories of HINE Section 2 without the category of voluntary grasp; defined as (1) at least 2-point improvement or achievement of the maximal score (touching toes) in the category of ability to kick or at least 1-point improvement in the category of head control, rolling, sitting, crawling, standing, or walking, and (2) more categories with improvement than categories with worsening. For the category of ability to kick, similar to the definition of improvement, worsening was defined as at least a 2-point decrease or decrease to the lowest possible score (no kicking).
d. After 26 weeks (day 183), the proportion of patients with event was 100%, so the median time to event is ≤ 26 weeks.
e. 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").

AE: adverse event; BSC: best supportive care; CI: confidence interval; HINE: Hammersmith Infant Neurological Examination; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; SAE: serious adverse event; SMN: survival motor neuron; SOC: System Organ Class; vs.: versus

Consistently across all benefit outcomes considered, there was a better result of pre-symptomatic start of therapy with nusinersen in comparison with early symptomatic start of

therapy. No usable data are available for outcomes in the outcome category of side effects. However, this does not call into question the advantages in the benefit outcomes.

The results presented thus support a transfer of the added benefit in patients with early symptomatic start of therapy and 2 SMN2 gene copies from the ENDEAR study to pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

2.5.3 Probability and extent of added benefit

As outlined in Section 2.5.2, the added benefit from the ENDEAR study can be transferred to pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies. Based on the total population of the RCT ENDEAR, an indication of a major added benefit was derived for patients with early onset of disease (type 1) and 2 SMN2 gene copies, i.e. including the patients with early symptomatic start of therapy considered here for comparison (see Section 2.3.3.2).

Due to the uncertainty in transferring evidence to pre-symptomatic patients, a hint of a non-quantifiable added benefit for patients with 2 SMN2 gene copies was derived for the present research question. No suitable data are available for patients with a different number of SMN2 gene copies.

In summary, there is a hint of a non-quantifiable added benefit of nusinersen versus BSC for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

The assessment deviates from that of the company, which derived a hint of a major added benefit on the basis of the presented comparison of individual arms of different studies on nusinersen in pre-symptomatic patients and BSC in patients with early symptomatic start of therapy.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nusinersen in comparison with the ACT is summarized in Table 24.

Table 24: Nusinersen – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Patients with 5q SMA and early onset of disease (infantile form, SMA type 1)	BSC[b]	Indication of major added benefit[c]
Patients with 5q SMA and later onset of disease (SMA type 2, type 3 and type 4)		Added benefit not proven
Pre-symptomatic patients with 5q SMA		Hint of a non-quantifiable added benefit[d]

a. Presentation of the ACT specified by the G-BA.
b. 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 [7]), 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. In addition, it is assumed that BSC is implemented in both study arms. In patients with pre-symptomatic SMA, BSC also includes watchful waiting.
c. Only patients with 2 SMN2 gene copies were included in the ENDEAR study. It remains unclear whether the observed effects can be transferred to patients with another number of SMN2 gene copies.
d. For patients with 2 SMN2 gene copies. No suitable data are available for patients with a different number of SMN2 gene copies.

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.

Supplementary note

The result of the assessment partly deviates from the result of the G-BA assessment in the framework of the market access in 2017. Separated by type of 5q SMA, the G-BA assessment had determined a major added benefit for patients with SMA type 1 corresponding to research question 1 of the present benefit assessment, a considerable added benefit for patients with SMA type 2, and a non-quantifiable added benefit both for patients with type 3 and for patients with type 4. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs. Pre-symptomatic patients (in accordance with research question 3 of the present benefit assessment) were not part of the G-BA assessment.

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Please see full dossier assessment for full reference list.

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

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