

# Justification

for the Resolution of the Federal Joint Committee (G-BA) on  
the Finding in the Procedure of Routine Practice Data  
Collection and Evaluations according to Section 35a,  
paragraph 3b SGB V:

Risdiplam (spinal muscular atrophy) – Review of study  
protocol, statistical analysis plan and interim analyses

From 17 September 2026

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## **1. Legal basis**

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136 from 30.04.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4 from 07.01.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No. 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

According to Section 35a, paragraph 3b, sentence 10 SGB V in conjunction with Chapter 5 Section 60 Rules of Procedure of the G-BA (VerfO), the G-BA review the data obtained and the obligation to collect data at regular intervals, at least every eighteen months.

## **2. Key points of the resolution**

At their session on 21 July 2022, the G-BA decided on the requirement of routine practice data collection and evaluations for the active ingredient risdiplam in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

In order to check whether the requirements of the G-BA for the routine practice data collection and evaluations of the data obtained have been implemented, the pharmaceutical company submitted the revised versions of the study protocol and the statistical analysis plan (SAP) (version 5.0 of 10 April 2026) to the G-BA in due time on 30 March 2026. The study documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

It is noted that the pharmaceutical company have not fully implemented the requirements for the implementation of the routine practice data collection (RPDC) and evaluations in the submitted, revised versions of the study protocol and the statistical analysis plan (SAP) (version 5.0 of 10 April 2026) as stated in the declaratory resolution of 19 September 2024. Furthermore, the submitted, revised versions of the study protocol and the SAP as well as the review of the approach taken in the 1<sup>st</sup> interim analysis indicate that further adaptations are required. This declaratory resolution defines and justifies the further adaptations to the study protocol and the SAP (version 5.0 of 10 April 2026) that are considered mandatory.

### **2.1 Necessary adaptations to the study protocol and statistical analysis plan**

On the mandatory adaptations in detail:

a) Interpretation of the data: Assessment of baseline characteristics

The fact that baseline characteristics are collected on the index date was added to the study documents. However, the collection may have been carried out up to 4 months prior to the index date. Given the patients' age at enrolment and disease progression, the period of up to 4 months prior to the index date appears to be too long. The pharmaceutical company must make every effort to ensure that the baseline assessment is carried out at the index date. Any deviation must take place within a reasonable timeframe, which must be justified. Data on the distribution of the actual time period between the baseline assessment and the index date must be presented.

b) Data evaluation: Endpoints: HFMSE and RULM

For the HFMSE and RULM endpoints, an additional analysis of the total score at month 36 after the index date was included. The analysis is to be merely descriptive, using mean values and mean differences. A purely descriptive analysis of the total score at month 36 after the index date for the HFMSE and RULM endpoints (without taking the baseline value into account) is insufficient for the benefit assessment. An appropriate comparator analysis must be included in the study documents.

c) Data evaluation: Achievement of motor milestones endpoint

The included endpoints "loss of the ability to sit unaided" and "loss of the ability to stand unaided" are inappropriate given the operationalisation described. Some patients can only be at risk of losing the motor milestones in the course of RPDC (after achievement of the respective motor milestone). It is only meaningful to consider the time until loss of motor milestones if a significant percentage of patients have already achieved them at baseline. This must be checked, depending on the research question and the motor milestones. For example, it can be assumed that a significant percentage of patients with type 3 SMA are already able to sit and walk.

Alternatively, an analysis of the percentage of patients who have reached the respective milestone by month 36 after the start of treatment should be carried out. In addition to the endpoint of achievement of the respective motor milestone, a suitable operationalisation could be a combined analysis of the achievement and the maintenance of the respective motor milestone.

d) Study design: Confounder

There is still no appropriate description of how patients under the age of 2 years are to be handled when assessing the HFMSE, and this must be included in the study documents. Simply stating that the confounder with the fewest missing values in the respective population is selected is not sufficient. A clear and prospective specification of which confounder is to be used for which population must also be included. In this context, it is also important to take into account the likely age of this population, as well as the age-dependent applicability of the survey tools.

e) Data evaluation: Estimand

The changes regarding the application of the treatment policy strategy (corresponding to the ITT principle) to the secondary endpoints as well are appropriate. However, the

deletion of patients included in the respective analyses necessitates changes to the statistical methodology, particularly with regard to the handling of missing values. The study documents do not provide any information on this. Specifically, this concerns the multiple imputation of missing values when estimating the propensity score and the subsequent effect estimate of the endpoints. Furthermore, this relates to the assessment of balance and overlap, as well as the choice of propensity score method. When combining propensity score methods with multiple imputation for missing endpoint data values, an appropriate method must be selected with justification, and accordingly pre-specified in the study documents.

f) Data evaluation: Sensitivity analyses

According to the information provided in the study documents, sensitivity analyses are to be carried out for both the primary endpoint and relevant secondary endpoints. However, there is no information as to which secondary endpoints are relevant. In the G-BA's guidelines, these were clearly identified as being patient-relevant. The study documents must specify which secondary endpoints are included in the sensitivity analyses. With regard to the conduct of the sensitivity analyses, it is merely stated that appropriate regression models are used and that the data are treated as if they were from a triple-arm study. No further information is available regarding the heterogeneity test and specific statistical methods. The study documents must provide a more comprehensive and detailed description of the statistical methodology used in the sensitivity analyses (e.g. the specific model to be used), in particular the assessment of effect modification by the therapy options in the control arm.

g) Data evaluation: Subgroup analyses

The details provided on the methodology of the subgroup analysis are insufficient. The underlying base model is not specified in detail. There is no description of how the subgroup analyses are to be combined with the calculations of propensity scores and multiple imputation. This is inappropriate. As it is explicitly stated that the missing and unknown subgroup categories are not taken into account when calculating the interaction p value, there is still a lack of information on possible sensitivity analyses that include these categories. An appropriate method for the analysis of the subgroups must be selected with justification, and accordingly pre-specified in the study documents. Furthermore, sensitivity analyses that take into account the "missing" and "unknown" categories must be included in the study documents.

h) Data evaluation: Dealing with missing values

The additions made are insufficient. The documents do not indicate what the exclusion of a confounder means for the validity of the propensity score adjustment. The assessment of balance using SMDs for confounders with 40% or more missing values is not significant, particularly as it cannot be expected that the "missing completely at random" or "missing at random" assumption applies to the missing values. Thus, assessing the balance of these confounders should be avoided. An adequate adjustment for these confounders is not possible. Depending on the confounders in question, it should be assessed whether a switch should be made to a naïve comparison without using the propensity score. Furthermore, there is a lack of information on how to interpret the results when using a naïve comparison, such as a definition of a dramatic effect. The implications of excluding confounders for the validity of propensity score adjustment, and information on the interpretation of

results when using a naïve comparison (definition of a dramatic effect) must be included in the study documents.

Mandatory adjustments that go beyond the scope of the requirements set out in the declaratory resolution of 19 September 2024:

i) Differentiation between type II SMA and type I SMA

Type 1 SMA is defined by the following criteria: the patients are not presymptomatic at the time of diagnosis; symptoms first appear at the age of  $\leq 6$  months; or they have never acquired the ability to sit. If these criteria are applied without assessing the ability to sit, there is a risk that patients who are unable to walk will automatically be classified as having type 2 SMA, even though they may actually have type 1 SMA. In order to distinguish from patients with type 1 SMA, the study documents for type 2 SMA need to specify that these patients are able to sit unaided.

j) Specific SAEs

In the available study documents, the pharmaceutical company have omitted the analysis of serious specific adverse events (AEs) and do not present them in these interim analyses. They justify the omission on the grounds that the current version of the benefit assessment dossier template no longer requires the description of specific AEs. However, the requirements regarding the analyses to be submitted for the benefit assessment have been amended so that a-priori-defined adverse events of special interest (AESI) no longer need to be presented. The specific AEs required here, by contrast, are selected, potentially relevant specific adverse effects that have been identified on the basis of the treatment setting to be analysed and the treatment options used. The deletion of the specific SAEs (retinopathy, impact on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory events) must be reversed; the serious specific AEs must be assessed as required by the resolution.

k) Analysis of the RULM

In the study documents, the operationalisation of the primary endpoint "change in total score from baseline to month 36 of the RULM" for patients with type 2 SMA was specified in detail. From the second interim analysis onwards, RULM values should only be included in the analysis if the tested side corresponds to the side tested at baseline. Whilst it is appropriate to test the same (preferred) hand in each examination wherever possible, excluding the patient from the analyses compared to the baseline is inappropriate. The pharmaceutical company is free to carry out a sensitivity analysis excluding these patients. The study documents must specify that patients for whom the RULM was assessed on a different hand at baseline than at the time of analysis are not to be excluded from the analyses.

l) Selected operationalisations for endpoints

For the first interim analysis, the pharmaceutical company submitted time-to-event analyses relating, among other factors, to the achievement and loss of the motor milestones of sitting, standing and walking. Patients who had already achieved the respective motor milestone at the start of the study were excluded from the analyses of milestone achievement. The time until loss of milestones is defined as the time from achievement to loss of the respective milestone. Consequently, some patients can only be at risk of losing the motor milestones in the course of RPDC (after achievement of

the respective motor milestone). This operationalisation cannot be interpreted meaningfully. For all endpoints, operationalisations are to be selected such that, at the start of the observation period, the vast majority of patients are at risk of the event of interest.

m) Analysis of the endpoints on walking ability and swallowing ability

For the first interim analysis, the analysis of the endpoints on walking ability and swallowing ability was conducted on a purely descriptive basis, according to the information provided by the pharmaceutical company. That is insufficient. An appropriate response criterion for the analyses of the "swallowing ability" endpoint must therefore be specified in the study documents.

n) Use of a weighted propensity score method

The information provided by the pharmaceutical company regarding the effect estimate for the first interim analysis does not indicate whether these are weighted analyses (e.g. a weighted Cox regression model). When using a weighted propensity score method, it is mandatory to carry out weighted analyses; otherwise, the weights derived from the propensity score method will not be taken into account and, in effect, no adjustment will be made. This must be added in the study documents.

o) Causes of implausible data

The patient characteristics presented in the first interim analysis are not plausible for all 4 research questions, particularly not for patients with type 1 SMA. Information provided by the pharmaceutical company showed, for example, that patients with type 1 SMA in the risdiplam arm had a median age of 22 years at the index date (min; max: 0.0; 58.0 years). Given that the life expectancy of untreated patients with type 1 SMA is normally less than 2 years, this is implausible. The pharmaceutical company also describe these implausibilities in the data submitted for the first interim analysis. As a possible explanation, the pharmaceutical company also stated that, at the time of data cut-off, not all participating study sites had been covered by a monitoring programme designed to improve data quality and completeness. Given the implausible data available, it is unclear to what extent the remaining data can be trusted. The presented results of the first interim analysis are therefore considered to be insufficiently valid. The causes of the implausible data must be identified and rectified. If the causes cannot be fully rectified, the reasons for this must be explained.

In addition to the adaptations that must be implemented as mandatory requirements, the G-BA make the following recommendations for further adaptation to the study protocol and the statistical analysis plan:

1. In the study documents, the index date was defined in the description of the endpoints as the time when the observation for the analyses of the motor milestones commenced. In the study documents, the index date should also be specified in all tables as the start of the observation period for the analyses of motor milestones (time-to-event analyses).
2. With regard to the 6-minute walk test endpoint, it was added that the relevance of the results is interpreted on the basis of the distance covered. In addition, for the analysis

of the 6-minute walk test endpoint, an effect estimate should be included for both the relative change from baseline and the absolute distance covered.

## **2.2 Deadline for submission of the revised study protocol and statistical analysis plan**

The revised study protocol and the revised SAP must be submitted to the G-BA by 30 April 2027 for review.

When submitting the revised version of the SAP and the study protocol, the pharmaceutical company must ensure that the changes made can be completely and clearly understood. For this purpose, a version of the documents must usually be submitted in which the changes have been marked in detail, as well as a current version of the documents without marking the changes. Amendments that do not result from the need for adaptation set out in this resolution and the justification shall be justified separately.

## **3. Process sequence**

In order to check whether the requirements of the G-BA for routine practice data collection and evaluations for the active ingredient risdiplam have been implemented as specified in the resolution of 19 September 2024, the pharmaceutical company submitted revised drafts of a study protocol and an SAP to the G-BA. The documents were reviewed by the G-BA with the involvement of IQWiG.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At their session on 17 September 2026, the plenum decided on the outcome of the review regarding the submitted study protocol and the SAP (version 5.0 of 10 April 2026).

### **Chronological course of consultation**

| <b>Session</b>                     | <b>Date</b>                                         | <b>Subject of consultation</b>                                                                                |
|------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| WG RPDC                            | 6 August 2026<br>17 August 2026<br>3 September 2026 | Consultation on the review of study documents (study protocol and SAP) and the interim analysis               |
| Subcommittee on Medicinal Products | 8 September 2026                                    | Consultation on the review of study documents (study protocol and SAP) and the interim analysis               |
| Plenum                             | 17 September 2026                                   | Adoption of the resolution on the review of study documents (study protocol and SAP) and the interim analysis |

Berlin, 17 September 2026

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

Dr Optendrenk