Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nusinersen (exceeding €50 million turnover limit: Spinal Muscular Atrophy)

of 20 May 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first submission on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nusinersen (Spinraza) was listed for the first time on 1 July 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Spinraza for the treatment of 5q spinal muscular atrophy is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In its session on 21 December 2017, the G-BA decided on the benefit assessment of nusinersen in the therapeutic indication 5q spinal muscular atrophy in accordance with Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of €50 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 29 June 2020, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2020, due to exceeding the €50 million turnover limit. The pharmaceutical company submitted in due time

the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 01 December 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 01 March 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nusinersen compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nusinersen.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of nusinersen (Spinraza) in accordance with the product information

Spinraza is indicated for the treatment of 5q spinal muscular atrophy.

Therapeutic indication of the resolution (resolution from the 20/05/2021):

“see approved therapeutic indication”

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients with 5q spinal muscular atrophy:

Appropriate comparator therapy for nusinersen:

- Best supportive care

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The active ingredient onasemnogene abeparvovec is approved for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. The active ingredient risdiplam was approved at the end of March 2021 for the following indication: “Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.”

on 2. Supportive measures and symptom treatment include, for example, physiotherapy, occupational therapy as well as voice, speech and language therapy in accordance with the remedies catalogue, surgical measures (e.g. tracheostomy), ventilation, respiratory hygiene, nutrition management, aids.

on 3. In the mentioned therapeutic indication, there is a resolution of the G-BA on the benefit assessment of nusinersen in accordance with Section 35a SGB V.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V”. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

Overall, the evidence in the therapeutic indication of SMA is very limited.

Even if the active ingredient nusinersen has a therapeutic value in the therapeutic indication, it is not considered for the determination of an appropriate comparator therapy compared to a treatment with nusinersen in the question of the early benefit assessment. The two further therapy alternatives approved in the therapeutic indication onasemnogene abeparvovec and risdiplam have only been available in Germany for a short and very short time, respectively.

The evidence synopsis included a guideline with recommendations for the non-pharmacological treatment of SMA. On the basis of the evidence synopsis, no evidence is available for the active ingredients onasemnogene abeparvovec or risdiplam, which are approved in the present indication and relevant for the present research question. Likewise, the AkdÄ does not classify the recently approved active ingredient onasemnogene abeparvovec as standard therapy in the therapeutic indication at present. The statement of the German Society of Neurology explicitly refers to the treatment of adult patients with 5q SMA and describes the current data situation

regarding the currently possible medicinal treatment, as well as its limitations to certain patient groups due to marketing authorisation or application. The statement of the Society of Neuropaediatrics also describes the current data situation on the two drug therapy options nusinersen and onasemnogene abeparvovec and points out that better therapy results can be achieved in both cases by an early, ideally pre-symptomatic therapy start. Comparative studies were not available.

In summary, there is no aggregate or higher-quality evidence for the agents onasemnogene abeparvovec and risdiplam. A resolution on a benefit assessment for the active ingredient onasemnogene abeparvovec, which will be approved in May 2020, is still pending due to the fact that the €50 million turnover limit has been exceeded. The benefit assessment process for the active ingredient risdiplam, which was approved in March 2021, began in May 2021. Therefore, and due to the fact that they are not yet available on the market for a long time, the active ingredients cannot be considered as an appropriate comparator therapy for the present procedure.

Based on the available evidence, the G-BA determined best supportive care as the appropriate comparator therapy for the active ingredient nusinersen for the treatment of 5q spinal muscular atrophy for all patient groups. Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life. In this indication, various measures, including, e.g. physiotherapy in accordance with the therapeutic products catalogue, may be suitable for treating the patient-individual symptoms of spinal muscular atrophy, or appropriate ventilation of the patient, if this is necessary.

In patients with pre-symptomatic SMA, BSC also includes monitoring wait-and-see approach.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nusinersen is assessed as follows:

a) Patients with 5q spinal muscular atrophy (5q SMA) type 1:

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

Indication of a major additional benefit

b) Patients with 5q SMA type 2

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

Hint of a considerable additional benefit

c) Patients with 5q SMA type 3 / 4

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

An additional benefit is not proven.

d1) Pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

Hint of a major additional benefit

d2) Pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

Hint for a non-quantifiable additional benefit

d3) Pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies

Appropriate comparator therapy:

BSC

Extent and probability of the additional benefit of nusinersen compared to BSC:

An additional benefit is not proven.

Justification:

a) Patients with 5q SMA type 1:

The two double-blind randomised controlled trials (RCT) ENDEAR and EMBRACE are available to assess the additional benefit of nusinersen for the treatment of spinal muscular atrophy. In addition, the pharmaceutical company presents the open-label long-term study SHINE as a supplement, which, however, he does not present for the derivation of an additional benefit, but only as support.

ENDEAR study

In the ENDEAR study, 122 children with genetically documented 5q SMA and 2 SMN2 gene copies and an age at start of study ≤ 7 months and an age at symptom onset ≤ 6 months were

randomised in a 2:1 ratio to either treatment with nusinersen (N = 81) or a sham intervention (N = 41). Stratification factor was duration of disease (≤ 12 weeks vs > 12 weeks), determined from the difference in the child's age at start of study and the child's age at symptom onset. Nusinersen was applied in the intervention arm at an age-adjusted dose on study days 1, 15, 29, 64 for saturation and on days 183 and 302 for maintenance as an intrathecal bolus injection. The age-adjusted dosage deviated from the instructions given in the product information. In the comparator arm, patients received sham treatment in the form of a needle puncture to the lower back (no lumbar puncture) at the appropriate time points. Furthermore, in the opinion of the medical investigators, the care of the patients at start of study as well as during the course of the study should correspond to international SMA treatment standards. During the study, the medical investigators were generally free to use concomitant medications (except for concomitant medications not allowed under the study protocol) and treatments at their discretion to provide adequate supportive care. The planned duration of the study was approximately 14 months. Based on the proof of concept of nusinersen for the endpoint Achievement of motor milestones, the study was terminated early after a prespecified interim analysis. The median duration of observation at the final data cut-off was 280 days in the nusinersen arm and 187 days in the sham intervention arm.

Coprimary endpoints of the study were the combined endpoint Time to death or permanent ventilation and the proportion of patients who achieved motor milestones as measured by the Hammersmith Infant Neurological Examination (HINE) subscale 2. After the last study visit, patients had the opportunity to participate in the open-label long-term SHINE study. The ENDEAR study was conducted between July 2014 and December 2016 (final data cut-off) in 31 centres in Australia, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, the United Kingdom, and the United States.

EMBRACE study

The EMBRACE study included a total of 21 patients with genetically documented 5q SMA who were not eligible to participate in the ENDEAR study nor the CHERISH study. Inclusion criteria were age at symptom onset ≤ 6 months and 3 SMN-2 gene copies, *or* age at symptom onset ≤ 6 months, age at start of study > 7 months and 2 SMN2 gene copies, *or* age at symptom onset > 6 months, age at start of study ≤ 18 months and 2 or 3 SMN2 gene copies. Patients were treated in a 2:1 ratio with either nusinersen (N = 14) or a sham intervention (N = 7). Stratification factor was age at symptom onset (≤ 6 months vs > 6 months). Treatment with nusinersen was age-related, as in the ENDEAR study. In addition, patients in both study arms should receive treatment according to BSC (e.g., evidence of routine immunisations and care according to international standards of care as assessed by the principal investigator). Primary endpoints of the study were side effects, changes in laboratory parameters, electrocardiogram (ECG) and vital signs, and neurological examination results compared to start of study.

Due to the proof of concept achieved with nusinersen in the ENDEAR and CHERISH studies, the double-blind treatment of the EMBRACE study was terminated prematurely. Patients who completed the double-blind phase of the study (as scheduled or early due to proof of concept) were eligible to participate in an open-label extension phase of the study. Following this open-label extension phase of the EMBRACE study, patients were eligible to participate in the open-label long-term SHINE study. The study was conducted between August 2015 and March 2017 (final data cut-off of the double-blind phase) in 7 centres in Germany and the USA.

The EMBRACE study included patients with early disease onset (SMA type 1, age at symptom onset ≤ 6 months) and with later disease onset (age at symptom onset > 6 and ≤ 18 months). However, the pharmaceutical company only presents results of the total population of the EMBRACE study in the dossier, as well as meta-analyses of sub-populations of the EMBRACE study with the total population of the ENDEAR study and the CHERISH study, respectively. However, in accordance with the different inclusion criteria of the EMBRACE and ENDEAR studies with regard to age at start of study, the patients of the two studies included by the pharmaceutical company in the two meta-analyses differed significantly. The analyses of the

total population of the EMBRACE study, as well as the meta-analytical summaries of the ENDEAR and EMBRACE studies, are not used for the benefit assessment.

Long-term study SHINE

The SHINE study is an open-label, long-term study of SMA patients who had previously participated in a study with nusinersen (ENDEAR, CS3A, CHERISH, CS12 or EMRACE). All included patients were treated with nusinersen. Patients were assigned to one of 5 groups depending on which study they had previously participated in. The design of the study included a blinded build-up dosing 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. The study is ongoing with a planned study duration of 5 years (from day 1 of maintenance dose to day 1800) and a planned end of study in 2023. The results of the SHINE-ENDEAR and SHINE-CHERISH evaluations will be used to assess the long-term efficacy of nusinersen in addition to the benefit assessment.

Extent and probability of the additional benefit

Mortality

Mortality was assessed in the ENDEAR study as part of the adverse event (AE) survey as survival rate and as part of the combined endpoint “time to death”.

Overall survival
The time from administration of the first dose of study medication or randomisation to the occurrence of death over the entire study period was recorded. There were 13 (16%) deaths in the nusinersen group compared to 16 (39%) deaths in the BSC group, resulting in a statistically significant reduction in the risk of death with nusinersen. Median survival was not achieved in either study arms.
The extent of this effect is assessed as a major improvement in overall survival.
For this endpoint, there is an effect modification in the characteristic Age at symptom onset (age at symptom onset ≤ 12 weeks / > 12 weeks): A statistically significant difference exists for patients ≤ 12 weeks of age at symptom onset, but not for patients > 12 weeks of age at symptom onset.

Morbidity

Death or permanent ventilation

The endpoints evaluated were the combined endpoint Death or permanent ventilation and Permanent ventilation as a separate endpoint. Permanent ventilation was defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy.

For the combined endpoint Death or permanent ventilation, there are effect modifications by the characteristics Sex and Duration of disease, which are exclusively due to effect modifications in the included endpoint component Permanent ventilation. Since the effect modifications for the combined endpoint cannot therefore be meaningfully interpreted, the components included in the combined endpoint (death and permanent ventilation) are considered separately for the benefit assessment. The endpoint component Mortality (death) is already reflected via the endpoint overall survival as an independent endpoint.

Permanent ventilation

For the endpoint Permanent ventilation no statistically significant difference was detected between the treatment groups. However, there are effect modifications by the characteristics Gender and Duration of disease.

For patients with a duration of disease ≤ 12 weeks, there is a statistically significant difference in the proportion of patients requiring permanent ventilation in favour of treatment with nusinersen compared with BSC treatment, the extent of which is classified as major. For the subgroup of patients with a duration of disease > 12 weeks, no statistically significant difference was found. The subgroup characteristic Gender is not considered for the present benefit assessment.

Hammersmith Infant Neurological Examination - HINE (subscale 2)

The HINE was developed for routine neurological examination of infants and children between the ages of 2 and 24 months. It consists of 3 subscales: (1) neurological examination (posture, cranial nerve function, reflexes, tone, movements), (2) assessment of motor development (conscious grasping, kicking, head control, turning, sitting, crawling, standing, and walking), and (3) behavioural assessment (awareness, social orientation, and emotional state). No data are available on the validation of the HINE in children with SMA. However, because HINE subscale 2 maps the milestones in a child's development analogous to the World Health Organization (WHO) milestones, HINE subscale 2 is used for this benefit assessment.

Responder analyses are presented in the form of the time to 1st. event. The definition of total score responders is based on 7 (excluding the "conscious grasping" category) of the 8 milestone categories of HINE subscale 2, each measured using scales of 3 to 5 possible developmental levels. The total score (maximum 26 points) is higher the more motor milestones are achieved.

As prespecified response criterion was an improvement of at least 2 points or reaching the maximum value (touching toes) in the category "kicking" or improvement of at least 1 point in the category "head control", "turning", "sitting", "robbing/crawling", "standing" or "walking" and more categories with an improvement than categories with a deterioration. In children with SMA type 1, any improvement in the individual motor milestones or the achievement of a motor milestone can be classified as patient-relevant.

For the endpoint Achievement of motor milestones measured by HINE subscale 2, there is a statistically significant difference in favour of treatment with nusinersen compared to BSC treatment, which is classified as major.

Taking into account the results of the long-term SHINE-ENDEAR study, it can be seen that the improvement in the endpoint Achievement of motor milestones is sustained until day 578 (approx. 1.5 years). No statement can be made about a longer period due to the low number of patients at the later survey points.

For this endpoint there is an effect modification by the characteristic Duration of disease (≤ 12 weeks / > 12 weeks), a statistically significant difference in favour of nusinersen exists only for patients with a duration of disease ≤ 12 weeks. For the subgroup of patients with a duration of disease > 12 weeks, no statistically significant difference was found.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disease - CHOP INTEND

The CHOP INTEND was developed for SMA type 1 patients and measures motor skills. It consists of 16 domains, each of which is assigned a value from 0 (non-functional) to 4 (fully functional). A higher total score (maximum 64 points) corresponds to better motor functioning. For the benefit assessment, the results of the evaluations on the mean value differences of the CHOP INTEND for the assessment of motor function are used. Due to the high proportion of missing values at start of study, which differed between the therapy arms (difference > 10 %),

there is a high risk of bias. The high proportion of missing values in the course of the study, which differed between the arms, is due to the premature discontinuation of the ENDEAR study because of the premature proof of concept of nusinersen. The observed effect becomes larger as the study progresses, with the magnitude, as measured by the confidence interval, also increasing, despite increasing uncertainty due to the premature end of the study and the associated missing values. Therefore, it is not assumed that the effect, even in its magnitude, is solely due to systematic bias.

For the endpoint motor function measured by the CHOP INTEND, there was a statistically significant difference in the benefit of nusinersen compared to BSC treatment at all measurement points during the course of the study (day 64, day 183, day 302 and day 394), the extent of which is classified as non-quantifiable. The resolution shows the results at the last observation date (day 394). Since the confidence interval for Hedges' g is completely outside the irrelevance range [-0.2; 0.2] at all times, the difference is interpreted as a relevant effect.

Serious respiratory events

Serious respiratory events were defined in the ENDEAR study as SAEs classified in SOC "Respiratory, thoracic and mediastinal disorders" as primary SOC or secondary SOC. The adjusted event rate is used. For the endpoint serious respiratory events no statistically significant difference was detected between the treatment arms.

Hospitalisations
The resolution presents the results on the frequency of hospitalisations.
The assessment of the endpoint Hospitalisation and the evaluation of the frequency were predefined. The frequency of hospitalisations was recorded due to "monitoring for general observation", due to symptoms after "dosing or sham intervention under BSC", due to "serious adverse events (SAEs)" or due to "additional investigations" (e.g. planned surgery). The results of the endpoint are subject to uncertainty, because, according to the operationalisation of the endpoint, events such as planned interventions or surveillance for general observation, which need not be associated with disease, may also be included. For the endpoint Hospitalisation no statistically significant difference was detected between the treatment arms.

Quality of life

No quality of life data were collected in the ENDEAR study.

Side effects

An adverse event (AE) occurred in 96% of patients in the intervention group and 98% in the control group. When recording SAEs and discontinuations due to SAEs, events that belong to the symptomatology of the underlying disease or events that can be both a side effect and symptomatology of the underlying disease (e.g. system organ class [SOC] Respiratory, thoracic and mediastinal disorders) were also recorded to a large extent. The results on SAEs and discontinuations due to AEs are therefore not usable.

Overall assessment/conclusion

For patients with 5q SMA type 1, assessments of the direct comparison study ENDEAR, and the long-term study SHINE-ENDEAR are available for the comparison of nusinersen with BSC.

In summary, there are statistically significant advantages for nusinersen in mortality (overall survival) and in the morbidity endpoints "Permanent ventilation" and "Achievement of motor milestones (HINE)" for the subgroup of patients with an age of ≤ 12 weeks at symptom onset (mortality) and for the subgroup of patients with a duration of disease ≤ 12 weeks (morbidity

endpoints), respectively. For the endpoints Overall survival and “Achievement of motor milestones”, the differences are also statistically significant for the total population of patients in the ENDEAR study. Based on the results of the long-term SHINE-ENDEAR study, the improvement in the endpoint “Achievement of motor milestones (HINE)” is sustained until day 578 (approximately 1.5 years). For the endpoint “Motor function (CHOP INTEND)”, there is also a statistically significant advantage for nusinersen.

The results of the subgroups cannot be interpreted conclusively. Data for the investigation of possible dependencies between the subgroup characteristic Age at symptom onset and the subgroup characteristic Duration of disease are lacking, nevertheless a correlation between the severity of the disease (age at symptom onset) and the duration of disease cannot be excluded. With regard to the characteristic Duration of disease, it can also be assumed that, even taking into account the recently enacted newborn screening for 5q SMA, early treatment is initiated in patients with SMA type 1 directly after symptom onset and the subgroup of patients with a treatment initiation at a duration of disease ≤ 12 weeks corresponds to the current German health care context. For the characteristic Age at symptom onset (≤ 12 weeks / > 12 weeks), uncertainty arises from the unequal distribution of patients into the two subgroups and the resulting small size of the subgroup Age at symptom onset > 12 weeks, which comprises only 8 of a total of 80 (Nusinersen arm) and 9 of a total of 32 (BSC arm) patients, respectively, as well as the small number of events that occurred.

In summary, the effect modifications are taken into account for the present benefit assessment, but the derivation of the additional benefit is performed for the overall population of the ENDEAR study (patients with SMA type 1).

There was no statistically significant difference for the endpoint “Serious respiratory events” and the endpoint “Hospitalisations” in the morbidity category.

No data were collected in the quality of life category.

In the category of side effects, no usable data are available overall.

In the overall view, there are exclusively positive effects for nusinersen compared to BSC, which are not offset by any disadvantages. However, it must be taken into account that the results on side effects can only be assessed to a very limited extent. The positive effects of nusinersen compared to the appropriate comparator therapy in the mortality category and in important morbidity endpoints are assessed as a previously unachieved large improvement in the therapy-relevant benefit.

Based on these considerations, the information in the dossier and the results of the benefit assessment, the extent of additional benefit for nusinersen compared with the appropriate comparator therapy BSC for the treatment of patients with SMA type 1 is classified as major.

Reliability of data (probability of additional benefit)

With the ENDEAR study, a randomised, double-blind Phase III study is available for the assessment of the additional benefit. The risk of bias of the ENDEAR study is considered to be low.

The risk of bias in the outcomes of endpoints Overall survival, death or permanent ventilation, Achievement of motor milestones measured by HINE subscale 2, and Serious respiratory events is also considered low. For the endpoint Motor functioning (CHOP INTEND), there is a high risk of bias due to the high proportion of missing values at start of study, but the effect supports the results for the endpoint Achievement of motor milestones measured by HINE subscale 2.

Based on the study population of the ENDEAR study, the statements on additional benefit can essentially only be made for patients with SMA type 1 and 2 SMN2 gene copies. Uncertainties arise from the lack of data for patients with SMA type 1 with a different SMN2 gene copy number. It remains unclear whether the observed effects can be transferred to patients with a different number of SMN2 gene copies. However, it should be noted that approximately 80% of patients with SMA type 1 have 2 SMN2 gene copies[2]. In the present case, the uncertainty does not lead to a downgrading of the reliability of data.

In summary, an indication for an additional benefit is derived on the basis of the available data.

b) Patients with 5q SMA type 2

The two double-blind randomised controlled trials (RCT) CHERISH and EMBRACE are available to assess the additional benefit of nusinersen for the treatment of spinal muscular atrophy. In addition, the pharmaceutical company presents the open-label long-term study SHINE as a supplement, which, however, he does not present for the derivation of an additional benefit, but only as support.

For the sub-population of patients with 5q SMA type 2, no suitable data are available from the EMBRACE study; moreover, the patient populations in the EMBRACE and CHERISH studies differ significantly. The analyses of the total population of the EMBRACE study, as well as the meta-analytical summaries of the CHERISH and EMBRACE studies, are therefore not used for the benefit assessment.

CHERISH study

The randomised, double-blind, parallel-group CHERISH study enrolled 126 patients with genetically documented 5q SMA and an age of 2 to 12 years at start of study and an age at symptom onset > 6 months and assigned in a 2:1 ratio to either treatment with nusinersen (N = 84) or the sham intervention (N = 42). Stratification factor was age at start of study (< 6 years vs ≥ 6 years). In deviation from the product information, the patients received only 3 instead of 4 saturation doses during the course of the study and only 1 maintenance dose after 6 months instead of 2 maintenance doses after every 4 months. Patients were required to have a Hammersmith Functional Motor Scale-Expanded (HFMSE) score between 10 and 54 at start of study, be able to sit freely but never have been able to walk freely. Patients with severe impairments such as respiratory insufficiency, medical need for a feeding tube, and severe contractures or severe scoliosis at start of study were excluded. In addition to the study treatment, supportive measures should be used at the discretion of the treating medical staff. The primary endpoint of the study was the change in motor function measured by the HFMSE compared to baseline.

The planned duration of the study was approximately 15 months. The study was terminated early due to the proof of concept of nusinersen after a prespecified interim analysis. After the last study visit, patients had the opportunity to participate in the open-label long-term SHINE study.

The CHERISH study was conducted between November 2014 and March 2017 (final data cut-off) in 24 centres in Canada, France, Germany, Hong Kong, Italy, Japan, Spain, Sweden, South Korea, and the United States.

Uncertainties of the CHERISH study:

In the CHERISH study, uncertainties arise on the one hand from the dosing interval, which deviates from the product information, since the patients in the intervention arm received only

[2] Calucho M, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord 2018; 28(3): 208-215

3 instead of 4 saturation doses of nusinersen during the course of the study and only 1 maintenance dose after 6 months instead of 2 maintenance doses after every 4 months.
On the other hand, there are uncertainties regarding the adequate implementation of the appropriate comparator therapy BSC. According to the study protocol of the CHERISH study, the medical investigators were generally free to use concomitant medications and treatments at their discretion to provide adequate supportive care. Likewise, the clinical experts argued in the written statement procedure that, in their opinion, BSC treatment was provided in the CHERISH study in accordance with the German health care context. However, the study documents of the CHERISH study do not contain any specific guidelines on the use of supportive therapies, and the dossier does not contain any information on the extent to which supportive therapies were provided in the course of the CHERISH study and whether they were comparable in both treatment arms. For this reason, it cannot be assumed with sufficient certainty that the best possible supportive therapy in accordance with the German health care context was implemented in the study.

Despite the uncertainties mentioned above, the randomised, controlled and blinded CHERISH study can be used for the benefit assessment from the perspective of the G-BA.

In the CHERISH study, duration of disease was prespecified in terciles (< 25, ≥ 25 to < 44, ≥ 44 months) as a subgroup characteristic. Since duration of disease plays a crucial role in SMA, which is characterised by progressive degeneration of motor neurons, subgroup analysis is considered. However, the rationale for dividing duration of disease into the above terciles is unclear. The further prespecified subgroup characteristics Age at screening (< 6 years vs ≥ 6 years) and geographic region (North America vs Europe vs Asia-Pacific) or the post hoc analysed subgroup characteristic Gender are not considered for the present benefit assessment.

Mortality

Overall mortality

Fatalities were recorded as part of the safety assessment. No patient died during the study.

Morbidity

Frequency of serious respiratory events

For the endpoint, serious AEs assigned to SOC “Respiratory, thoracic and mediastinal disorders” were analysed post-hoc. There are no signs of statistically significant differences between the treatment groups.

Hammersmith Functional Motor Scale Expanded - HFMSE

The HFMSE has been validated to assess clinical progression in patients with type 2 and 3 SMA and measures changes in motor function with 33 items. Change in HFMSE score is mapped at day 456 compared to baseline.

Since the HFMSE adequately depicts motor function and individual items of the HFMSE depict the motor milestones according to the WHO (“standing with assistance” and “standing alone”), the endpoint “motor development milestones according to WHO”, which was additionally assessed in the study, is not presented here.

For the endpoint “Achievement for motor milestones (HFSME)”, there is a statistically significant difference in favour of treatment with nusinersen compared to BSC treatment. The effect can be assessed as clinically relevant, as the confidence interval of the Hedges’ g lies completely outside the irrelevance range of -0.2 to 0.2, and its magnitude is rated as considerable.

For this endpoint, there is effect modification by the characteristic Duration of disease (< 25 months, ≥ 25 months to < 44 months, ≥ 44 months): A significant difference exists for patients with duration of disease < 25 months, but not for patients with duration of disease ≥ 25 months to < 44 months and ≥ 44 months.

Taking into account the results of the long-term SHINE-CHERISH study, it can be seen that the improvement in the endpoint HFMSE is sustained until day 1410 (approximately 3.5 years). No statement can be made about a longer period due to the low number of patients at the later survey points.

Revised Upper Limb Module - RULM

The instrument represents the revised version of the shorter questionnaire ULM, which was developed for the motor assessment of children with SMA who lost walking ability. The RULM measures upper limb functions across 20 items with different constructs than the HFMSE. Change in RULM score is mapped at day 456 compared to baseline.

For the endpoint "Motor function of the upper limbs (RULM)", there is a statistically significant difference in favour of treatment with nusinersen compared to BSC treatment. The effect can be assessed as clinically relevant, as the confidence interval of the Hedges' g lies completely outside the irrelevance range of -0.2 to 0.2, and its magnitude is rated as considerable.

For this endpoint, there is effect modification by the characteristic Duration of disease (< 25 months, ≥ 25 months to < 44 months, ≥ 44 months): A significant difference exists for patients with duration of disease < 25 months, but not for patients with duration of disease ≥ 25 months to < 44 months and ≥ 44 months.

Taking into account the results of the long-term SHINE-CHERISH study, it can be seen that the improvement in the endpoint RULM is sustained until day 1410 (approximately 3.5 years). No statement can be made about a longer period due to the low number of patients at the later survey points.

Disease-related hospitalisations
The resolution presents the results on the frequency of disease-related hospitalisations.

The assessment of the endpoint Disease-related hospitalisation and the evaluation of the frequency were predefined. Disease-related hospitalisations were defined as SAEs that required inpatient hospitalisation or for which hospitalisation was prolonged. The classification of an SAE as a disease-related hospitalisation was made by a blinded committee.

For the endpoint "Disease-related hospitalisation", there is a statistically significant difference in favour of treatment with nusinersen compared to BSC treatment. It should be noted that the observed effect in favour of nusinersen was largely due to the serious respiratory events included in this endpoint (11 events in 84 patients in the nusinersen arm, 14 events in 42 patients in the sham intervention arm). However, the endpoint "Frequency of serious respiratory events" showed no difference between the treatment arms.

<u>Quality of life</u>

Pediatric Quality of Life Inventory (PedsQL)

The validated measurement instrument PedsQL, which is suitable for this age group, was used to assess health-related quality of life. For 2 to 4 year olds only a parent questionnaire is available in the dossier, for other age groups also patient questionnaires.

The total score of the generic scale of the PedsQL 4.0 includes the physical, emotional, and social domains, as well as the school/kindergarten domain. Since comparative statistical analyses are only available for the total score, only this score is presented in the benefit

assessment. The Neuromuscular Module 3.0 of the PedsQL was developed to map dimensions of quality of life specifically for children with neuromuscular diseases aged 2 to 18 years, including children with SMA. The module includes 3 dimensions: neuromuscular disease, communication and family options. Usable data are only available for the area of neuromuscular disease, therefore only this area is presented in the benefit assessment.

The change in the total score of the generic scale of the PedsQL 4.0 and the Neuromuscular Disease score of the neuromuscular module 3.0 of the PedsQL is mapped at day 456 compared to baseline. There are no statistically significant differences between the treatment groups.

Side effects

An adverse event (AE) occurred in 93 % of patients in the intervention group and 100 % in the control group. When recording SAEs and discontinuations due to SAEs, events that belong to the symptomatology of the underlying disease or events that can be both a side effect and symptomatology of the underlying disease (e.g. system organ class [SOC] Respiratory, thoracic and mediastinal disorders) were also recorded to a large extent. The results on SAEs and discontinuations due to AEs are therefore not usable. Based on the common AEs and SAEs encountered in the CHERISH study and their differences between treatment arms, and considering patient relevance, the specific AE endpoints of vomiting, headache, and back pain were identified. For all 3 endpoints, there was a statistically significant difference to the disadvantage of nusinersen compared to BSC.

Overall assessment/conclusion

For patients with 5q SMA type 2, evaluations of the direct comparison CHERISH study, and the long-term SHINE-CHERISH study are available for the comparison of nusinersen versus BSC.

There were no deaths in the CHERISH study. In the morbidity endpoints “Achievement of motor milestones (HFSME)” and “Motor function of the upper limbs (RULM)” there are statistically significant advantages for nusinersen for patients with a duration of disease < 25 months. Based on the results of the long-term SHINE-CHERISH study, the improvement in both endpoints is sustained until day 1410 (approximately 3.5 years). For the endpoint “Disease-related hospitalisation”, there is a statistically significant advantage of nusinersen compared to BSC. There is no statistically significant difference for the endpoint “Frequency of serious respiratory events”.

The results of the subgroups cannot be interpreted conclusively. With regard to the characteristic Duration of disease, it can also be assumed that, even taking into account the recently enacted newborn screening for 5q SMA, early treatment is initiated in patients with SMA type 2 directly after symptom onset and the subgroup of patients with a treatment initiation at a duration of disease< 25 months corresponds to the current German health care context. In summary, the effect modifications are taken into account for the present benefit assessment, but the additional benefit is derived for the overall population of the CHERISH study (patients with SMA type 2).

In the category Quality of life, for the endpoint PedsQL, there was no statistically significant difference between treatment groups.

In the category of side effects, there was a statistically significant difference for the specific AE endpoints Vomiting, Headache and Back pain to the disadvantage of nusinersen compared to BSC. Overall, however, no advantages or disadvantages can be derived for nusinersen compared to BSC based on the available data on the side effect profile.

In the overall picture, there are mainly positive effects for nusinersen compared to BSC. It must be taken into account here that the results on side effects can only be assessed to a very limited extent. However, the effects of nusinersen compared to BSC are not questioned by the available data on the side effect profile. The positive effects of nusinersen in important morbidity endpoints are assessed as a previously unachieved significant improvement in therapy-relevant benefit.

Based on these considerations, the information in the dossier and the results of the benefit assessment, the extent of additional benefit for nusinersen compared with the appropriate comparator therapy BSC for the treatment of patients with SMA type 2 is classified as considerable.

Reliability of data (probability of additional benefit)

With the CHERISH study, a randomised, double-blind Phase III study is available for the assessment of the additional benefit. The risk of bias of the CHERISH study is rated as low.

The risk of bias at the endpoint level is also rated as low.

However, the remaining uncertainties relevant to the assessment regarding the adequate implementation of the specific appropriate comparator therapy BSC in the CHERISH study (see study description) justify a downgrading of the reliability of data overall, so that a hint of an additional benefit is assumed.

c) Patients with 5q SMA type 3 / 4

For the assessment of the additional benefit of nusinersen for the treatment of spinal muscular atrophy, analyses from 3 register sources are available: the SMArtCARE register in German-speaking countries, the Spanish CuidAME register, and the Italian part of the ISMAR register (cross-national register from Italy, Great Britain and the USA). All 3 registries were or are financially supported by the pharmaceutical company. The pharmaceutical company presents 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) and data on 37 patients not treated with drug therapy for SMA (of which, according to the company, n = 34 with SMA type 3 and n = 3 with SMA type 4). These data come from the German part of the SMArtCARE registry, the Italian part of the ISMAR registry and the Spanish registry CuidAME. The data for the comparison group come exclusively from Italy and Spain. In addition, the pharmaceutical company presents a comparison of the 1-arm CS12 study of nusinersen treatment in late disease onset SMA and the Montes 2018[3] study, a collaborative analysis of 3 prospective natural history studies in the US, Italy, and the UK of patients with SMA type 3.

Verification of the suitability of the register data

Since the aforementioned register sources for the register study also draw on data generated outside the German care context, it would be necessary to describe basic requirements for the care of SMA patients derived from the existing standard of care in Germany. The pharmaceutical company uses the registry data from Italy and Spain, but excludes the US data for the registry study due to what he considers a different standard of care. However, the procedure remains unclear, as the pharmaceutical company does not specify any basic requirements for the standard of care or does not explain which differences exist in the standard of care in the respective countries compared to Germany.

[3] Montes et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. PLoS One 2018; 13(6): e0199657.

Furthermore, the two patient populations in the registry study are not sufficiently comparable. Patients in the comparison group are significantly younger with significantly shorter duration of disease and show significantly better motor status across all characteristics presented by the pharmaceutical company at start of study. Due to the clearly different starting position with regard to the motor abilities of the two groups, the possibility of a potential improvement in the course of observation in the comparison group compared to the group of patients treated with nusinersen is strongly limited.

Furthermore, for the patient-relevant endpoints used to assess motor function (HFMSE, RULM and 6-minute walk test), a high proportion of missing values were already available at start of study. The pharmaceutical company justifies this in its written statement with the systematic collection of registry data only since the market launch of nusinersen and explains that the values missing at the start of study were methodically taken into account in the calculation using linear interpolation in the "mixed effects models" and in two additional imputation methods. However, there is no information on missing values during the observation.

A further uncertainty arises from the data on the mean observation period (follow-up time) of the two patient populations. In the course of the written statement, the pharmaceutical company submitted data on the mean observation period, according to which the patients treated with nusinersen were followed up for a mean of approx. 410 days and the untreated patients for approx. 640 days. However, it remains unclear whether the information refers to all patients in the respective population or only to a part of the patient population.

Examination of the suitability of the comparison of individual arms of different studies

The study population of study CS12 consists of a selective patient population, as it included only patients who already tolerated nusinersen in the preliminary studies and did not discontinue the preliminary study. Furthermore, only 3 confounders were considered in the comparison, although further relevant confounders in the indication SMA were identified by the pharmaceutical company during the evaluation of the registry data. The comparison presented also did not address the context of care. It remains unclear, for example, why the pharmaceutical company uses data from the USA on the natural course of the disease for the comparison, while it excludes these data from the register evaluation described above due to lack of transferability.

In summary, due to the large uncertainties, the data presented are inappropriate for assessing the additional benefit of nusinersen over BSC in patients with 5q SMA and are not used for the benefit assessment. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of nusinersen, the severity of the disease and the statements of the medical societies on the current reality of care, nusinersen may represent a relevant therapeutic option for patients with 5q SMA type 3 / 4.

(d) <u>pre-symptomatic patients with 5q SMA</u>

For the assessment of the additional benefit of nusinersen for the treatment of spinal muscular atrophy, data are available from the ongoing, open-label, 1-arm NURTURE studies, as well as an unadjusted indirect comparison of treatment with nusinersen from the NURTURE study in comparison with the BSC arm from the ENDEAR study. With regard to the data of the unadjusted indirect comparison, the pharmaceutical company also refers to the requirements and the assessment of the benefit of a pre-symptomatic start of therapy made within the scope of the analysis and evaluation of a newborn screening for 5q SMA[4] on the benefit of a pre-symptomatic start of therapy.

[4] IQWiG Final Report (S18-02): Newborn screening for 5q spinal muscular atrophy

Study NURTURE

In the NURTURE study, 25 children with genetic evidence of 5q SMA (including 15 with 2 SMN2 gene copies and 10 with 3 SMN2 gene copies) who did not have clinical symptoms of the disease at the time of time of enrolment (pre-symptomatic patients) will be treated with nusinersen. At the 1. administration of nusinersen, patients were not allowed to be older than 6 weeks. The children received nusinersen as an intrathecal bolus injection (saturation) on each of study days 1, 15, 29, and 64. From study day 183, 1 maintenance dose is given every 4 months for a total of 5 years. The dosage was age-adjusted until just under 2 years after the start of the study and then 12 mg in accordance with the product information. The primary endpoint of the study is the combined endpoint Time to death or Time to ventilation. Patient-relevant secondary endpoints were Overall survival, Morbidity endpoints, and AEs. The study has been conducted since May 2015 in 15 study centres in Australia, Germany, Italy, Qatar, Taiwan, Turkey and the USA.

The results of the 1-arm NURTURE study are inappropriate for assessing the additional benefit of nusinersen compared with the appropriate comparator therapy, as no comparative data are available. The comparison of a pre-symptomatic patient population (NURTURE study) with a patient population with early symptomatic onset of therapy (BSC arm of the ENDEAR study) presented by the pharmaceutical company is also not relevant for the assessment of the additional benefit of nusinersen in pre-symptomatic patients with 5q SMA.

As the evidence considered for the benefit assessment differs for pre-symptomatic patients based on the number of SMN2 gene copies, a division into subsequent patient populations is made. It is assumed that patients with only 1 SMN2 gene copy are already prenatally or at birth severely symptomatic and consequently not included in the patient population of pre-symptomatic patients.

d1) Pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies

Transfer of the results of patients with early symptomatic therapy initiation to pre-symptomatic patients with 2 SMN2 gene copies

Based on the ENDEAR study, the present benefit assessment for patients with SMA type 1 derives an indication of major additional benefit. Furthermore, statistically significant advantages of considerable magnitude for nusinersen over BSC are shown for morbidity endpoints only in patients with a duration of disease ≤ 12 weeks (early symptomatic onset of therapy).

It was therefore examined whether the additional benefit from the comparison of nusinersen vs BSC in patients with early symptomatic start of therapy (duration of disease ≤ 12 weeks) of the ENDEAR study can be transferred to pre-symptomatic patients. For this purpose, only patients with 2 SMN2 gene copies were considered from the NURTURE study, as only patients with 2 SMN2 gene copies were included in the ENDEAR study.

A basic comparability between the patient populations used is assumed, since it can be assumed that the pre-symptomatic patients of the NURTURE study with 2 SMN2 gene copies will develop SMA type 1 in the natural course of the disease[2].

In the resolution, the results of nusinersen in pre-symptomatic patients are compared with the results of nusinersen in patients with early symptomatic start of therapy to examine whether the results of pre-symptomatic nusinersen administration are equal to or better than those of early symptomatic start of therapy (duration of disease ≤ 12 weeks).

Consistently across all benefit endpoints considered, a better outcome was seen with a pre-symptomatic initiation of therapy with nusinersen compared with an early symptomatic initiation of therapy. For endpoints of the endpoint category Side effects, no usable data are available. However, this does question the advantages in the benefit endpoints.

Despite the large uncertainties associated with an evidence transfer, it can be used for the benefit assessment if the following special circumstances are taken into account: SMA is a rare neuromuscular disease associated with a high mortality rate in the natural history of the disease. Although no clear prognosis can be derived, the number of SMN2 copies correlates with the severity of the disease. pre-symptomatic patients with 2 SMN2 gene copies develop a very severe type 1 disease course in about 80%[2], with a life expectancy of 1-2 years without therapy. The demonstrated advantages of a pre-symptomatic start of therapy in children with 2 SMN2 gene copies are supported by the proven risk of degeneration of the motor neurons until the appearance of first clinical symptoms and the knowledge that if clinical symptoms have already appeared, therapy has only limited success. In addition, young children with SMA are a particularly vulnerable patient population.

Consequently, the major additional benefit of treatment with nusinersen compared to BSC derived from the ENDEAR study can be applied to pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

Due to the uncertainty in translating evidence to pre-symptomatic patients, there is a hint of a major additional benefit of nusinersen in comparison to the appropriate comparator therapy BSC for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies.

d2) Pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies

Examination of the transfer of the results of the patients with SMA type 2 to pre-symptomatic patients with 3 SMN2 gene copies

Analogous to the evidence transfer for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies, it was examined whether the additional benefit from the comparison of nusinersen vs BSC in patients with SMA type 2 of the CHERISH study can be transferred to pre-symptomatic patients. For this purpose, patients with 3 SMN2 gene copies were considered from the NURTURE study, as the CHERISH study predominantly included patients with 3 SMN2 gene copies (88% of the study population). In the CHERISH study, duration of disease was prespecified in terciles (< 25, ≥ 25 to < 44, ≥ 44 months) as a subgroup characteristic. Within the subgroup with a duration of disease < 25 months, advantages for nusinersen over BSC are shown for the patient-relevant endpoints of morbidity HFMSE and RULM at day 456 (last available survey time point) for both endpoints. Furthermore, because the sub-population with the shortest duration of disease is more suitable for comparison with pre-symptomatic patients, the subpopulation with < 25 months duration of disease of the CHERISH study was considered.

However, a transfer of evidence based on the available data is not reasonably possible, as the morbidity endpoints HFMSE and RULM, for which the CHERISH study showed statistically significant advantages for nusinersen for patients with SMA type 2, were not collected in the NURTURE study or were only collected in patients who were > 2 years old at the time of the survey.

Referring to the reference on the assessment of the benefit of a pre-symptomatic start of therapy in the context of the analysis and evaluation of newborn screening for 5q SMA[4], this was reviewed for the present question regarding the benefit of a pre-symptomatic start of therapy for patients with 5q SMA and 3 SMN2 gene copies. As a result, the data provided for children with 3 SMN2 copies could only be used as a supplement for the assessment due to insufficient case numbers, but these point in the same direction as the results for children with 2 SMN2 copies and support the advantages of a pre-symptomatic start of therapy as shown above. The results of the IQWiG final report were used and taken into account by the G-BA in its resolution of 17 December 2020 to include 5q SMA in the extended newborn screening.

In the present written statement procedure, the clinical experts emphasised with reference to the follow-up data of the pilot project on newborn screening in Germany[5]. that better therapy results are achieved if treatment with nusinersen is already carried out pre-symptomatically.

It should be taken into account that patients with 3 SMN2 copies can be expected to develop the clinical symptomatology of a type 2 SMA (approx. 55%) or a type 1 SMA (approx. 15%) with increased disease severity, faster disease onset and poor prognosis in the natural course of the disease. However, some of the pre-symptomatic children with 3 SMN2 copies may also develop a milder form of the disease (type 3, approx. 30%); the variability is correspondingly greater than in pre-symptomatic children with 2 SMN2 copies.

Despite the very limited evidence-based on descriptive presentations and the associated very large uncertainties, these can be used for the benefit assessment by way of exception, taking into account the following special circumstances: SMA is a rare neuromuscular disease associated with a high mortality rate in the natural history of the disease. Although no clear prognosis can be derived, the number of SMN2 copies correlates with the severity of the disease. Pre-symptomatic patients with 3 SMN2 joint copies develop in majority (approx. 55%) a severe disease course of type 2[2], which without therapy is associated with a shorter life expectancy and severe limitations of motor function. The demonstrated signs of an advantage of pre-symptomatic therapy in children with 3 SMN2 gene copies is supported by the proven risk of degeneration of the motor neurons by the time the first clinical symptoms appear and the realisation that if clinical symptomatology is already present, therapy has only limited success. In addition, young children with SMA are a particularly vulnerable patient population.

Taken together, based on the evidence considered, there is evidence that pre-symptomatic initiation of treatment with nusinersen in children with 5q SMA and 3 SMN2 gene copies may lead to improved development in terms of achievement of motor milestones compared with disease progression without medicinal therapy. The evidence considered comprises only descriptive presentations and is accordingly very limited, so that no quantification of the extent of an additional benefit is possible. Due to the uncertainties associated with the strong limitation of evidence, only a hint of additional benefit can be derived.

In summary, for nusinersen for the treatment of pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies, taking into account the G-BA decision on the inclusion of 5q associated SMA in the expanded newborn screening, the additionally used data on pre-symptomatically treated patients with 5q SMA and 3 SMN2 gene copies, the written and oral statements presented in the hearing procedure, as well as the expected natural course of the disease in the patient population, there is a hint for an additional benefit compared to the appropriate comparator therapy BSC, which is non-quantifiable due to the limited evidence available.

d3) Pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies

No data are available to assess the additional benefit of pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of nusinersen, the severity of the disease and the statements of the medical societies on the current reality of care, nusinersen may represent a relevant therapeutic option for patients with 5q SMA type 3 / 4.

[5] Vill et al, 2021: Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. Orphanet J Rare Dis. PMID: 33789695

2.1.4 Summary of the assessment

The present evaluation is a new benefit assessment of the active ingredient nusinersen (Spinraza) due to the exceeding of the 50 million Euro turnover limit. Spinraza was approved as an orphan drug for the treatment of 5q spinal muscular atrophy.

In the therapeutic indication to be considered, 6 patient groups were distinguished:

a) Patients with 5q SMA type 1

b) Patients with 5q SMA type 2

c) Patients with 5q SMA type 3 / 4

d1) Pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies

d2) Pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies

d3) Pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies

Patient population a)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy. Data from the RCT ENDEAR are available to assess the additional benefit of nusinersen compared with the appropriate comparator therapy in patients with 5q SMA type 1. In mortality (overall survival) and in the morbidity endpoints “Permanent ventilation” and “Achievement of motor milestones”, there are statistically significant advantages for nusinersen for the subgroup patients with an age of ≤ 12 weeks at symptom onset (mortality) and for the subgroup patients with a duration of disease ≤ 12 weeks (morbidity endpoints), respectively. For the endpoint “Motor function (CHOP INTEND)”, there is also a statistically significant advantage for nusinersen.

The results of the subgroups cannot be interpreted conclusively due to the lack of studies on possible dependencies and in some cases the very small size of the subgroups, as well as with reference to the German health care context. Therefore, the additional benefit is derived for the total population of the ENDEAR study (patients with SMA type 1). There was no statistically significant difference for the endpoint “Serious respiratory events” and the endpoint “Hospitalisations” in the morbidity category. No data were collected in the quality of life category. In the category of side effects, there are no assessable data for nusinersen versus BSC overall.

The risk of bias in the ENDEAR study and the endpoints Overall survival, Death or Permanent ventilation, achievement of motor milestones measured by the HINE subscale 2, and serious respiratory events is considered low. For the endpoint motor function (CHOP INTEND), there is a high risk of bias due to the high proportion of missing values at start of study.

The overall conclusion is that there is indication of a major additional benefit of nusinersen over BSC.

Patient population b)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy. Data from the RCT CHERISH are available to assess the additional benefit of nusinersen compared with the appropriate comparator therapy in patients with 5q SMA type 2. Due to remaining uncertainties, it cannot be assumed with sufficient certainty that the best possible supportive therapy was implemented in the study in accordance with the German health care context, despite consideration of the study.

There were no deaths in the CHERISH study. In the morbidity endpoints “Achievement of motor milestones (HFSME)”, “Motor function of the upper limbs (RULM)”, statistically significant advantages for nusinersen are shown for patients with a duration of disease < 25 months. For the endpoint “Disease-related hospitalisation”, there is a statistically significant advantage of nusinersen compared to BSC. In the category Quality of life, for the endpoint “PedsQL”, there was no statistically significant difference between treatment groups.

In the category of side effects, there was a statistically significant difference for the specific AE endpoints Vomiting, Headache and Back pain to the disadvantage of nusinersen compared to BSC. Overall, however, no advantages or disadvantages can be derived for nusinersen compared to BSC based on the available data on the side effect profile.

The risk of bias in the CHERISH study and the potential for bias at the endpoint level are rated as low. However, the remaining uncertainties regarding the adequate implementation of BSC in the CHERISH study justify an overall downgrading of the reliability of data.

In the overall view, a hint of considerable additional benefit is identified of nusinersen in comparison with BSC.

Patient population c)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy. For the assessment of the additional benefit of nusinersen compared to the appropriate comparator therapy in patients with 5q SMA type 3/4, analyses from 3 registry sources and a comparison of individual arms of different studies are available.

After reviewing the suitability of the registry data, these cannot be considered for the benefit assessment due to ambiguities in the consideration of data generated outside the German health care context and in the information on the mean observation duration, as well as due to a lack of sufficient comparability of the patient populations and a high proportion of values for patient-relevant endpoints for the assessment of motor function that were already missing at the start of the study.

Similarly, the data from the comparison of individual arms of different studies are inappropriate for the benefit assessment due to a selective patient population, insufficient consideration of relevant confounders and a lack of consideration of the transferability of the data to the German health care context.

Therefore, the overall conclusion is that an additional benefit is not proven.

Nusinersen may be a relevant therapeutic option for patients with 5q SMA type 3 / 4.

Patient populations d1)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy. For the assessment of the additional benefit of nusinersen compared to the appropriate comparator therapy in pre-symptomatic patients, data from the 1-arm NURTURE study are available, as well as an unadjusted indirect comparison of treatment with nusinersen from the NURTURE study versus the BSC arm from the ENDEAR study.

The results of the 1-arm NURTURE study are inappropriate for assessing the additional benefit of nusinersen compared with the appropriate comparator therapy, as no comparative data are available. The comparison of a pre-symptomatic patient population with a patient population with early symptomatic onset of therapy presented by the pharmaceutical company is also not relevant for the assessment of the additional benefit of nusinersen in pre-symptomatic patients with 5q SMA.

Based on the ENDEAR study, the present benefit assessment for patients with SMA type 1 derives an indication of major additional benefit. It was therefore examined whether the additional benefit from the comparison of nusinersen vs BSC in patients with early symptomatic start of therapy (duration of disease ≤ 12 weeks) of the ENDEAR study can be transferred to pre-symptomatic patients. For this purpose, only patients with 2 SMN2 gene copies were considered from the NURTURE study, as only patients with 2 SMN2 gene copies were included in the ENDEAR study.

Consistently across all benefit endpoints considered, a better outcome was seen with a pre-symptomatic initiation of therapy with nusinersen compared with an early symptomatic initiation of therapy. For endpoints of the endpoint category Side effects, no usable data are available.

Despite the great uncertainties associated with an evidence transfer, this can be used for the benefit assessment in the present special case, since it is taken into account that pre-symptomatic patients with 2 SMN2 gene copies develop a very severe type 1 disease course in approx. 80% and the demonstrated advantages of a pre-symptomatic start of therapy are supported by the proven risk of degeneration of the motor neurons until the appearance of the first clinical symptoms.

Overall, there is a hint for a major additional benefit of nusinersen compared to the appropriate comparator therapy BSC.

Patient populations d2)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy.

For the assessment of the additional benefit of nusinersen compared to the appropriate comparator therapy in pre-symptomatic patients, data from the 1-arm NURTURE study are available.

Analogous to the evidence transfer for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies, it was examined whether the additional benefit from the comparison of nusinersen vs BSC in patients with SMA type 2 of the CHERISH study can be transferred to pre-symptomatic patients. However, it is not reasonably possible to transfer evidence on the basis of the available data.

Taking into account the G-BA decision on the inclusion of 5q SMA in the expanded newborn screening, the supplementary data on pre-symptomatically treated patients with 5q SMA and 3 SMN2 gene copies, the statements presented in the written and oral hearing procedure with reference to the follow-up data of the pilot project on newborn screening in Germany, as well as the expected natural course of the disease in the patient population, there are hints that a pre-symptomatic start of treatment with nusinersen in children with 5q SMA and 3 SMN2 gene copies leads to an improved development with regard to the achievement of motor milestones compared to the course of the disease without medicinal therapy.

Despite the very limited evidence based on descriptive presentations and the associated very large uncertainties, these can be used for the benefit assessment in the present special case, since it is taken into account that pre-symptomatic patients with 3 SMN2 gene copies mostly (approx. 55%) develop a severe type 2 disease course and the demonstrated advantages of a pre-symptomatic start of therapy are supported by the proven risk of degeneration of the motor neurons until the appearance of the first clinical symptoms.

Overall, there is a hint for a non-quantifiable additional benefit of nusinersen compared to the appropriate comparator therapy BSC.

Patient populations d3)

The G-BA determined Best supportive care (BSC) to be the appropriate comparator therapy.

No data are available to assess the additional benefit of pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies. An additional benefit is not proven.

Nusinersen may be a relevant therapeutic option for pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. Overall, the number of patients in the target population reported by the pharmaceutical company in the present procedure is slightly higher with respect to the lower limit and upper limit compared to the previous procedure. The group of patients with infantile SMA is larger in comparison mainly due to the included patients with incidence from previous years who are still alive in the current year of observation. The data are subject to uncertainty, partly because of the combination of a calculated prevalence rate with a cumulative incidence. Furthermore, there are uncertainties regarding the reported prevalence rate for SMA with later disease onset, especially for SMA type 2 and SMA type 3, as in the underlying study patients without evidence of a mutation of the SMN1 gene were excluded from the calculation, and it remains unclear whether these patients might also be included in the target population.

A reliable indication of the number of SHI patients for the group of pre-symptomatic patients with 5q SMA is currently not possible. This is justified subsequently:
Based on an incidence between 1:6,000 to 1:11,000 in newborns[6] based on the total population of SMA patients in Germany, a hint for the number of pre-symptomatic patients could be derived. However, this approach is subject to great uncertainty, as it can be assumed that only very few pre-symptomatic patients have been identified in Germany to date. A diagnosis before symptom onset was probably made mainly on the basis of a positive family history and accordingly covered only a small proportion of the total population of SMA patients in Germany. However, the number of patients diagnosed before symptom onset is expected to change in the future, as SMA has been introduced into general newborn screening in Germany in 2021.

Since it can be assumed that newborn screening for 5q SMA has a relevant influence on the number of pre-symptomatically diagnosed patients in Germany, in the sense of an expected increase, the present resolution refrains from stating the number of SHI patients for the group of pre-symptomatic patients with 5q SMA.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Spinraza (active ingredient: nusinersen) at the following publicly accessible link (last access: 16 February 2021):

https://www.ema.europa.eu/documents/product-information/spinraza-epar-product-information_de.pdf

The initiation and monitoring of treatment with nusinersen should only be carried out by specialists in paediatrics and adolescent medicine with a focus on neuropaediatrics or neurology who are experienced in the treatment of patients with spinal muscular atrophy

[6] Children's Policy: Newborn screening for 5q spinal muscular atrophy, resolution of 17.12.2020

(SMA). Since nusinersen is intended for intrathecal use, it should be administered only by physicians experienced in performing lumbar punctures.

Molecular genetic diagnostics regarding deletion or mutation of the SMN1 gene including determination of the SMN2 gene copy number for the presence of SMA should be performed.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 01 May 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments / patient / year”, time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Nusinersen 1st year	Day 0, 14, 28, 63, after that every four months	6,5	1	6,5
Nusinersen Subsequent years	every 4 months	3	1	3
Best supportive care	varies patient-individual			
Appropriate comparator therapy				
Best supportive care	varies patient-individual			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nusinersen 1st year	12 mg	12 mg	1 x 12 mg	6,5	6.5 x 12 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Nusinersen Subsequent years	12 mg	12 mg	1 x 12 mg	3	3 x 12 mg
Best supportive care	varies patient-individual				
Appropriate comparator therapy					
Best supportive care	varies patient-individual				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nusinersen	1 ILO	€ 92,473.94	€ 1.77	€ 5,280.63	€ 87,191.54
Best supportive care	varies patient-individual				
Appropriate comparator therapy					
Best supportive care	varies patient-individual				
Abbreviations: ILO = solution for injection					

LAUER-TAXE® last revised: 1 May 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken

into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Additionally required SHI services for the application of the medicinal product to be evaluated result from the intrathecal application via lumbar puncture according to the product information. At the time of the resolution, however, there is no fee structure item in the uniform assessment scale for the use of an antisense oligonucleotide, which is why the resulting costs are non-quantifiable.

Type of service Lumbar puncture	Costs per treatment	Number/patient per year	Costs/patient per year
1st year	Non-quantifiable	6,5	Non-quantifiable
Subsequent years	Non-quantifiable	3	Non-quantifiable

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 11 August 2020.

On 01 December 2020, the pharmaceutical company submitted a dossier for the benefit assessment of nusinersen to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 02 December 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nusinersen.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statements was 22 March 2021.

The oral hearing was held on 06 April 2021.

By letter dated 7 April 2021, the IQWiG was commissioned with a supplementary assessment of data submitted. The addendum prepared by IQWiG was submitted to the G-BA on 30 April 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	20 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	31 March 2021	Information on statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 April 2021 21 April 2021 5 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken