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Risdiplam (spinal muscular atrophy) – Addendum to Commission A21-50[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Sascha Abbas
- Lars Beckmann
- Lisa Junge
- Beate Wieseler

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
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)
MAIC	matching-adjusted indirect comparison
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMA	spinal muscular atrophy

1 Background

On 7 September 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-50 (Risdiplam – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had presented a comparison of individual arms from the FIREFISH study [3-6] with risdiplam and of the nusinersen arm of the ENDEAR study [7-9] for patients with 5q spinal muscular atrophy (SMA), 2 months of age and older, with SMA type 1 (research question 1 of the benefit assessment). For the FIREFISH study, results were available for 2 data cut-offs (1 year and 2 years after inclusion of the last patient). For the comparison presented in the dossier, the company used the data cut-off at 1 year after inclusion of the last patient for the FIREFISH study, and the final data cut-off from 16 December 2016 for the ENDEAR study. Results of the ISIS 396443-CS11 study (hereinafter referred to as the "SHINE" study) [10-12] were not considered. The SHINE study is an open-label, long-term study with patients who had previously participated in a nusinersen study, including the ENDEAR study.

In the context of the commenting procedure, the company presented a comparison of individual arms of the studies FIREFISH and ENDEAR with longer observation periods, using the data cut-off at 2 years after inclusion of the last patient for the FIREFISH study and the data cut-off from 27 August 2019 for the SHINE study. It presented, on the one hand, a matching-adjusted indirect comparison (MAIC) analysis without a common comparator and, on the other hand, an unadjusted comparison, referred to by the company as "naive" comparison.

The G-BA commissioned IQWiG to assess the "naive" comparison for SMA type 1 with the longer observation period presented with the comments, taking into account the information provided in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Comparison of individual arms of different studies

In the following, the data of the comparison of individual arms of the studies FIREFISH and ENDEAR with longer observation periods, which were subsequently submitted in the commenting procedure, are assessed. The data cut-off at 2 years after inclusion of the last patient was used for the FIREFISH study, and the data cut-off from 27 August 2019 for the SHINE study.

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

- Mortality
  - overall survival
- Morbidity
  - death or permanent ventilation
  - motor functioning measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND)
  - motor milestone achievement measured by the Hammersmith Infant Neurological Examination (HINE) Section 2
  - serious respiratory events
- health-related quality of life
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - further specific AEs, if any

Table 1 shows which of the outcomes for which the company presented comparative analyses of the studies FIREFISH and ENDEAR in its comments can be considered in the benefit assessment. Further outcomes considered as patient-relevant are additionally included in the matrix.

Table 1: Matrix of outcomes – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1)

	Outcomes								
	Overall survival	**Death or permanent ventilation[a]**	**Motor functioning (CHOP INTEND)**	**Motor milestone achievement (HINE Section 2)**	**Serious respiratory events**	**Hospitalization**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**
Comparison of individual arms of the studies FIREFISH and ENDEAR	Consid-ered[b]	Consid-ered	Not consid-ered[c]	Not consid-ered[d]	Not consid-ered[d]	Not consid-ered[e]	No[f]	Not consid-ered[g]	Not consid-ered[g]

a. Composite outcome consisting of the individual components "death" and "permanent ventilation" (defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy); see dossier assessment A21-50 [1] for comparability of the operationalizations used in the studies FIREFISH and ENDEAR.
b. Considered in the framework of the presentation of the composite outcome "death or permanent ventilation".
c. Regardless of the validity of the response criterion, no sufficiently large effect that could not be based on systematic bias alone.
d. No statistically significant group difference or no sufficiently large effect that could not be based on systematic bias alone.
e. According to the operationalization, both studies also include events that do not have to be associated with the disease (FIREFISH: any hospitalizations; ENDEAR: hospitalizations for monitoring for general observation, due to symptoms after dosing, due to SAEs or additional investigations [e.g. planned surgery such as placement of a gastric feeding tube for preventive reasons]).
f. Health-related quality of life was not recorded in either study.
g. In the ENDEAR study, high proportion of events of the underlying disease or events that can be both side effects and symptoms of the underlying disease (e.g. SOC "respiratory, thoracic and mediastinal disorders"). In Appendix 4G of its dossier, the company presented analyses for the FIREFISH study without consideration of disease-related events. It cannot be inferred from Module 4A of the dossier which events were excluded from the analyses. There is no comparison with the ENDEAR study without consideration of disease-related events.

AE: adverse event; CHOP INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease; HINE: Hammersmith Infant Neurological Examination; SAE: serious adverse event; SOC: System Organ Class

Observation periods in the analyses presented

For the present assessment, the data from the SHINE study are used for long-term data of the patients from the nusinersen arm of the ENDEAR study (SHINE-ENDEAR). Of the 81 patients randomized to the nusinersen arm of the ENDEAR study, 65 patients crossed over to the SHINE-ENDEAR study. The basis for the analyses presented are the 81 patients who were

originally randomized into the nusinersen arm of the ENDEAR study. A description of the SHINE study can be found in dossier assessment A20-114 [13].

According to the information provided by the company in the comments, the median observation period for the patients in the nusinersen arm of the ENDEAR study was 2.8 patient years. A reference is not available. Module 4 A.4 of the dossier for the benefit assessment of nusinersen in 2020 [12] provided information on the observation period of the SHINE study only for the 65 patients who crossed over from the nusinersen arm of the ENDEAR study to SHINE-ENDEAR, but not for all 81 patients in the nusinersen arm of the ENDEAR study. The mean observation period for the 65 patients was 2.8 years, and the median observation period was 2.9 years. Data on the observation period of all 81 patients in the nusinersen arm of the ENDEAR study are not available.

For the FIREFISH study, the company reported a median observation period of 2.2 years for the data cut-off presented for this addendum.

The presented event time analyses considered potentially different observation periods, however.

Results

For the assessment of the added benefit of risdiplam in comparison with nusinersen in patients with SMA type 1, the results of the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR presented by the company are shown below. Only the outcomes for which there were clear effects under the assumption of comparable operationalizations are considered. The outcome "overall survival" is considered in the framework of the presentation of the composite outcome "death or permanent ventilation".

Kaplan-Meier curves on the presented outcomes can be found in Appendix A.

Table 2: Results (mortality and morbidity, time to event) – comparison of individual arms of different studies: risdiplam vs. nusinersen (SMA type 1)

Outcome category Outcome	Risdiplam (study FIREFISH part 1, cohort 2 + part 2)[a]		Nusinersen (study SHINE-ENDEAR)[b]		Risdiplam 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][c]; p-value
Mortality					
Overall survival[d]	58	ND 5 (8.6)	81	ND 18 (22.2)	0.35 [0.10; 0.81] ND
Morbidity					
Death or permanent ventilation[e]	58	ND 9 (15.5)	81	ND 40 (49.4)	0.24 [0.09; 0.44] ND
Permanent ventilation	58	ND 4 (6.9)	81	ND 24 (29.6)	0.18 [0.04; 0.40]; ND

a. Data cut-off 2 years after inclusion of the last patient.
b. Data cut-off from 27 August 2019.
c. HR and CI based on unstratified Cox model.
d. Considered in the framework of the presentation of the composite outcome "death or permanent ventilation".
e. Composite outcome consisting of the individual components "death" and "permanent ventilation" (defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy); see dossier assessment A21-50 [1] for comparability of the operationalizations used in the studies FIREFISH and ENDEAR.

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; ND: no data; SMA: spinal muscular atrophy

Individual aspects of bias for the 2 studies or for the outcomes presented are not assessed, as the available data involve the use of individual arms of different studies. No more than hints can be derived on the basis of the data presented.

Mortality

Overall survival

Operationalization

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome "overall survival".

Result

Based on a comparison of individual arms of the studies FIREFISH and ENDEAR, there was a statistically significant difference between the treatment arms with regard to the outcome "overall survival".

Morbidity

Death or permanent ventilation and individual component of permanent ventilation

Operationalization

The outcome operationalization in the 2 studies is sufficiently comparable and both components (permanent ventilation, death) were assessed as sufficiently similar in terms of their severity (see dossier assessment A21-50 [1]). The results for time to death or permanent ventilation were used for the composite outcome.

Result

Based on the comparison of individual arms of the studies FIREFISH and ENDEAR, there was a clear statistically significant difference in favour of risdiplam in comparison with nusinersen for the composite outcome "death or permanent ventilation" as well as for the individual component "permanent ventilation".

Also for the analysis with longer observation periods, in the present situation of a comparison of individual arms of different studies, it cannot be ruled out with certainty that the effects were solely due to a systematic bias caused by confounding variables. The reasons lie in the inclusion of patients with potentially different prognoses in the studies FIREFISH and ENDAR (see dossier assessment A21-50 [1]). For this reason, the balancing for the added benefit remains unchanged.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of risdiplam from dossier assessment A21-50.

The following Table 3 shows the result of the benefit assessment of risdiplam under consideration of dossier assessment A21-50 and the present addendum.

Table 3: Risdiplam – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
	Patients with 5q SMA, 2 months of age and older, with		
1	SMA type 1	Nusinersen	Hint of non-quantifiable added benefit[b]
2	SMA type 2		Added benefit not proven
3	SMA type 3	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven
4	Pre-symptomatic patients with 5q SMA, 2 months of age and older, with		
4a	1 to 3 SMN2 gene copies	Nusinersen	Added benefit not proven
4b	4 SMN2 gene copies	Treatment of physician's choice choosing from nusinersen or BSC[c, d]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. The results of the comparison presented using individual arms of different studies suggest that risdiplam is at least not inferior to nusinersen. The added benefit of risdiplam in the present situation results from its oral form of administration and a high probability of morbidity associated with the intrathecal administration of nusinersen (see Section 2.3.4 of dossier assessment A21-50 [1]). Only data on patients with 2 SMN2 gene copies are available.
c. According to the G-BA's note, a single-comparator study is generally not sufficient for patients with this ACT.
d. 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. Furthermore, it is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. In pre-symptomatic patients 2 months of age and older with 5q 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; SGB: Social Code Book; SMA: spinal muscular atrophy; SMN: survival motor neuron

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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

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Appendix A – Kaplan-Meier curves

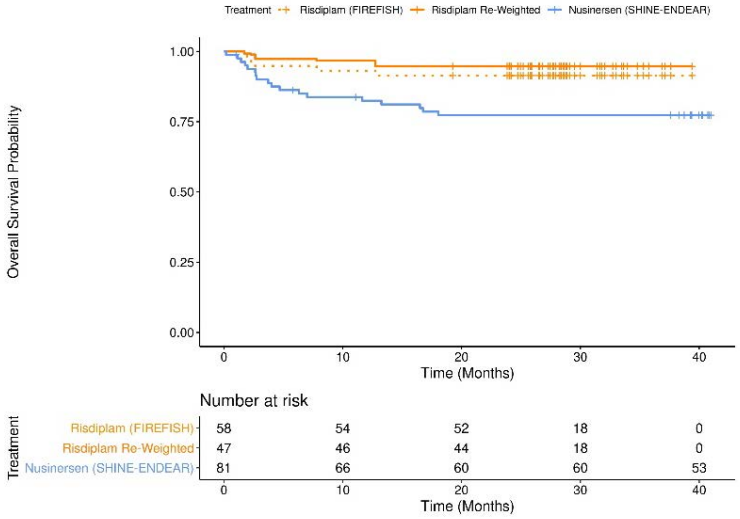

Figure 1: Kaplan-Meier curves for overall survival, comparison of individual arms of the studies FIREFISH (risdiplam, data cut-off 2 years after inclusion of the last patient) and SHINE-ENDEAR (nusinersen, data cut-off 27 August 2019); SMA type 1

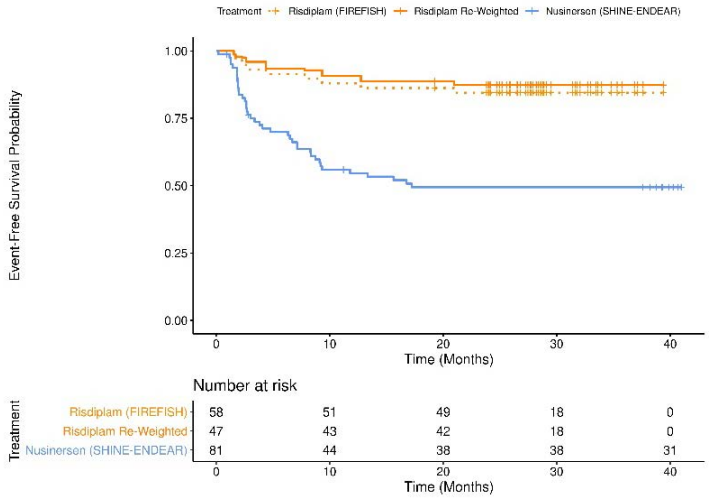

Figure 2: Kaplan-Meier curves for symptoms: composite outcome “death or permanent ventilation”, comparison of individual arms of the studies FIREFISH (risdiplam, data cut-off 2 years after inclusion of the last patient) and SHINE-ENDEAR (nusinersen, data cut-off 27 August 2019); SMA type 1

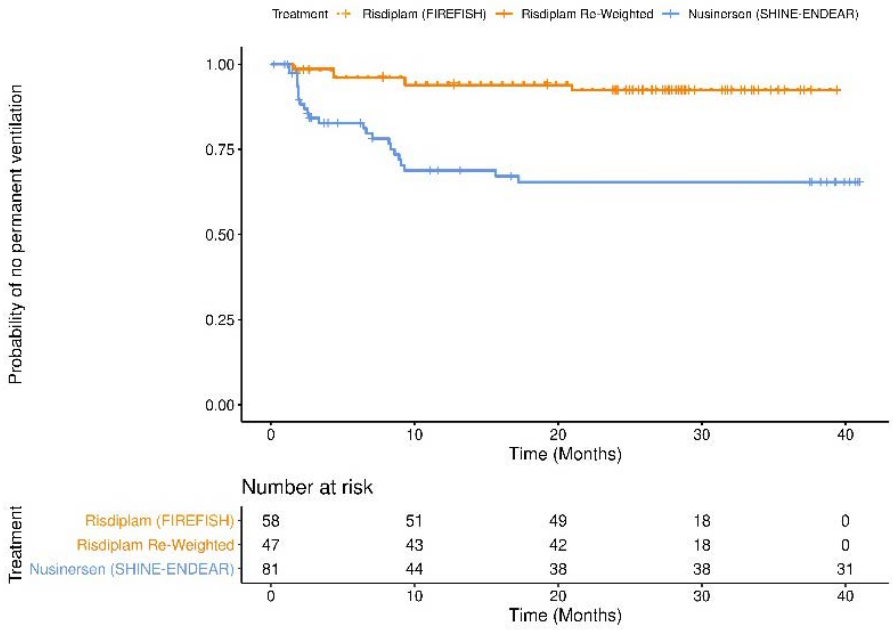

Figure 3: Kaplan-Meier curves for symptoms: permanent ventilation, comparison of individual arms of the studies FIREFISH (risdiplam, data cut-off 2 years after inclusion of the last patient) and SHINE-ENDEAR (nusinersen, data cut-off 27 August 2019); SMA type 1