Risdiplam
(spinal muscular atrophy, < 2 months)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CMAP	compound muscle action potential
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
SMA	spinal muscular atrophy
SMN	survival motor neuron
SPC	Summary of Product Characteristics
WHO	World Health Organization

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug risdiplam. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 September 2023.

Research question

The aim of the present report is to assess the added benefit of risdiplam in comparison with the appropriate comparator therapy (ACT) in patients with 5q-associated spinal muscular atrophy (SMA), aged < 2 months, with a clinical diagnosis of SMA type 1 or with 1 to 4 copies of the survival of motor neuron (SMN) 2 gene.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of risdiplam

Research question	**Therapeutic indication**	**ACT**[a]
	5q-associated SMA in patients < 2 months of age	
1	Presymptomatic, with up to 3 copies of the SMN2 gene	Treatment of physician's choice, selecting from nusinersen and onasemnogene abeparvovec[b]
2	Symptomatic, with clinically diagnosed SMA type 1	
3	Presymptomatic, with up to 4 copies of the SMN2 gene	Treatment of physician's choice choosing from nusinersen and BSC[b, c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for these patient groups.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In this therapeutic indication, suitable treatments may include various interventions, e.g. physiotherapy as per catalogue of remedies, for treating the patient-specific symptoms of SMA or, if necessary, appropriate ventilation. Furthermore, it is assumed that BSC in the context of a study is (additionally) offered both in the control groups and in the intervention groups. In presymptomatic patients with 5q-associated SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; 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 body of the text:

- research question 1: presymptomatic patients with up to 3 copies of the SMN2 gene

- research question 2: symptomatic patients with SMA type 1
- research question 3: presymptomatic patients with 4 copies of the SMN2 gene

In deviation from the specification by the G-BA, the company identified 2 research questions without differentiating between symptomatic and presymptomatic patients. For its research question, the company named as the ACT treatment of physician's choice, taking into account nusinersen and onasemnogene abeparvovec for patients with up to 3 copies of the SMN2 gene and nusinersen and BSC for its research question on patients with 4 copies of the SMN2 gene. The present benefit assessment was conducted using the research questions and ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit.

Results

Data and argumentation on added benefit presented by the company

RAINBOWFISH study

The RAINBOWFISH study is an ongoing single-arm study of risdiplam in presymptomatic patients with genetic evidence of 5q-associated SMA. A total of 26 patients were included who were not older than 6 weeks at the time of the first dose. There was no restriction on the number of copies of the SMN2 gene. Risdiplam treatment was largely in compliance with the Summary of Product Characteristics (SPC). The primary outcome of the study is the proportion of patients with 2 copies of the SMN2 gene and a baseline compound muscle action potential (CMAP) amplitude ≥ 1.5 mV who can sit unsupported for 5 seconds after 12 months of treatment. Secondary outcomes are outcomes on mortality, morbidity, and adverse events (AEs). The company presents results of the planned primary analysis after all patients have been treated for at least 12 months, both separately for children with 2, 3 and ≥ 4 SMN2 gene copies and for all included patients combined.

Company's argumentation

Based on the results of the RAINBOWFISH study, the company argues that the development of the children who were presymptomatically diagnosed and treated with risdiplam largely represents age-appropriate development. This also applies to motor development, which is reportedly largely within the range expected for healthy children according to the World Health Organization (WHO). In addition, the company states that the studies on presymptomatically diagnosed patients treated with nusinersen (NURTURE study) and onasemnogene abeparvovec (SPR1NT study) likewise showed that the standards of age-appropriate development to be expected in healthy children were approximately met. It is reportedly a safe assumption that age-appropriate development can be achieved regardless

of the type of disease-modifying therapy if the patient receives a presymptomatic diagnosis and earliest possible start of therapy. However, the company did not present corresponding comparative data on presymptomatic patients from the RAINBOWFISH study on risdiplam, the NURTURE study on nusinersen, or the SPR1NT study on onasemnogene abeparvovec (see below). The company further argues that the oral form of risdiplam precludes the side effects of intrathecal administration of nusinersen. In addition, the company sees an advantage in the daily administration of risdiplam compared to the single application of onasemnogene abeparvovec because it deems the continuous administration to prevent the occurrence of clinically relevant trough levels and to thus ensure continuous protection of motor neurons. In summary, the company concludes that the oral dosage form and the continuous administration of risdiplam for all patients treated with risdiplam in the therapeutic indication result in a hint of a non-quantifiable added benefit.

Assessment of the presented data and the company's reasoning

The single-arm RAINBOWFISH study presented by the company does not enable a comparison versus the ACT. Thus, there are no suitable data for assessing the added benefit as per any of the 3 research questions for risdiplam in patients with genetic evidence of 5q-associated SMA who are aged < 2 months. The company’s approach of deriving added benefit solely based on the oral and continuous administration of risdiplam is not appropriate. In principle, it is plausible for the oral administration of risdiplam to be preferable to the intrathecal administration of nusinersen due to the high probability of morbidity associated with intrathecal administration. However, it is unclear whether continuous administration is advantageous when compared with a single dose of onasemnogene abeparvovec, as argued by the company. No comparative data are available (see below) to support the advantages claimed by the company for risdiplam based on oral administration (compared to nusinersen) and continuous administration (compared to onasemnogene abeparvovec). In its argumentation for deriving added benefit, the company furthermore generally disregards the specified ACT – treatment of physician’s choice – by merely noting that age-appropriate motor development is also approximately achieved under onasemnogene abeparvovec and nusinersen. In addition, no information retrieval was conducted on other investigations for the ACT.

Below, the data presented by the company for the individual research questions are assessed separately, using the overarching aspects mentioned above.

Research question 1: presymptomatic patients with up to 3 copies of the SMN2 gene

For presymptomatic patients with up to 3 copies of the SMN2 gene, results are available at least from the single-arm studies RAINBOWFISH on risdiplam, NURTURE on nusinersen, and SPR1NT on onasemnogene abeparvovec. Overall, the company's dossier lacks a comparative analysis of the evidence on the 3 treatment options which would be necessary to show

approximately equal, age-appropriate development as claimed by the company or potential differences between the treatment options in a comparison of individual arms of different studies. However, it is questionable overall to what extent it would be possible to derive an advantage for 1 of the 3 therapies of risdiplam, nusinersen, or onasemnogene abeparvovec for research question 1 on the basis of a comparison of individual arms of the 3 studies RAINBOWFISH, NURTURE, and SPR1NT.

Research question 2: symptomatic patients with SMA type 1

No data are available for symptomatic patients with clinically diagnosed SMA type 1 aged < 2 months.

Research question 3: presymptomatic patients with 4 copies of the SMN2 gene

The company's dossier presents no data for presymptomatic patients with 4 copies of the SMN2 gene. Regarding the RAINBOWFISH results on risdiplam which were presented by the company for the 5 included patients with ≥ 4 copies of the SMN2 gene, it remains unclear what proportion of patients possessed exactly 4 copies of the SMN2 gene. Irrespective of this question, the NURTURE study provides no data on patients with 4 copies of the SMN2 gene on the ACT for the treatment option of nusinersen because the study enrolled no children with 4 SMN2 gene copies. The dossier likewise contains no data on the treatment option of BSC.

Results on added benefit

Since no suitable data are available for the benefit assessment of risdiplam, there is no hint of an added benefit of risdiplam in comparison with the ACT for any of the 3 research questions; an added benefit is therefore not proven.

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 risdiplam.

[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: Risdiplam – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
	5q-associated SMA in patients < 2 months of age		
1	Presymptomatic, with up to 3 copies of the SMN2 gene	Treatment of physician's choice, selecting from nusinersen and onasemnogene abeparvovec[b]	Added benefit not proven
2	Symptomatic, with clinically diagnosed SMA type 1		Added benefit not proven
3	Presymptomatic, with up to 4 copies of the SMN2 gene	Treatment of physician's choice choosing from nusinersen and BSC[b, c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for these patient groups.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In this therapeutic indication, suitable treatments may include various interventions, e.g. physiotherapy as per catalogue of remedies, for treating the patient-specific symptoms of SMA or, if necessary, appropriate ventilation. Furthermore, it is assumed that BSC in the context of a study is (additionally) offered both in the control groups and in the intervention groups. In presymptomatic patients with 5q-associated SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of risdiplam in comparison with the ACT in patients with 5q-associated SMA, aged < 2 months, with a clinical diagnosis of SMA type 1, or with 1 to 4 copies of the SMN 2 gene.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of risdiplam

Research question	Therapeutic indication	ACT[a]
	5q-associated SMA in patients < 2 months of age	
1	Presymptomatic, with up to 3 copies of the SMN2 gene	Treatment of physician's choice, selecting from nusinersen and onasemnogene abeparvovec[b]
2	Symptomatic, with clinically diagnosed SMA type 1	
3	Presymptomatic, with up to 4 copies of the SMN2 gene	Treatment of physician's choice choosing from nusinersen and BSC[b, c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for these patient groups.
c. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In this therapeutic indication, suitable treatments may include various interventions, e.g. physiotherapy as per catalogue of remedies, for treating the patient-specific symptoms of SMA or, if necessary, appropriate ventilation. Furthermore, it is assumed that BSC in the context of a study is (additionally) offered both in the control groups and in the intervention groups. In presymptomatic patients with 5q-associated SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; 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: presymptomatic patients with up to 3 copies of the SMN2 gene
- research question 2: symptomatic patients with SMA type 1
- research question 3: presymptomatic patients with 4 copies of the SMN2 gene

In deviation from the specification by the G-BA, the company identified 2 research questions without differentiating between symptomatic and presymptomatic patients. It notes that, since the introduction of newborn screening for SMA, patients have generally been diagnosed presymptomatically. For its research question, the company named as the ACT treatment of physician's choice, taking into account nusinersen and onasemnogene abeparvovec for patients with up to 3 copies of the SMN2 gene and nusinersen and BSC for its research

question on patients with 4 copies of the SMN2 gene. The present benefit assessment was conducted using the research questions listed in Table 4 and the ACT specified by the G-BA.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risdiplam (status: 21 August 2023)
- bibliographical literature search on risdiplam (last search on 24 July 2023)
- search in trial registries / trial results databases for studies on risdiplam (last search on 24 July 2023)
- search on the G-BA website for risdiplam (last search on 21 August 2023)

To check the completeness of the study pool:

- search in trial registries for studies on risdiplam (last search on 26 September 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no randomized controlled trials (RCTs) for the comparison of risdiplam versus the ACT for any of the 3 research questions in the therapeutic indication to be assessed. Due to the lack of directly comparative studies versus the ACT, the company additionally conducted an information retrieval on other investigations for risdiplam, identifying the single-arm study RAINBOWFISH [3-5] (see following section). The company has conducted no information retrieval on other investigations for the ACT. To derive added benefit, the company has presented the results of the RAINBOWFISH study and derived an added benefit from what it considered to be an advantage of the oral dosage form and the continuous administration of risdiplam for all patients in this therapeutic indication.

The data presented by the company are unsuitable for drawing any conclusions on the added benefit of risdiplam in comparison with the ACT in patients with 5q-associated SMA, aged < 2 months, with a clinical diagnosis of SMA type 1, or with 1 to 4 copies of the SMN2 gene. Below, the evidence presented by the company is described, and the reasons for its unsuitability for deriving added benefit for the individual research questions are provided.

I 3.1 Data and argumentation on added benefit presented by the company

RAINBOWFISH study

In Module 4 A, the company presents the RAINBOWFISH study. Study and intervention characteristics of the study are presented in I Appendix B of the full dossier assessment. The study is an ongoing single-arm study of risdiplam in presymptomatic patients with genetic evidence of 5q-associated SMA. A total of 26 patients were included. Patients were to have

no clinical signs/symptoms strongly suggestive of SMA at screening or at baseline and were not be older than 6 weeks at the time of the first dose. There was no restriction on the number of copies of the SMN2 gene. Eight patients had 2 copies of the SMN2 gene, 13 patients had 3 copies, and 5 patients had ≥ 4 copies. It is unclear how many of the enrolled patients had > 4 copies of the SMN2 gene and were therefore not covered by the marketing authorization. However, the maximum possible proportion is 19% (5/26).

Risdiplam was administered once daily orally. Participants were treated with a target area-under-the-curve-at-steady-state ($AUC_{024h,\ ss}$) of 2000 ng*h/mL. Before reaching the age of 2 months, 20 of 26 patients were treated continuously with 0.2 mg/kg instead of the 0.15 mg/kg specified by the SMC [6]. Six patients received a lower dose (between 0.04 and 0.08 mg/kg) for a short period of time (between 15 and 53 days) at the start of the study for the purpose of investigating safety and pharmacokinetics, receiving 0.2 mg/kg only after this period. From an age of approximately 2 months, all patients were treated with 0.2 mg/kg, and from approximately 2 years, with 0.25 mg/kg as per SPC [6]. At the start of treatment, participants were aged between 16 and 41 days. Since all children – except 1 patient with treatment discontinuation after 323 days – were treated for at least 12 months at the data cutoff of the primary analysis available in the dossier (20 February 2023), the dosing in departure from the SPC in the first 2 months of life is deemed negligible compared to the total treatment duration.

As per study protocol, all included children were to receive SMA treatment according to local standards. Physiotherapy, occupational therapy, or other exercise therapies were encouraged. As per study protocol, however, the frequency was not to be changed over the course of the study. It is impossible to deduce from the available documentation the extent to which the frequency of these therapeutic interventions remained unchanged in the study and whether this requirement restricted optimal individualized care. A total of 2 patients received physiotherapy during the course of the study, but the study report rated this treatment to be unrelated to SMA. Further, the study protocol explicitly mentioned drugs which are generally recommended as suitable supportive therapies in the therapeutic indication [7], e.g. inhaled drugs like anticholinergics, antibiotic treatments, and laxatives. While the study protocol did not explicitly list (noninvasive or invasive) ventilation as an allowed concomitant treatment, time to permanent ventilation was recorded as an outcome in the RAINBOWFISH study; therefore, ventilation therapy was presumably provided as needed during the course of the study. One patient required noninvasive ventilation at Month 12. Overall, the concomitant drug and nondrug interventions used in the study are deemed a sufficient implementation of BSC therapy for SMA.

The primary outcome of the study is the proportion of patients with 2 copies of the SMN2 gene and a baseline CMAP amplitude ≥ 1.5 mV who can sit unsupported for 5 seconds after

12 months of treatment (as per item 22 of the gross motor skills scale of the Bayley Scales of Infant and Toddler Development Third Edition [BSID-III]). Secondary outcomes are outcomes on mortality, morbidity, and AEs.

The company presents results of the planned primary analysis after all patients have been treated for at least 12 months, both separately for children with 2, 3 and ≥ 4 SMN2 gene copies and for all included patients combined. In addition, the company presents results of an interim analysis with data cutoff date 1 July 2021 in Appendix 4G of Module 4 A.

Argumentation of the company

Based on the results of the RAINBOWFISH study, the company argues that the development of the children who were presymptomatically diagnosed and treated with risdiplam largely represents age-appropriate development. This also applies to motor development, which is largely within the range expected for healthy children according to the WHO [8,9]. In addition, the company states that the studies on presymptomatically diagnosed patients treated with nusinersen (NURTURE study) and onasemnogene abeparvovec (SPR1NT study) likewise showed that the standards of age-appropriate development to be expected in healthy children were approximately met. It is reportedly a safe assumption that age-appropriate development can be achieved regardless of the type of disease-modifying therapy if the patient receives a presymptomatic diagnosis and earliest possible start of therapy. However, the company did not present corresponding comparative data on presymptomatic patients from the RAINBOWFISH study on risdiplam, the NURTURE study on nusinersen, or the SPR1NT study on onasemnogene abeparvovec (see below). The company further argues that the oral form of risdiplam precludes the side effects of intrathecal administration of nusinersen. In addition, the company sees an advantage in the daily administration of risdiplam compared to the single application of onasemnogene abeparvovec because it deems the continuous administration to prevent the occurrence of clinically relevant trough levels and to thus ensure continuous protection of motor neurons. In summary, the company concludes that the oral dosage form and the continuous administration of risdiplam for all patients treated with risdiplam in the therapeutic indication result in a hint of a non-quantifiable added benefit.

I 3.2 Assessment of the presented data and the company's reasoning

The single-arm RAINBOWFISH study presented by the company does not enable a comparison versus the ACT specified by the G-BA. Thus, there are no suitable data for assessing the added benefit as per any of the 3 research questions for risdiplam in patients with genetic evidence of 5q-associated SMA who are aged < 2 months. The company’s approach of deriving added benefit solely based on the oral and continuous administration of risdiplam is not appropriate. In principle, it is plausible for the oral administration of risdiplam to be preferable to the intrathecal administration of nusinersen due to the high probability of morbidity associated with intrathecal administration. However, it is unclear whether continuous administration is

advantageous when compared with a single dose of onasemnogene abeparvovec, as argued by the company. No comparative data are available (see below) to support the advantages claimed by the company for risdiplam based on oral administration (compared to nusinersen) and continuous administration (compared to onasemnogene abeparvovec). Furthermore, in its argumentation for deriving the added benefit, the company generally disregards the specified ACT – treatment of physician's choice – by merely noting that age-appropriate motor development is also approximately achieved with onasemnogene abeparvovec and nusinersen. The company conducted no information retrieval on other investigations for the ACT (see Section I 3).

Below, the data presented by the company for the individual research questions are assessed separately, using the overarching aspects mentioned above.

Research question 1: presymptomatic patients with up to 3 copies of the SMN2 gene

For presymptomatic patients with up to 3 copies of the SMN2 gene, results are available at least from the single-arm studies RAINBOWFISH on risdiplam, NURTURE on nusinersen [10,11], and SPR1NT on onasemnogene abeparvovec [12,13]. These 3 studies each enrolled presymptomatic patients with genetic evidence of 5q-associated SMA who were to be ≤ 6 weeks old at the time of the first dose and were not to exhibit any clinical signs/symptoms strongly suggestive of SMA at screening or at the start of the study. All 3 studies record patient-relevant outcomes on mortality, morbidity (e.g. permanent ventilation, motor function, or achievement of motor milestones) and side effects. For this purpose, more current data with longer treatment durations from 2 later data cutoffs from the NURTURE study [14,15] and from the final data cutoff of the SPR1NT study [16,17] are available regarding the treatment options of nusinersen and onasemnogene abeparvovec as part of the ACT, alongside results on early data cutoffs which are available in the respective dossiers of the benefit assessment procedures for nusinersen and onasemnogene abeparvovec [18,19].

Overall, the company's dossier lacks a comparative analysis of the evidence on the 3 treatment options which would be necessary to show approximately equal, age-appropriate development as claimed by the company or potential differences between the treatment options in a comparison of individual arms of different studies. This review was to include in particular the comparative presentation of the study, intervention, and patient characteristics, including the patient-relevant outcomes recorded and corresponding operationalizations, as well as the comparative presentation of the results on all patient-relevant outcomes between the children treated with risdiplam and with the ACT in the present therapeutic indication. However, it is overall questionable to what extent it would be possible to derive an advantage for 1 of the 3 therapies of risdiplam, nusinersen, or onasemnogene abeparvovec for research question 1 on the basis of a comparison of individual arms of the 3 studies RAINBOWFISH, NURTURE, and SPR1NT.

Research question 2: symptomatic patients with SMA type 1

In its dossier, the company distinguished between patients with 5q-associated SMA aged < 2 months who had up to 3 versus those with 4 copies of the SMN2 gene, without differentiating between symptomatic and presymptomatic patients (see Section I 2). The company's dossier therefore did not separately consider the research question of symptomatic patients with SMA type 1 aged < 2 months. The company describes that, since the nationwide introduction of newborn screening for SMA in Germany, patients aged < 2 months have usually been diagnosed presymptomatically. Even though the introduction of newborn screening has caused patients with SMA type 1 aged <2 months to make up a smaller proportion of all patients with SMA indicated for this treatment, they are included in this therapeutic indication. For risdiplam in patients aged < 2 months with available results, the company only identified the RAINBOWFISH study in presymptomatic patients (see Section I 3.1). No study for risdiplam in symptomatic patients with SMA type 1 aged < 2 months was identified during the review of the completeness of the study pool. Only in the FIREFISH study [20] do the inclusion criteria allow the enrolment of children with SMA type 1 aged < 2 months. However, no child of this age was included. Thus, no data are available for assessing the added benefit of risdiplam for symptomatic patients with SMA type 1 in the present therapeutic indication.

Research question 3: presymptomatic patients with 4 copies of the SMN2 gene

The company's dossier presents no data for presymptomatic patients with 4 copies of the SMN2 gene. Regarding the RAINBOWFISH results on risdiplam presented by the company for the 5 included patients with ≥ 4 copies of the SMN2 gene, it remains unclear which proportion of patients possessed exactly 4 copies of the SMN2 gene (see Section I 3). Irrespective of this question, the NURTURE study provides no data on patients with 4 copies of the SMN2 gene on the ACT for the treatment option of nusinersen because the study enrolled no children with 4 SMN2 gene copies. The dossier likewise contains no data on the treatment option of BSC.

I 3.3 Summary and conclusion

The company's derivation of an added benefit for all patients treated with risdiplam in the present therapeutic indication solely based on the oral and continuous administration is not appropriate. Due to the lack of comparative evidence on the ACT, including a lack of information retrieval, it is impossible to properly assess the added benefit of risdiplam for presymptomatic patients with up to 3 copies of the SMN2 gene (research question 1). However, it is questionable overall to what extent an advantage for one of the 3 therapies risdiplam, nusinersen, or onasemnogene abeparvovec could be derived on the basis of a comparison of individual arms of the 3 studies RAINBOWFISH, NURTURE, and SPR1NT. For symptomatic patients with SMA type 1 (research question 2) and presymptomatic patients with 4 copies of the SMN2 gene (research question 3), no (suitable) data are available to assess the added benefit of risdiplam compared with the ACT.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of risdiplam compared with the ACT in presymptomatic patients with 5q-associated SMA who are aged < 2 months and possess 1 to 3 copies (research question 1) or 4 copies of the SMN2 gene (research question 3). No data are available for symptomatic patients with 5q-associated SMA type 1 aged < 2 months (research question 2). There is no hint of added benefit of risdiplam in comparison with the ACT for any of the research questions; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of risdiplam in comparison with the ACT is summarized in Table 5.

Table 5: Risdiplam – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
	5q-associated SMA in patients < 2 months of age		
1	Presymptomatic, with up to 3 copies of the SMN2 gene	Treatment of physician's choice, selecting from nusinersen and onasemnogene abeparvovec[b]	Added benefit not proven
2	Symptomatic, with clinically diagnosed SMA type 1		Added benefit not proven
3	Presymptomatic, with up to 4 copies of the SMN2 gene	Treatment of physician's choice choosing from nusinersen and BSC[b, c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA's note, a single-comparator study is generally not sufficient for these patient groups.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In this therapeutic indication, suitable treatments may include various interventions, e.g. physiotherapy as per catalogue of remedies, for treating the patient-specific symptoms of SMA or, if necessary, appropriate ventilation. Furthermore, it is assumed that BSC in the context of a study is (additionally) offered both in the control groups and in the intervention groups. In presymptomatic patients with 5q-associated SMA with 4 SMN2 gene copies, watchful waiting appears to be an adequate implementation of BSC.

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

The assessment described above deviates from that by the company. Without differentiating between symptomatic and presymptomatic patients, the company derives a hint of nonquantifiable added benefit for patients with 5q-associated SMA who are aged < 2 months and possess up to 3 copies of the SMN2 gene as well as for those with 4 copies of the SMN2 gene.

The G-BA decides on the added benefit.

I 6 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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