

Resolution

of the Federal Joint Committee on a 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

At their session on 17 September 2026, the Federal Joint Committee (G-BA) decided the following in the procedure of routine practice data collection and evaluations according to Section 35a, paragraph 3b SGB V for the active ingredient risdiplam (spinal muscular atrophy):

- I. 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 1st interim analysis indicate that further adaptations are required. The routine practice data collection can therefore only be continued under the condition that the following adaptations to the study protocol and the statistical analysis plan (version 5.0 of 10 April 2026), which are deemed mandatory for the implementation of the requirements pursuant to Section 58, paragraph 1, number 1 Rules of Procedure (VerfO), are made:
 - a) Interpretation of the data: Assessment of baseline characteristics
The pharmaceutical company should 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. 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.

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.

e) Data evaluation: Estimand

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

The study documents must specify which secondary endpoints are included in the sensitivity analyses.

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

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 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

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

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

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 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

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. Data 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. 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.

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

III. The resolution will enter into force on the day of its publication on the G-BA website on

17 September 2026.

The justification for this resolution will be published on the G-BA website at www.g-ba.de.

Berlin, 17 September 2026

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

Dr Optendrenk