Gemeinsamer Bundesausschuss

Justification

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

of 4 November 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 studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing 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:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient onasemnogene abeparvovec (Zolgensma) was listed for the first time on 1 July 2020 in the "LAUER-TAXE®", the extensive German registry of available medicinal products and their prices. Zolgensma 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 3 December 2020, the G-BA provisionally suspended the resolution on the adoption of the benefit assessment of Zolgensma with the active ingredient onasemnogene abeparvovec for the treatment of spinal muscular atrophy in accordance with Section 35a, paragraph 1, sentence 3 SGB V after the €50 million turnover limit for orphan drugs was exceeded.

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 27 November 2020, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a paragraph 1, sentence 3 SGB V by 15 May 2021, due to exceeding the €50 million turnover limit within the period from November 2019 up to and including October 2020. 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 12 May 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 August 2021, 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 onasemnogene abeparvovec 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, and the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by 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 onasemnogene abeparvovec.

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 onasemnogene abeparvovec (Zolgensma®) in accordance with the product information

Zolgensma is indicated for the treatment of:

- patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

Therapeutic indication of the resolution (resolution of 04.11.2021):

- see the approved therapeutic indication

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a. Pre-symptomatic patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as

   Symptomatic patients with 5q SMA type 1 and 2 with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Appropriate comparator therapy for onasemnogene abeparvovec: Nusinersen

b. Symptomatic patients with 5q SMA type 3 with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

Appropriate comparator therapy for onasemnogene abeparvovec: Treatment according to the doctor's instructions with selection of nusinersen or BSC

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.

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 Federal Joint Committee has already determined the patient-relevant benefit 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 nusinersen is approved for the treatment of 5q spinal muscular atrophy. The active ingredient risdiplam is approved 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 gene 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. For the present therapeutic indications, the G-BA has passed resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient nusinersen on the 20 May 2021 and the active ingredient risdiplam on the 21 October 2021.

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 Section 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 limited.

In its resolution of 20 May 2021, the G-BA conducted a new benefit assessment for the active ingredient nusinersen after the €50 million turnover limit was exceeded. For patients with 5q SMA type 1, the G-BA found an indication of a considerable additional benefit for nusinersen compared with the appropriate comparator therapy best supportive care (BSC), and a hint of considerable additional benefit for patients with 5q SMA type 2, and for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies a hint for a considerable additional benefit and for pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies a hint for a non-quantifiable additional benefit. An additional benefit for nusinersen compared to BSC is not proven for patients with 5q SMA type 3 / 4, as well as for pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies. However, the G-BA indicated that nusinersen might be a relevant treatment option for patients with 5q SMA type 3 / 4 and for pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies, taking into account the evidence presented on the medical benefit, the severity of the disease and the statements of the scientific-medical societies on the current reality of care.

Cochrane reviews on the medicinal treatment of patients with spinal muscular atrophy type 1 and for type 2, and 3 and a systematic review on the treatment of SMA with nusinersen were included in the evidence synopsis. Accordingly, treatment with nusinersen to improve motor function is recommended for patients with early and late onset SMA based on a high level of evidence. It should be noted that there is currently insufficient evidence to support efficacy in SMA types 3 and 4 or to initiate treatment in adults. The evidence synopsis also includes a guideline with recommendations for the non-medicinal treatment of SMA.

A resolution on the benefit assessment procedure for the active ingredient risdiplam, which received marketing authorisation in March 2021, was passed only on 21 October 2021. Therefore, and due to the fact that they are not yet available on the market for a

long time, the active ingredient cannot be considered as an appropriate comparator therapy for the present procedure.

Based on the available evidence, the G-BA determined nusinersen as an appropriate comparator therapy for pre-symptomatic patients with 5q SMA and up to 3 copies of the SMN2 gene and for symptomatic patients with 5q SMA types 1 and 2 and up to 3 copies of the SMN2 gene. For symptomatic patients with 5q SMA type 3 and up to 3 copies of the SMN2 gene, the G-BA considers therapy according to doctor's instructions with the selection of nusinersen or BSC to be an appropriate comparator therapy.

"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 symptomatology of spinal muscular atrophy, or appropriate ventilation of the patient, as necessary.

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

2.1.3 Extent and probability of the additional benefit

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

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

Appropriate comparator therapy:

Nusinersen

Extent and probability of the additional benefit of onasemnogene abeparvovec compared to the appropriate comparator therapy:

An additional benefit is not proven

b) Patients with 5q SMA type 2 and up to 3 copies of the SMN2 gene

Appropriate comparator therapy:

Nusinersen

Extent and probability of the additional benefit of onasemnogene abeparvovec compared to the appropriate comparator therapy

An additional benefit is not proven

c) Patients with 5q SMA type 3 and up to 3 copies of the SMN2 gene

Appropriate comparator therapy:

Treatment according to the doctor's instructions with the selection of nusinersen or BSC

Extent and probability of the additional benefit of onasemnogene abeparvovec compared to the appropriate comparator therapy:

An additional benefit is not proven

d) Pre-symptomatic patients with 5q SMA and up to 3 copies of the SMN2 gene

Appropriate comparator therapy:

Nusinersen

Extent and probability of the additional benefit of onasemnogene abeparvovec compared to the appropriate comparator therapy:

An additional benefit is not proven

Justification:

a) Patients with 5q SMA type 1

For the present patient population, no randomised controlled trials (RCTs) were identified by the pharmaceutical company that allow a direct or an adjusted indirect comparison via a common bridge comparator versus the appropriate comparator therapy nusinersen. Therefore, the pharmaceutical company submits individual arms from different studies for a comparison between onasemnogene abeparvovec and nusinersen.

Patients with SMA type 1 include the 1-arm studies START, STR1VE-EU and STR1VE-US for onasemnogene abeparvovec and the ENDEAR RCT and the 1-arm CS3A study, as well as its extension study SHINE, for nusinersen.

Evidence on onasemnogene abeparvovec

The 1-arm START, STR1VE-EU, and STR1VE-US studies enrolled patients with genetic evidence of a biallelic SMN1 mutation, 2 SMN2 gene copies, clinical SMA symptoms, and an age of 6 months or less at the time of treatment. The START study included 15 patients in 2 cohorts (cohort 1 with low dosage: N = 3 and cohort 2 with therapeutic dosing: N = 12), the STR1VE-EU study included 33 patients, and the STR1VE-US study included 22 patients. Cohort 1 of the START study will not be considered further due to dosing not being compliant with the marketing authorisation. The study design of all 3 studies included a screening phase of up to 30 days, a treatment phase in which patients were treated with onasemnogene abeparvovec once as inpatients, and a follow-up phase up to 24 months after the administration of the study medication (START) or until patients reached 18 months of age (STR1VE-US and STR1VE-EU). Subsequently, the patients had the opportunity to participate in a long-term study. In addition to the treatment with onasemnogene abeparvovec, the patients received additional

supportive measures, which are to be regarded as sufficient implementation of therapy in the sense of BSC according to the recommendations for SMA.

The START study was conducted at a centre in the United States between May 2014 and December 2017. The STR1VE-US study was conducted at 12 centres in the United States between October 2017 and December 2019, and the STR1VE-EU study was conducted at 10 centres in Belgium, France, Italy, and the United Kingdom between August 2018 and November 2020.

Evidence on the appropriate comparator therapy with nusinersen

The ENDEAR study consists of a double-blind RCT that includes patients with genetically documented 5q SMA, age at the start of study ≤ 7 months, age at symptom onset ≤ 6 months, and 2 SMN2 gene copies. In the study, 81 patients received treatment with nusinersen, and 41 patients received a sham intervention, each in addition to supportive measures equivalent to a BSC. Only the nusinersen arm is relevant for the comparison presented by the pharmaceutical company. Treatment with nusinersen was given as an intrathecal bolus injection on study days 1, 15, 29, 64 (saturation), and 183 and 302 (maintenance). The age-adjusted dosage deviated from the instructions given in the product information. Due to the proof of the efficacy of nusinersen through positive effects for the endpoint achievement of motor milestones, the study was terminated before the end of the planned study duration (14 months). The median observation period to the final data cut-off 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. The 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.

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

Treatment with nusinersen was given as an intrathecal bolus injection. After the last study visit, patients could participate in the open-label long-term SHINE study. The study was conducted in 4 centres in Canada and the United States between May 2013 and June 2017.

The SHINE study is an open-label long-term study with patients who had previously participated in a study with nusinersen. All included patients were treated with nusinersen according to the product information. No information on supportive measures is available. Patients were assigned to one of 5 groups depending on which study they had previously participated in. Only the groups of the SHINE study with patients who have already been treated with nusinersen in the ENDEAR and CS3A studies are relevant for the present research question. The study has been running since May 2015 at 42 centres worldwide, with a planned end date of 2023.

Comparability of the patient populations considered and suitability of the indirect comparisons presented

Patients in the onasemnogene abeparvovec and nusinersen studies were similar in age at symptom onset. However, at the time of gene therapy, patients in the onasemnogene abeparvovec studies were significantly younger (START: 14.8 weeks, STR1VE-EU: 17.8 weeks and STR1VE-US: 16.1 weeks) compared to patients in the nusinersen studies at 1st dose (ENDEAR: 23.3 weeks; CS3A: not specified [age at screening: 20.1 weeks]). As a result, there are also significant differences in the mean duration of disease, measured as the time from symptom onset to the 1st dose or gene therapy (START: 8.7 weeks, STR1VE-EU: 10.8 weeks, STR1VE-US: 7.8 weeks vs ENDEAR: 15.4 weeks, CS3A: not specified).

The disease duration is a very significant confounder. In the benefit assessment of the active ingredient nusinersen, it was shown in this respect that the effectiveness of the treatment is greater the earlier the patients included in the ENDEAR study are treated with nusinersen after the symptom onset. For the endpoints death or permanent ventilation, permanent ventilation and achievement of motor milestones measured by the Hammersmith Infant Neurological Examination (HINE) subscale 2, for example, there is an effect modification by the characteristic disease duration, a statistically significant difference in favour of nusinersen is shown only for the subgroup of patients with a disease duration ≤ 12 weeks. If for the present procedure for nusinersen only the data of this subgroup from the ENDEAR study are compared with the pooled data of the onasemnogene abeparvovec studies, it can be seen that the observed effect estimate becomes significantly smaller for the combined endpoint death or permanent ventilation and the individual components.

With its written statement, the pharmaceutical company submitted a recalculation of the indirect comparison for the subgroup of patients in the onasemnogene abeparvovec and the nusinersen studies with a disease duration ≤ 12 weeks for the endpoints death and permanent ventilation as well as for the combined endpoint death or permanent ventilation.

However, methodological uncertainties exist in the subsequently submitted indirect comparison of the subgroups of patients with a disease duration of ≤ 12 weeks. Among other things, the time from symptom onset to screening was used as an approximation of the time to first dose for patients treated with nusinersen, whereas the time from symptom onset to the date of the signed consent form was used for patients treated with onasemnogene abeparvovec. Given the small number of patients and events in both the onasemnogene abeparvovec and nusinersen studies, the unjustified deviation from the operationalisation of disease duration is potentially important. On the basis of the available information, it remains questionable whether the different operationalisation allows an adequate formation of comparable sub-populations with a duration of disease < 12 weeks. Furthermore, the subsequently submitted analyses for the subgroups with a disease duration < 12 weeks are not complete because evaluations for the endpoint "achievement of motor milestones" are missing.

Furthermore, there are differences in the inclusion and exclusion criteria between the onasemnogene abeparvovec and nusinersen studies with respect to ventilation and respiratory symptomatology. In the onasemnogene abeparvovec studies, patients with non-

invasive ventilation, invasive ventilation or tracheostomy were excluded, while in the nusinersen studies, there were no restrictions on ventilation for study enrolment. Thus, patients with a less favourable prognosis regarding respiratory events at the start of the study were potentially enrolled in the nusinersen studies. Also, with regard to the severity of the disease at the start of the study, no clear conclusions can be drawn regarding the comparability of the study populations based on the information provided by the patient characteristics.

The subsequently submitted data on the ventilation status before start of study of patients with a disease duration < 12 weeks from the ENDEAR study confirm that the extended inclusion criteria of the nusinersen studies potentially bias the result to the disadvantage of nusinersen.

Due to the large uncertainties mentioned above, the presented comparisons of individual arms from different studies between onasemnogene abeparvovec and nusinersen are unsuitable for the benefit assessment of onasemnogene abeparvovec and accordingly cannot be used to derive an additional benefit. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 1.

b) Patients with 5q SMA type 2 and up to 3 copies of the SMN2 gene

The pharmaceutical company does not present any data for the assessment of the additional benefit of onasemnogene abeparvovec compared to nusinersen. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 2 and up to 3 copies of SMN2 gene.

c) Patients with 5q SMA type 3 and up to 3 copies of the SMN2 gene

The pharmaceutical company does not present any data for the assessment of the additional benefit of onasemnogene abeparvovec compared to therapy according to doctor's instructions with the selection of nusinersen or BSC. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 3 and up to 3 copies of SMN2 gene.

d) Pre-symptomatic patients with 5q SMA and up to 3 copies of the SMN2 gene

For the present research question, the pharmaceutical company identifies the ongoing 1-arm SPR1NT study for onasemnogene abeparvovec and the 1-arm NURTURE study for nusinersen

but does not compare individual arms from the two studies. Therefore, no appropriate data are available to assess the added benefit of onasemnogene abeparvovec compared with nusinersen. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for pre-symptomatic patients with 5q SMA and up to 3 copies of SMN2 gene.

2.1.4 Summary of the assessment

The present evaluation is a benefit assessment of the medicinal product "Zolgensma" with the active ingredient onasemnogene abeparvovec due to exceeding the 50 million Euro turnover limit. The initial resolution for the first placing of Zolgensma on the (German) market was temporarily suspended after the 50 million Euro turnover limit for orphan drugs was exceeded. Zolgensma was approved under special conditions for the treatment of patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.
In the therapeutic indication to be considered, 4 patient groups were distinguished.

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

The G-BA determined nusinersen as appropriate comparator therapy. The pharmaceutical company submits single arms from the START, STR1VE-EU and STR1VE-US studies (1-arm studies with onasemnogene abeparvovec) and ENDEAR and CS3A (RCT and 1-arm study with nusinersen) for a comparison between onasemnogene abeparvovec and nusinersen.

However, in the considered patient populations for onasemnogene abeparvovec and nusinersen, there are significant differences regarding the mean disease duration, which is a very significant confounder. In addition, there are differences in the inclusion and exclusion criteria regarding ventilation and respiratory symptomatology, so that potential patients with a less favourable prognosis regarding respiratory events at the start of the study were included in the nusinersen studies. The recalculation of the indirect comparison for the subgroup of patients in the onasemnogene abeparvovec and nusinersen studies with a disease duration ≤ 12 weeks submitted in the written comments of the pharmaceutical company also shows uncertainties.

The presented comparisons of individual arms from different studies between onasemnogene abeparvovec and nusinersen are unsuitable for the benefit assessment of onasemnogene abeparvovec due to the large uncertainties and, consequently, cannot be used to derive an additional benefit. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies

on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 1.

b) Patients with 5q SMA type 2 and up to 3 copies of the SMN2 gene

The G-BA determined nusinersen as appropriate comparator therapy. The pharmaceutical company does not present any data for the assessment of the additional benefit of onasemnogene abeparvovec compared to nusinersen. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 2 and up to 3 copies of SMN2 gene.

c) Patients with 5q SMA type 3 and up to 3 copies of the SMN2 gene

The G-BA determined the appropriate comparator therapy to be a therapy according to the doctor's instructions with the selection of nusinersen or BSC. The pharmaceutical company does not present any data for the assessment of the additional benefit of onasemnogene abeparvovec compared to therapy according to doctor's instructions with the selection of nusinersen or BSC. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for patients with 5q SMA type 3 and up to 3 copies of SMN2 gene.

d) Pre-symptomatic patients with 5q SMA and up to 3 copies of the SMN2 gene

The G-BA determined nusinersen as appropriate comparator therapy. For the present research question, the pharmaceutical company identifies the ongoing 1-arm SPR1NT study for onasemnogene abeparvovec and the 1-arm NURTURE study for nusinersen but does not compare individual arms from the two studies. Therefore, no appropriate data are available to assess the added benefit of onasemnogene abeparvovec compared with nusinersen. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of onasemnogene abeparvovec, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, onasemnogene abeparvovec may represent a relevant therapeutic option for pre-symptomatic patients with 5q SMA and up to 3 copies of SMN2 gene.

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 range given is an underestimate. For its estimation of the target population, the pharmaceutical company only takes into account incident patients and consequently no prevalent patients. The pharmaceutical company operationalises the target population as patients with SMA type 1 and 2. This leads to uncertainties in the determination of patient numbers. In addition, there are ambiguities or discrepancies in the underlying studies.

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[2] 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 positive family history and accordingly covered only a small percentage of the total population of SMA patients in Germany. However, the number of patients and patients diagnosed before and after 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 Zolgensma (active ingredient: onasemnogene abeparvovec) at the following publicly accessible link (last access: 11 August 2021):

https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf

The resolution of 20 November 2020 on requirements for a quality-assured application for the use of onasemnogene abeparvovec in spinal muscular atrophy provides further details.

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

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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: 15 October 2021).

Onasemnogene abeparvovec is a gene therapy intended for administration as a single dose by intravenous infusion.

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.

The dosage of onasemnogene abeparvovec is based on body weight. The costs of the infusion solutions of different dosages do not differ from the LAUER-TAXE®'s last revision that was used. The product information for Zolgensma (last revised May 2021) lists dosage recommendations for patients weighing between 2.6 kg and 21 kg.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Onasemnogene abeparvovec	Single dose	1	1	1
Patient population c:				
Best supportive care	different from patient to patient			
Appropriate comparator therapy				
Patient population a, b and d				
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

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Patient population c				
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	different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Onasemnogene abeparvovec	1.1 x 10^{14} vector genomes (vg)/kg	3.3 × 10^{14} vg - 2.31 × 10^{15} vg	16.5 ml - 115.5 ml	1	1 infusion solution
Patient population c:					
Best supportive care	different from patient to patient				
Appropriate comparator therapy					
Patient population a, b and d					
Nusinersen 1st year	12 mg	12 mg	1 x 12 mg	6.5	6.5 x 12 mg
Nusinersen Subsequent years	12 mg	12 mg	1 x 12 mg	3	3 x 12 mg
Patient population c					
Nusinersen 1st year	12 mg	12 mg	1 x 12 mg	6.5	6.5 x 12 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ 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	different from patient to patient				

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 Section 130 and Section 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. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Onasemnogene abeparvovec is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance, and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19 % value-added tax, in deviation from the LAUER-TAXE® data usually taken into account.

Costs of the medicinal products:

Medicinal product to be assessed					
Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value-added tax)			
Onasemnogene abeparvovec	1 INF	€ 2,314,550			
Patient population c:					
Best supportive care	different from patient to patient				
Appropriate comparator therapy					
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
Nusinersen 12 mg	1 SFI	€ 92,473.94	€ 1.77	€ 5,280.63	€ 87,191.54

Best supportive care	different from patient to patient
Abbreviations: INF = infusion solution; SFI = solution for injection	

LAUER-TAXE® last revised: 15 October 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.

Prior to the use of onasemnogene abeparvovec, an AAV9 antibody test should be performed using an appropriately validated test. There is not yet a billing number for the test in the EBM catalogue. AAV tests, in general, are billed via code 32641, "Similar investigations with an indication of antibody specificity".

The pharmaceutical company states in module 3 of the dossier that he is currently making the genetic test freely available.

According to the product information, immunomodulatory pre- and concomitant medication with a corticosteroid (e.g. prednisolone) is required. Due to the weight-dependent dosage and the different treatment durations, the necessary costs for immunomodulatory therapy vary from patient to patient and are not quantified here.

Measurement of troponin I level is required prior to the use of Zolgensma according to the product information, and monitoring of troponin I level following administration should be considered for at least 3 months. For the immunological evidence of troponin-I, there is only one EBM number in the EBM catalogue for billing in the presence of clinical symptomatology.

Additionally required SHI services for the application of nusinersen 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 calculation

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

At its session on 24 November 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of onasemnogene abeparvovec to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 17 May 2021, 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 onasemnogene abeparvovec.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 16 August 2021. The deadline for submitting written statements was 6 September 2021.

The oral hearing was held on 28 September 2021.

By letter dated 28 September 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 15 October 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 was discussed at the session of the subcommittee on 26 October 2021, and the proposed resolution was approved.

At its session on 4 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	24 November 2020	Determination of the appropriate comparator therapy

Working group Section 35a	14 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	28 September 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 October 2021 19 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken