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Onasemnogene abeparvovec (spinal muscular atrophy) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Onasemnogen-Abeparvovec (spinale Muskelatrophie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CDC	Centers for Disease Control and Prevention
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
ddPCR	droplet digital polymerase chain reaction
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HINE	Hammersmith Infant Neurological Examination
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
qPCR	quantitative polymerase chain reaction
RCT	randomized controlled trial
RSV	respiratory syncytial virus
SGB	Sozialgesetzbuch (Social Code Book)
SMA	spinal muscular atrophy
SMN	survival motor neuron
SPC	Summary of Product Characteristics

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 onasemnogene abeparvovec. 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 17 May 2021.

Research question

The aim of the present report is the assessment of the added benefit of onasemnogene abeparvovec in comparison with the appropriate comparator therapy (ACT) in patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron (SMN)1 gene and either a clinical diagnosis of SMA type 1 or up to 3 copies of the SMN2 gene.

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

Table 2: Research questions of the benefit assessment of onasemnogene abeparvovec

Research question	Subindication	ACT[a]
	Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene with	
1	SMA type 1	Nusinersen
2	SMA type 2	
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b]
4	Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Nusinersen

a. Presentation of the respective 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.

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

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

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

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

Research question 1: patients with SMA type 1

Evidence provided by the company

There are no randomized controlled trials (RCTs) of direct comparison between onasemnogene abeparvovec and the ACT nusinersen or a corresponding indirect comparison based on RCTs for patients with SMA type 1. The company therefore presented a comparison of individual arms from different studies. For onasemnogene abeparvovec, the company included the single-arm studies AVXS-101-CL-101 (hereinafter referred to as "START" study), AVXS-101-CL-302 (hereinafter referred to as "STR1VE-EU" study) and AVXS-101-CL-303 (hereinafter referred to as "STR1VE-US" study) for patients with SMA type 1. For nusinersen, the company included the RCT ISIS 396443-CS3B (hereinafter referred to as "ENDEAR" study) and the single-arm study ISIS 396443-CS3A (hereinafter referred to as "CS3A" study) as well as the extension study ISIS 396443-CS11 (hereinafter referred to as "SHINE" study) to the ENDEAR study (SHINE-ENDEAR) and to the CS3A study (SHINE-CS3A).

However, the data presented by the company are unsuitable to draw conclusions on the added benefit of onasemnogene abeparvovec in comparison with nusinersen. This is justified below.

Evidence on onasemnogene abeparvovec

- Studies START, STR1VE-EU and STR1VE-US

The single-arm studies START, STR1VE-EU and STR1VE-US included patients with genetic documentation of a bi-allelic SMN1 mutation, 2 SMN2 gene copies, clinical SMA symptoms and an age of 6 months or less at the time of treatment. The patient populations include the subpopulation with 2 SMN2 gene copies of patients with SMA type 1.

The START study included 15 patients in 2 cohorts (cohort 1 [low dose]: N = 3, cohort 2 [therapeutic dose]: N = 12), the STR1VE-EU study included 33 patients, and the STR1VE-US study included 22 patients.

With the exception of cohort 1 of the START study, treatment with onasemnogene abeparvovec in all 3 studies was in compliance with the specifications of the Summary of Product Characteristics (SPC). Cohort 1 was not considered further due to the dosage, which was not in compliance with the approval. In addition to treatment with onasemnogene abeparvovec, the patients received supportive measures that can be regarded as sufficient implementation of a therapy in the sense of best supportive care (BSC) according to the recommendations for SMA.

Evidence on the appropriate comparator therapy nusinersen

- Study ENDEAR

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

Only the nusinersen arm (N = 81) is relevant for the comparison presented by the company. Treatment with nusinersen was by intrathecal bolus injection. After the last study visit, patients had the opportunity to participate in the open-label long-term SHINE study (see below).

- Study CS3A

The CS3A study is a single-arm dose-escalation study, which included patients with genetic documentation of 5q SMA who were 21 days to 7 months of age at screening and with symptom onset at ≥ 21 days and < 6 months of age. A total of 21 patients were included in the study, of which 20 patients in 2 cohorts (cohort 1: N = 4, cohort 2: N = 16) were treated with nusinersen. The patients received additional supportive measures that can be regarded as sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA.

Treatment with nusinersen was by intrathecal bolus injection. After the last study visit, patients could participate in the open-label long-term SHINE study (see below).

- Study SHINE

The SHINE study is an open-label, long-term study with patients who had previously participated in a nusinersen study (ENDEAR, CS3A, CHERISH, CS12 or EMBRACE). All included patients were treated with nusinersen in compliance with the SPC. No information on supportive measures is available. The patients were assigned to one of 5 groups depending on which study they had previously participated in. For the present research question, only the groups of the SHINE study are relevant that included patients who had already been treated with nusinersen in the studies ENDEAR and CS3A (hereinafter referred to as “SHINE-ENDEAR” or “SHINE-CS3A”).

Comparison of individual arms from different studies

For onasemnogene abeparvovec, the company used the pooled population from the studies START, STR1VE-EU and STR1VE-US for the comparison of individual arms of different studies. For nusinersen, the company used results from the pooled population of the studies SHINE-ENDEAR and SHINE-CS3A for the efficacy outcomes. On the nusinersen side, the company used the pooled safety populations of the studies ENDEAR and CS3A for the comparison for the harm outcomes.

Insufficient similarity of the study populations of the comparison of individual study arms presented by the company

The studies used by the company basically correspond to the research question. However, due to the lack of randomization, results from a comparison of individual arms of different studies are subject to inherent uncertainty, so that an added benefit can only be derived if the effects are sufficiently large. Among other things, a sufficient similarity of the study populations is assumed in the present data constellation. However, this is not the case in the comparison presented:

- Marked difference in disease durations

Although patients in the studies on onasemnogene abeparvovec and nusinersen had a similar age at symptom onset, patients in the onasemnogene abeparvovec studies were notably younger at the time of gene therapy compared with patients in the nusinersen studies at the first dose. Thus, the patients also differed notably with regard to the mean disease duration, measured as the time from symptom onset to the first dose or gene therapy (START: 8.7 weeks, STR1VE-EU: 10.8 weeks, STR1VE-US: 7.8 weeks versus ENDEAR: 15.4 weeks, CS3A: no data, taking into account available parameters, a mean period of 13.8 weeks is assumed).

Disease duration is a very important confounder. For example, the benefit assessment of nusinersen showed that the earlier the patients included in the ENDEAR study were treated with nusinersen after symptom onset, the greater the effectiveness of the treatment. A statistically significant and relevant effect in the outcomes “death or permanent ventilation”, “permanent ventilation” and “motor milestone achievement” (measured by the Hammersmith Infant Neurological Examination [HINE] Section 2) was only shown in the subgroup of patients with a disease duration ≤ 12 weeks (N = 34). However, this subgroup overall had a comparable median age at first dose and a comparable median disease duration as the patients included in the onasemnogene studies. If for nusinersen only the data of this subgroup of patients with a disease duration ≤ 12 weeks from the ENDEAR study are compared with the pooled data of the onasemnogene abeparvovec studies, it is shown that the effect becomes notably smaller for the composite outcome “death or permanent ventilation” and the individual components.

- Different inclusion and exclusion criteria regarding respiratory morbidity

Furthermore, when interpreting the results presented by the company, it must be taken into account that the inclusion and exclusion criteria with regard to ventilation and respiratory

symptoms differed between the studies on onasemnogene abeparvovec and nusinersen. As a result, the nusinersen studies potentially included patients with a less favourable prognosis regarding respiratory events at baseline than the onasemnogene abeparvovec studies. Data on ventilation subdivided according to type and duration of ventilation are not available for any of the studies. Furthermore, based on the available information on patient characteristics, no clear statements can be made on the comparability of the study populations with regard to disease severity at baseline.

Research question 2: patients with SMA type 2

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with nusinersen in patients with SMA type 2. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT nusinersen; an added benefit is therefore not proven.

Research question 3: patients with SMA type 3

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with treatment of physician's choice choosing from nusinersen or BSC in patients with SMA type 3. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT; an added benefit is therefore not proven.

Research question 4: pre-symptomatic patients

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with the ACT nusinersen for pre-symptomatic patients. The company did identify the ongoing single-arm study AVXS-101-CL-304 (hereinafter referred to as "SPR1NT" study) for onasemnogene abeparvovec, and the single-arm study 232SM201 (hereinafter referred to as "NURTURE" study) for nusinersen in pre-symptomatic patients with 2 or 3 SMN2 gene copies who were not allowed to be older than 6 weeks at the time of the first or one-dose treatment with the study medication. It did not conduct a comparison of the studies SPR1NT and NURTURE, however.

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

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Onasemnogene abeparvovec – extent and probability of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
	Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene with		
1	SMA type 1	Nusinersen	Added benefit not proven
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Nusinersen	Added benefit not proven

a. Presentation of the respective 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.

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 G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of onasemnogene abeparvovec in comparison with the ACT in patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and either a clinical diagnosis of SMA type 1 or up to 3 copies of the SMN2 gene.

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

Table 4: Research questions of the benefit assessment of onasemnogene abeparvovec

Research question	Subindication	ACT[a]
	Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene with	
1	SMA type 1	Nusinersen
2	SMA type 2	
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b]
4	Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Nusinersen

a. Presentation of the respective 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 [10]), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary.

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

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

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

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum treatment period of 12 months is required. This corresponds to the inclusion criteria of the company, which, however, also pointed out that in its view a longer observation period than 12 months may be necessary for specific outcomes.

2.3 Research question 1: patients with SMA type 1

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on onasemnogene abeparvovec (status: 12 April 2021)
- bibliographical literature search on onasemnogene abeparvovec (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on onasemnogene abeparvovec (last search on 18 February 2021)
- search on the G-BA website for onasemnogene abeparvovec (last search on 6 March 2021)
- bibliographical literature search on the ACT (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 18 February 2021)
- search on the G-BA website for the ACT (last search on 6 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on onasemnogene abeparvovec (last search on 20 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 20 May 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no relevant RCTs enabling a direct comparison or an adjusted indirect comparison with the ACT via a common comparator were identified from the check of the study pool.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it conducted a search for further investigations and presented a comparison of individual arms from different studies. In addition, it presented the results of the ongoing, single-arm long-term study AVXS-101-LT-001 [11,12] (hereinafter referred to as “LT-001” study) as supplementary information.

However, the data presented by the company are unsuitable to draw conclusions on the added benefit of onasemnogene abeparvovec in comparison with nusinersen. This is justified below.

2.3.1.1 Evidence provided by the company

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR[b] (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
Studies with onasemnogene abeparvovec						
AVXS-101-CL-101 (START[e])	Yes	Yes	No	No	Yes [13,14]	Yes [15-21]
AVXS-101-CL-302 (STR1VE-EU[e])	Yes	Yes	No	No	Yes [22,23]	Yes [20,21]
AVXS-101-CL-303 (STR1VE-US[e])	Yes	Yes	No	No	Yes [24,25]	Yes [20,21,26]
Studies with nusinersen						
ISIS 396443-CS3A (CS3A[e])	No	No	Yes	No	Yes [27,28]	Yes [29-31]
ISIS 396443-CS3B (ENDEAR[e])	No	No	Yes	No	Yes [32,33]	Yes [30,31,34-37]
ISIS 396443-CS11 (SHINE[e, f])	No	No	Yes	No	Yes [38,39]	Yes [30]

a. Study for which the company was sponsor.
b. 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.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
e. In the following tables, the study is referred to with this abbreviated form.
f. Patients from the studies ENDEAR and CS3A are followed up in the long-term SHINE study.

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

For onasemnogene abeparvovec, the company included the single-arm studies AVXS-101-CL-101 (hereinafter referred to as "START" study), AVXS-101-CL-302 (hereinafter referred to as "STR1VE-EU" study) and AVXS-101-CL-303 (hereinafter referred to as "STR1VE-US" study) for patients with SMA type 1. For nusinersen, the company included the RCT ISIS 396443-CS3B (hereinafter referred to as "ENDEAR" study) and the single-arm study ISIS 396443-CS3A (hereinafter referred to as "CS3A" study) as well as the extension study ISIS 396443-CS11 (hereinafter referred to as "SHINE" study) to the ENDEAR study (SHINE-ENDEAR) and to the CS3A study (SHINE-CS3A). The studies ENDEAR and SHINE-ENDEAR are already known from the benefit assessment of nusinersen [37].

Based on its search, in addition to the above-mentioned studies, the company identified the ongoing single-arm, long-term study LT-001, to which patients could cross over after completion of the START study, for patients with SMA type 1 for onasemnogene abeparvovec. The end of the study is planned for 2033. The company presented results for the data cut-off on 11 June 2020 as supplementary information because it considered these to show long-term efficacy of onasemnogene abeparvovec. A total of 13 patients from the START study (3 from cohort 1 [low dose] and 10 from cohort 2 [therapeutic dose], see below) crossed over into the long-term study. At the request of the parents, 7 of these 13 children (53.8%) started treatment with nusinersen during the first year of the study [20]. At the time of the data cut-off on 11 June 2020, the duration of follow-up observation was between 4.6 and 6.2 years. Concurring with the company, the results of this study are not considered for the present assessment. This is due to the fact that the results of the study cannot be meaningfully interpreted together with the other studies, as more than half of the patients included were also treated with nusinersen. The company itself excluded the LT-001 study from the comparison of individual arms of different studies on the grounds that the observation period of LT-001 study was longer than in SHINE-ENDEAR and SHINE-CS3A.

The evidence presented by the company in the comparison of individual arms of different studies is described below. Further information on study, intervention and patient characteristics of the studies included by the company can be found in Appendix B of the full dossier assessment.

Evidence on onasemnogene abeparvovec

Studies START, STR1VE-EU and STR1VE-US

The single-arm studies START, STR1VE-EU and STR1VE-US included patients with genetic documentation of a bi-allelic SMN1 mutation, 2 SMN2 gene copies (without c.859G>C mutation in exon 7), clinical SMA symptoms, and an age of 6 months or less at the time of treatment. In the START study, the inclusion of patients with an age ≤ 9 months at the time of treatment was possible until protocol version 2 of 24 June 2015; this concerned the first 9 patients recruited. The patient populations include the subpopulation with 2 SMN2 gene copies of patients with SMA type 1.

The START study included 15 patients in 2 cohorts (cohort 1 [low dose]: N = 3, cohort 2 [therapeutic dose]: N = 12, see below), the STR1VE-EU study included 33 patients, and the STR1VE-US study included 22 patients.

The study design of all 3 studies included a screening phase of up to 30 days, a treatment phase with a one-dose administration of onasemnogene abeparvovec in an inpatient setting, and a follow-up phase up to 24 months after administration of the study medication (START) or until the patients had reached 18 months of age (STR1VE-US and STR1VE-EU). Afterwards, the patients had the opportunity to participate in a long-term study. Patients from the START study could participate in the LT-001 study (see above), patients from the STR1VE studies in the AVXS-101-LT-002 study.

With the exception of cohort 1 (low dose [6.7 x 10^{13} vector genomes (vg)/kg body weight]) of the START study, treatment with onasemnogene abeparvovec in all 3 studies was in compliance overall with the specifications of the SPC [40]. Cohort 1 was not considered further by the company due to the dosage, which was not in compliance with the approval. The approach is appropriate. The dosage of 2.0 x 10^{14} vg/kg body weight in cohort 2 of the START study corresponds to the dosage of 1.1 x 10^{14} vg/kg body weight recommended in the SPC. The different concentration data are due to different measurement methods (quantitative polymerase chain reaction [qPCR] in the START study versus droplet digital PCR [ddPCR] in the STR1VE studies) [20]. In addition to treatment with onasemnogene abeparvovec, the patients received supportive measures.

Supportive measures

In accordance with the recommendations for the treatment of SMA [41,42], it is assumed that the patients in the studies always received supportive measures in the sense of BSC in addition to treatment with an active therapy. 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 all 3 studies on onasemnogene abeparvovec, patients were encouraged to follow the Centers for Disease Control and Prevention (CDC) recommendations or the recommendations of local European guidelines on routine vaccinations (including palivizumab prophylaxis to prevent respiratory syncytial virus [RSV] infection). Data on patients with ventilatory and nutritional support at baseline are available for all studies, but not for physiotherapeutic measures (see Table 13 in Appendix B.3 of the full dossier assessment). For the studies START and STR1VE-US, data on concomitant medications taken during the study are also available from the G-BA's benefit assessment [21]. In both studies, all included patients took at least one concomitant medication. The most commonly taken concomitant medications by ATC classification in the STR1VE-US study (N = 22) were vaccines (n = 21; 95.5%), analgesics (n = 16; 72.7%) and drugs for acid-related disorders (n = 15; 68.2%). The most commonly administered drugs in the START study (N = 12) were: paracetamol (n = 11; 91.7%), influenza vaccines (n = 9; 75.0%), ranitidine hydrochloride (n = 8; 66.7%), sodium chloride (n = 9; 75.0%), ibuprofen (n = 8; 66.7%), pneumococcal vaccine (n = 7, 58.3%), amoxicillin (n = 6; 50.0%), diphtheria/pertussis/tetanus vaccine (n = 6; 50.0%) and Haemophilus influenza type B vaccine (n = 7; 58.3%). Furthermore, none of the 3 studies explicitly excluded any drugs that could call into question the implementation of a BSC (see Table 12 in Appendix B.2 of the full dossier assessment).

In summary, the concomitant drug and non-drug measures used in the studies are considered a sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA [41,42].

The company did not comment on supportive measures in the dossier and therefore did not comment on whether it considered the supportive measures in the onasemnogene studies START, STR1VE-EU and STR1VE-US to correspond to a BSC.

Evidence on the appropriate comparator therapy nusinersen

Study ENDEAR

The ENDEAR study is a double-blind RCT. Patients in the study were either treated with nusinersen or received a sham intervention, each in addition to supportive measures, which correspond to a BSC (for a detailed description, see benefit assessment of nusinersen [37]). The study included patients with genetic documentation of 5q SMA and ≤ 7 months of age at study start as well as symptom onset at ≤ 6 months of age. According to the inclusion criteria, participation in the study was restricted to patients with 2 SMN2 gene copies. The included patient population thus only includes the subpopulation with 2 SMN2 gene copies of patients with SMA type 1.

A total of 122 patients were randomly allocated in a 2:1 ratio to treatment either with nusinersen (N = 81) or with a sham intervention (N = 41). Only the nusinersen arm is relevant for the comparison presented by the company. The BSC arm is therefore not considered further.

Treatment with nusinersen was given as an intrathecal bolus injection on study days 1, 15, 29, 64 (loading) and 183 and 302 (maintenance). In deviation from the recommendations in the SPC [43], dosing was age-adjusted in accordance with the regimen described in Table 12 in Appendix B.2 of the full dossier assessment. The deviation from the SPC had no overall influence on the present assessment and is not considered further (for information on the deviating dosage, see benefit assessment of nusinersen [37]).

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

Study CS3A

The CS3A study is a single-arm dose-escalation study, which included patients with genetic documentation of 5q SMA who were 21 days to 7 months of age at screening and with symptom onset at ≥ 21 days and < 6 months of age. The study population thus represents patients with SMA type 1. A total of 21 patients were included in the study, of which 20 patients in 2 cohorts (cohort 1: N = 4, cohort 2: N = 16) were treated with nusinersen and received additional supportive measures (see below).

Treatment with nusinersen was as an intrathecal bolus injection on study days 1, 15 and 85 (loading), followed by one maintenance dose on day 253 (i.e. 5.5 months after the last dose)

and then subsequent maintenance doses at 4-month intervals. According to the SPC [43], however, 4 loading doses should be given on days 0, 14, 28 and 63, followed by maintenance doses at 4-month intervals. In addition, in deviation from the specification provided in the SPC, the dosage was age-adjusted based on the volume of the cerebrospinal fluid: In cohort 1, patients received a dose equivalent to 6 mg from 2 years of age during the loading phase and a dose equivalent to 12 mg from 2 years of age during the maintenance phase. In cohort 2, patients received a dose equivalent to 12 mg from 2 years of age during both the loading phase and the maintenance phase. Overall, the deviation from the SPC is not that serious, so that consideration of the CS3A study is comprehensible in the present situation.

The study design of the CS3A study included a 21-day screening phase, a treatment phase (until day 1261) and a 3-month follow-up observation (until day 1352). After the last study visit, patients could participate in the open-label long-term SHINE study (see below).

Supportive measures

In accordance with the recommendations for the treatment of SMA [41,42], the patients in the CS3A study were to receive additional supportive measures in the sense of a BSC in addition to treatment with active therapy (for definition see earlier in this section).

In the CS3A 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 [9]. At study entry, patients had to receive adequate nutrition and hydration (with or without gastrostomy) in the opinion of the investigator, and had to have an age-appropriate body weight. In addition, baseline data are available on patients with ventilatory support and gastric feeding tubes, but not on physiotherapeutic measures (see Table 13 in Appendix B.3 of the full dossier assessment).

In summary, the concomitant drug and non-drug measures used in the study are considered a sufficient implementation of a therapy in the sense of a BSC according to the recommendations for SMA [41,42].

The company did not comment on supportive measures in the dossier and therefore did not comment on whether the supportive measures in the CS3A study corresponded to a BSC.

Study SHINE

The SHINE study is an open-label, long-term study with patients who had previously participated in a nusinersen study (ENDEAR, CS3A, CHERISH, CS12 or EMBRACE). All included patients were treated with nusinersen in compliance with the SPC [43]. No information on supportive measures is available. The patients were assigned to one of 5 groups depending on which study they had previously participated in (see Table 11 in Appendix B.1 of the full dossier assessment). For the present research question, only the groups of the SHINE study are relevant that included patients who had already been treated with nusinersen in the studies

ENDEAR and CS3A (hereinafter referred to as "SHINE-ENDEAR" or "SHINE-CS3A"). All patients in the nusinersen arm who completed the ENDEAR study entered the SHINE-ENDEAR study (N = 65). From the single-arm CS3A study, all patients who completed the study, with the exception of one child, also entered the SHINE-CS3A study (N = 13).

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.

2.3.1.2 Comparison of individual arms from different studies

For onasemnogene abeparvovec, the company used the pooled population (N = 66) from the studies START (cohort 2, N = 12), STR1VE-EU (N = 32) and STR1VE-US (N = 22) for the comparison of individual arms of different studies. For nusinersen, the company used results from the pooled population (N = 101) of the studies SHINE-ENDEAR (N = 81) and SHINE-CS3A for the efficacy outcomes (N = 20). The patient numbers refer to the patients originally included in the index studies ENDEAR and CS3A, as observation of these patients was continued in the studies SHINE-ENDEAR and SHINE-CS3A. On the nusinersen side, the company used the pooled safety populations (N = 100) of the studies ENDEAR (N = 80, nusinersen arm) and CS3A (N = 20) for the comparison for the harm outcomes.

In addition, the company presented the results of the individual studies START, STR1VE-EU and STR1VE-US as supplementary information in the dossier, and compared these results with those of the individual studies SHINE-ENDEAR and SHINE-CS3A for the efficacy outcomes, and with ENDEAR and CS3A for the harm outcomes.

Insufficient similarity of the study populations of the comparison of individual study arms presented by the company

The studies used by the company basically correspond to the research question. However, due to the lack of randomization, results from a comparison of individual arms of different studies are subject to inherent uncertainty, so that an added benefit can only be derived if the effects are sufficiently large.

With reference to IQWiG's *General Methods* [1] and the benefit assessment of onasemnogene abeparvovec by the G-BA [21], the company classified the effects in the comparison it presented for the composite outcome "death or permanent ventilation" and its individual components as "dramatic". The assessment of the company is not shared, as a sufficient similarity of the study populations is one of the prerequisites for the derivation of an added benefit in the present data constellation. However, this is not the case in the comparison presented (see below). Furthermore, it is pointed out that the comparison in the benefit assessment of the G-BA was made against BSC and not, as in the present benefit assessment, against nusinersen as the ACT.

Marked difference in disease durations

Although patients in the studies on onasemnogene abeparvovec and nusinersen had a similar age at symptom onset (see Table 13 in Appendix B.3 of the full dossier assessment), patients in the onasemnogene abeparvovec studies were notably younger at the time of gene therapy (START: 14.8 weeks, STR1VE-EU: 17.8 weeks, and STR1VE-US: 16.1 weeks) compared with patients in the nusinersen studies at the first dose (ENDEAR: 23.3 weeks; CS3A: no data [age at screening: 20.1 weeks]). Thus, the patients also differed notably with regard to the mean disease duration, measured as the time from symptom onset to the first dose or gene therapy (START: 8.7 weeks, STR1VE-EU: 10.8 weeks, STR1VE-US: 7.8 weeks versus ENDEAR: 15.4 weeks, see Table 13 in Appendix B.3 of the full dossier assessment). For the CS3A study, there is no information on the time between symptom onset and first dose, but only on the mean time between symptom onset and screening (11.6 weeks). Assuming a similar time between screening and first dose as in the ENDEAR study, the mean time between symptom onset and first dose for patients in the CS3A study was 13.8 weeks.

Disease duration is a very important confounder. For example, the benefit assessment of nusinersen showed that the earlier the patients included in the ENDEAR study were treated with nusinersen after symptom onset, the greater the effectiveness of the treatment. In particular, there was an effect modification by the characteristic of disease duration (≥ 12 weeks versus ≤ 12 weeks) for the outcomes “death or permanent ventilation”, “permanent ventilation” and “motor milestone achievement” (measured by the HINE Section 2). There was a statistically significant and relevant effect for all outcomes only in the subgroup of patients with a disease duration ≤ 12 weeks [37].

As described above, the patients in the onasemnogene abeparvovec studies had a notably shorter disease duration compared with the patient population of the ENDEAR study. However, the subgroup in the ENDEAR study with ≤ 12 weeks of disease duration (N = 34) had overall a comparable median age at first dose (16 weeks) and a comparable median disease duration (8 weeks) to patients enrolled in the onasemnogene abeparvovec studies (median age at first dose: 13.5 to 15.2 weeks; median disease duration: 7.4 to 10.9 weeks). If for nusinersen only the data of this subgroup of patients with a disease duration ≤ 12 weeks from the ENDEAR study are compared with the pooled data of the onasemnogene abeparvovec studies, it is shown that the observed effect estimation becomes notably smaller for the composite outcome “death or permanent ventilation” and the individual components (see Table 6).

Table 6: Influence of disease duration on treatment effect: onasemnogene abeparvovec vs. nusinersen

Outcome category Outcome	Onasemnogene abeparvovec (CL-303, CL-302 and CL-101)		Nusinersen (SHINE-ENDEAR and SHINE-CS3A)		Onasemnogene abeparvovec vs. nusinersen
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Mortality					
Overall survival	Comparison with nusinersen – pooled total populations				
	66	NA 2 (3.0)	101	NA 22 (21.8)	0.14 [0.03; 0.62]; < 0.001
	Comparison with nusinersen – subgroup ≤ 12 weeks disease duration				
	66	– 2 (3.0)	34[b]	– 3 (8.8)	RR: 0.34 [0.06; 1.96]; 0.260[c]
Morbidity					
Death or permanent ventilation[d]	Comparison with nusinersen – pooled total populations				
	66	NA 3 (4.5)	101	NA 49 (48.5)	0.08 [0.02; 0.26]; < 0.001
	Comparison with nusinersen – subgroup ≤ 12 weeks disease duration				
	66	– 3 (4.5)	34[b]	– 6 (17.6)	RR: 0.26 [0.07; 0.97]; 0.031[c]
Permanent ventilation	Comparison with nusinersen – pooled total populations				
	66	NA 1 (1.5)	101	NA 28 (27.7)	0.05 [0.01; 0.34]; < 0.001
	Comparison with nusinersen – subgroup ≤ 12 weeks disease duration				
	66	– 1 (1.5)	34[b]	– 3 (8.8)	RR: 0.17 [0.02; 1.59]; 0.085[c]

a. HR, 95% CI as well as p-value from a Cox model; no more detailed description of the model.
b. Subgroup of patients with a disease duration ≤ 12 weeks from the ENDEAR study.
c. Institute's calculation; effect RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [44]).
d. Composite outcome, composed of the individual components "death" and "permanent ventilation";
- nusinersen studies: for the ENDEAR study defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy; in the CS3A study defined as ventilation for ≥ 16 hours per day continuously for ≥ 14 days in the absence of acute reversible illness
- onasemnogene abeparvovec studies: ventilation defined as ≥ 16 hours per day continuously for ≥ 14 days in the absence of acute reversible illness and excluding perioperative ventilation

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RR: relative risk

Different inclusion and exclusion criteria regarding respiratory morbidity

Furthermore, when interpreting the results presented by the company, it must be taken into account that the inclusion and exclusion criteria with regard to ventilation and respiratory symptoms differed between the studies on onasemnogene abeparvovec and nusinersen. For example, the onasemnogene abeparvovec studies excluded patients with non-invasive ventilation, invasive ventilation or tracheostomy, whereas there were no restrictions regarding ventilation for inclusion in the nusinersen studies. As a result, the nusinersen studies potentially included patients with a less favourable prognosis regarding respiratory events at baseline than the onasemnogene abeparvovec studies. Data on ventilation subdivided according to type and duration of ventilation are not available for any of the studies. Furthermore, based on the available information on patient characteristics, no clear statements can be made on the comparability of the study populations with regard to disease severity at baseline (see Table 13 in Appendix B.3 of the full dossier assessment). For example, there were no differences at baseline for some disease characteristics (e.g. hypotension, weakness of the extremities, motor function measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease [CHOP INTEND]). For other characteristics, however, there were clear differences between the studies, both within the onasemnogene abeparvovec and nusinersen studies and between the studies on the intervention and comparator therapy (e.g. pneumonia or respiratory symptoms, patients with nutritional support, swallowing/feeding difficulties).

2.3.2 Results on added benefit

In its dossier, the company did not present any suitable data on the comparison of onasemnogene abeparvovec with nusinersen in patients with SMA type 1. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT nusinersen; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of onasemnogene abeparvovec in patients with SMA type 1. An added benefit of onasemnogene abeparvovec is not proven for this patient group.

This assessment differs from that of the company, which, based on the comparison of individual arms of different studies presented for patients with SMA type 1, derived a hint of non-quantifiable added benefit of at least considerable extent for the entire therapeutic indication of onasemnogene abeparvovec.

2.4 Research question 2: patients with SMA type 2

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on onasemnogene abeparvovec (status: 12 April 2021)
- bibliographical literature search on onasemnogene abeparvovec (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on onasemnogene abeparvovec (last search on 18 February 2021)
- search on the G-BA website for onasemnogene abeparvovec (last search on 6 March 2021)
- bibliographical literature search on the ACT (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 18 February 2021)
- search on the G-BA website for the ACT (last search on 6 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on onasemnogene abeparvovec (last search on 20 May 2021); for the search strategy, see Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

2.4.2 Results on added benefit

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with nusinersen in patients with SMA type 2. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT nusinersen; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of onasemnogene abeparvovec in patients with SMA type 2. An added benefit of onasemnogene abeparvovec is not proven for this patient group.

This assessment differs from that of the company, which, based on the comparison of individual arms of different studies presented for patients with SMA type 1, derived a hint of non-quantifiable added benefit of at least considerable extent for the entire therapeutic indication of onasemnogene abeparvovec.

2.5 Research question 3: patients with SMA type 3

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on onasemnogene abeparvovec (status: 12 April 2021)
- bibliographical literature search on onasemnogene abeparvovec (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on onasemnogene abeparvovec (last search on 18 February 2021)
- search on the G-BA website for onasemnogene abeparvovec (last search on 6 March 2021)

As the company did not identify any studies with patients with SMA type 3 on the basis of its information retrieval for onasemnogene abeparvovec, it conducted no search for the ACT of treatment of physician's choice choosing from nusinersen or BSC.

To check the completeness of the study pool:

- search in trial registries for studies on onasemnogene abeparvovec (last search on 20 May 2021); for the search strategy, see Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

2.5.2 Results on added benefit

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with treatment of physician's choice choosing from nusinersen or BSC in patients with SMA type 3. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of onasemnogene abeparvovec in patients with SMA type 3. An added benefit of onasemnogene abeparvovec is not proven for this patient group.

This assessment differs from that of the company, which, based on the comparison of individual arms of different studies presented for patients with SMA type 1, derived a hint of non-quantifiable added benefit of at least considerable extent for the entire therapeutic indication of onasemnogene abeparvovec.

2.6 Research question 4: pre-symptomatic patients

2.6.1 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 onasemnogene abeparvovec (status: 12 April 2021)
- bibliographical literature search on onasemnogene abeparvovec (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on onasemnogene abeparvovec (last search on 18 February 2021)
- search on the G-BA website for onasemnogene abeparvovec (last search on 6 March 2021)
- bibliographical literature search on the ACT (last search on 18 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 18 February 2021)
- search on the G-BA website for the ACT (last search on 6 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on onasemnogene abeparvovec (last search on 20 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 20 May 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no RCTs in pre-symptomatic SMA patients enabling a direct comparison or an adjusted indirect comparison with the ACT nusinersen via a common comparator were identified from the check of the study pool.

The company therefore conducted a search for further investigations and identified the ongoing single-arm study AVXS-101-CL-304 [45,46] (hereinafter referred to as “SPR1NT” study) for onasemnogene abeparvovec, and the single-arm study 232SM201 [47-49] (hereinafter referred to as “NURTURE” study) for nusinersen. The NURTURE study is already known from the benefit assessment of nusinersen [37].

The studies SPR1NT and NURTURE each included children with genetic documentation of a bi-allelic SMN1 mutation and 2 or 3 SMN2 gene copies. No clinical signs or symptoms of the disease were present at screening or immediately before administration of the study medication. Patients were not allowed to be older than 6 weeks at the time of the first or one-dose treatment

with the study medication. The studies thus correspond to research question 4 (pre-symptomatic patients).

The SPR1NT study included 30 children (14 with 2 SMN2 gene copies [cohort 1] and 15 with 3 SMN2 gene copies [cohort 2]). 4 SMN2 gene copies were detected in one patient in cohort 2. This patient was excluded from the cohort, but continued to be considered in the safety population. The NURTURE study included 25 children, comprising 15 children with 2 SMN2 gene copies and 10 children with 3 SMN2 gene copies.

Approach of the company

The company conducted no comparison of the studies SPR1NT and NURTURE. According to the company, final data in the form of a clinical study report are not yet available for either cohort. The SPR1NT study started on 10 April 2018 and ended on 29 January 2021 for cohort 1 (2 SMN2 gene copies). The expected end of the study for cohort 2 (3 SMN2 gene copies) is the second quarter of 2021. In the dossier, the company presented results of an interim analysis from 11 June 2020 for both cohorts as supplementary information, but did not use them for the derivation of the added benefit.

The company justified its approach of not comparing the studies SPR1NT and NURTURE with different follow-up observation periods and a necessary longer observation period, e.g. for the recording of motor milestones.

The argument of the company not to compare individual arms of different studies due to different follow-up observation periods in both studies is not appropriate. In the NURTURE study, patients with 2 SMN2 gene copies received follow-up observation for a median of 27 months and those with 3 SMN2 gene copies for 23 months. In the SPR1NT study, the median observation period at the interim data cut-off on 31 December 2019 was 9.9 months for patients with 2 SMN2 gene copies and 9.0 months for patients with 3 SMN2 gene copies. At the time of the further interim data cut-off from 11 June 2020 presented in the dossier, the median observation period for patients with 3 SMN2 gene copies was 14.5 months. For the patients with 2 SMN2 gene copies, no information on the observation period is available for this data cut-off, but it can be assumed that these patients were also observed for at least a similar length of time.

In summary, the median observation period in both studies, SPR1NT and NURTURE, was longer than 12 months. This corresponds to the inclusion criterion of a minimum duration of 12 months (see Section 2.2). An observation period of more than 12 months is generally desirable for the assessment of certain outcomes such as motor milestone achievement. However, this and the differences in follow-up observation periods between the studies are in principle not sufficient reasons for exclusion, provided that these different observation periods are taken into account in the analysis of the data and the interpretation of the results.

2.6.2 Results on added benefit

In its dossier, the company did not present any data on the comparison of onasemnogene abeparvovec with the ACT nusinersen for pre-symptomatic patients. This resulted in no hint of an added benefit of onasemnogene abeparvovec in comparison with nusinersen; an added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

The company presented no suitable data for the assessment of the added benefit of onasemnogene abeparvovec in comparison with nusinersen in pre-symptomatic patients. An added benefit of onasemnogene abeparvovec is not proven for this patient group.

This assessment deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit of at least considerable extent for the entire therapeutic indication of onasemnogene abeparvovec.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of onasemnogene abeparvovec in comparison with the ACT is summarized in Table 7.

Table 7: Onasemnogene abeparvovec – extent and probability of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
	Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene with		
1	SMA type 1	Nusinersen	Added benefit not proven
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[b]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene	Nusinersen	Added benefit not proven

a. Presentation of the respective 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 [10]), may be suitable in this therapeutic indication for treating the patient's individual symptoms of SMA or a corresponding ventilation of the patient, if necessary.

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 G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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