Gemeinsamer Bundesausschuss

Justification

on 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 and statistical analysis plan and start of RPDC

of 19 September 2024

Contents

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, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, 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 reviews the data obtained and the obligation to collect data at regular intervals, at least every eighteen months.

2. Key points of the resolution

At its session on 21 July 2022, the G-BA decided on the requirement of routine 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 G-BA's requirements for routine practice data collection and evaluations have been implemented, the pharmaceutical company submitted drafts for a study protocol and a statistical analysis plan (SAP) to the G-BA in due time in a letter dated 15 August 2023. The documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG). By G-BA's declaratory resolution of 4 April 2024, the pharmaceutical company was notified of the adjustments to the study protocol and the SAP that were considered necessary.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP to the G-BA in due time by 2 May 2024.

In the declaratory resolution of 4 April 2024, the G-BA requested, among other things, a systematic literature review to identify any further potential confounders, as patients with SMA type 3 are also part of the question for the required routine practice data collection for risdiplam compared to the routine practice data collection for onasemnogene abeparvovec.

When submitting the revised drafts for a study protocol and an SAP, the pharmaceutical company informed the G-BA that a corresponding systematic literature review would be conducted to identify any further potential confounders, but that it would take several weeks to complete. The results of the updated confounder research would be submitted once finalised.

The pharmaceutical company was therefore requested to submit a revised version of the study protocol, including the confounder research, and the SAP by 28 June 2024.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP including the confounder research to the G-BA in due time by 28 June 2024.

The revised draft study protocol and SAP were reviewed by the G-BA along with IQWiG.

On the basis of this review, the G-BA came to the conclusion that the implementation of the requirements for routine practice data collection and evaluations in the study protocol and statistical analysis plan prepared by the pharmaceutical company and submitted to the G-BA for review is to be considered fulfilled under the conditions that further adjustments to the study documents deemed necessary are made. This declaratory resolution defines and justifies the further adjustments to the study protocol (version 3.0, 25.06.2024) and the statistical analysis plan (version 3.0, 25.06.2024) that are considered necessary.

The G-BA assumes that the need for adjustment listed in the declaratory resolution will be implemented before the start of routine practice data collection.

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

a) Question according to PICO: Patient population

The study documents lack the description that all baseline characteristics are collected on the index date. This is to be supplemented.

For the inclusion criteria - analogous to the endpoints and confounders - the commissioned specification of the relevant data fields with their operationalisation in the SMArtCARE registry is missing in the study documents. The specification must be added.

b) Question according to PICO: Outcome, morbidity

The pharmaceutical company has described an age-appropriate use for the measurement instruments HFMSE (Hammersmith Functional Motor Scale-Extended) and RULM (Revised Upper Limb Module) in SMA types 2 and 3 in the study documents. In accordance with the data collection practice in the SMArtCARE registry, these should only be used for patients > 2 years of age (the HFMSE additionally only for patients who are able to sit). The evaluations of the change compared to baseline for these

endpoints should only include patients for whom a baseline value is available. However, the planned procedure means that no evaluations are carried out for patients who were ≤ 2 years old at the start of treatment (particularly relevant for SMA type 2). This is inappropriate.

For the morbidity endpoints HFMSE and RULM, an additional evaluation of the walking distance at month 36 after the start of treatment without consideration of the baseline values should be defined and the associated potential risk of bias should be taken into account when interpreting the results. Otherwise, the endpoints may not be usable for the benefit assessment and should be deleted, also in view of the large number of other motor endpoints.

If the morbidity endpoint RULM is deleted, this must be taken into account in the sample size estimate *(see study design: sample size planning*).

c) Question according to PICO: Outcome, achievement of motor milestones

For pre-symptomatic and SMA type 1 patients, the pharmaceutical company added a survey of the endpoints for maintaining the three milestones of sitting, standing and walking to the study documentation. For patients with SMA type 2 and SMA type 3, only the receipt of the walking milestone was included. For both patient populations, endpoints for maintaining the sitting and standing milestones should be added accordingly.

d) Question according to PICO: Outcome, bulbar function

For the planned operationalisation of the percentage of patients who achieve age-appropriate scores in the expressive language and receptive language subscales of the Bayley III, there is no justification for the fact that a growth score that is above the 5th percentile rank of healthy children represents a meaningful response threshold for the assessment as an age-appropriate score. The replacement of missing values as non-responders planned by the pharmaceutical company is also inappropriate. The single survey planned at the age of 24 months in accordance with the guidelines for the follow-up of the SMArtCARE registry is also inappropriate for the present question.

The survey of the Bayley III expressive language and receptive language subscales can be dispensed with against this background and in consideration of the other collected endpoints on bulbar function (swallowing ability and need for non-oral nutritional support) and should be deleted.

e) Question according to PICO: Outcome, serious adverse events (SAEs)

In the study documents, the operationalisation for SAEs was adjusted; these are planned to be collected approximately via AEs that lead to unplanned hospitalisation or prolong hospitalisation. However, the adjustment is inappropriate as the component "AEs leading to death" is missing. "AEs leading to death" are not collected directly in the SMArtCARE registry, but the information in the free text field of the variable "Cause of death" can be used to classify a death caused by an AE. The

component "AEs leading to death" should therefore be added approximately via the information in the free text field of the variable "Cause of death" for collecting the SAEs in the study documents. The corresponding documentation fields of the SMArtCARE registry must also be completed in the study documents.

f) Study design: Confounder

The pharmaceutical company has implemented the G-BA's requirement of conducting a systematic literature review for patients with SMA type 3 to identify possible further potential confounders by conducting a systematic literature review for potentially relevant confounders for the entire relevant therapeutic indication of the present routine practice data collection.

The basic procedure for the information procurement presented and the selection of potentially relevant confounders appears to be largely comprehensible.

In comparison with the confounders identified for the routine practice data collection of onasemnogene abeparvovec in the SMA therapeutic indication, 3 additional confounders were classified as potentially relevant: early diagnosis, multiple diseases and physical activity. The other identified confounders correspond to the confounders already identified for this therapeutic indication.

The present updated confounder identification did not identify any confounders that are only potentially relevant for patients with SMA type 3, so that there are no relevant gaps for this patient population. Compared to the identical core set of identified potential confounders for the routine practice data collection of risdiplam and onasemnogene abeparvovec, the above-mentioned additionally identified potential confounders do not represent any significantly new aspects from the G-BA's perspective.

The G-BA therefore considers it possible in the specific case at hand and in consideration of the ongoing routine practice data collection of onasemnogene abeparvovec to waive the collection of these additional potential confounders (early diagnosis, multiple diseases and physical activity) for the routine practice data collection of risdiplam.

The confounder motor function is planned to be operationalised via the highest motor milestone, CHOP-INTEND (Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders) and HFMSE. For the HFMSE, it remains unclear how patients under 2 years of age are handled *(see Outcome, morbidity*). This must be presented in a methodologically appropriate manner. Otherwise, the HFMSE can be dispensed with and the confounder motor function should be operationalised using the highest motor milestone and the CHOP-INTEND.

g) Study design: Index date

The index date was set as the day of the treatment decision. If this is undocumented, the date of the first treatment with the therapy to which the patient was assigned

should be used as the index date. This is inappropriate as the start of bridge therapy would not be counted as an index date in this case. In these cases, the start of bridge therapy is the index date in the case of bridge therapy. This must be specified in the study documents.

h) Study design: Sample size planning

Sample size planning for patients with SMA type 2 and SMA type 3 should continue to be based on the RULM, operationalised as a change in the total score compared to baseline with the corresponding Cohen's d effect size (as SMD). Irrespective of the inappropriate operationalisation *(see Outcome, morbidity*), the chosen shifted null hypothesis boundary for the RULM is inappropriate and should be adjusted accordingly. The limits for large or very large effects (SMD > 0.8 or SMD > 1.3) given in the publications of Cohen (1988)[1] and Rosenthal (1996)[2] can be used as guide values for appropriate limits for a shifted null hypothesis.

If the morbidity endpoint RULM is deleted (*see Outcome, morbidity*), an alternative endpoint must be used for sample size planning for patients with SMA type 2 and SMA type 3.

i) Study design: Discontinuation criteria

The commissioned addition to the study protocol that any decision to discontinue the RPDC will be made in consultation with the G-BA is still missing and must be added.

j) Data evaluation: Endpoints

The requirement that, in the case of evaluations at several time points, the evaluation that takes into account the longest possible observation period must always be presented as the primary analysis was only added for the primary endpoint in the study protocol and SAP. The implementation of the requirement is missing for secondary endpoints and must be supplemented accordingly.

The evaluations of the motor milestones were changed to time-to-event analyses (time from the first treatment to reaching the motor milestone), but the index date must be used as the start of observation. This must be added in the study documents.

k) Data evaluation: Estimand

An estimand is named for the primary endpoints and side effects endpoints in accordance with the treatment policy strategy. However, this has not been implemented for the secondary endpoints and must be added accordingly.

The evaluation of continuous endpoints does not correspond to the ITT-principle as only patients with a baseline value and an observed value at the time of evaluation are taken into account. It is only appropriate not to take them into account if the missing

1 Cohen J. Statistical power analysis for the behavioural sciences. Hillsdale: Erlbaum; 1988.
2 Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. Journal of Social Service Research 1996; 21(4): 37-59

values are due to the non-age-appropriate use of these instruments (however, the associated content-related problems still exist *(see Outcome, morbidity*)). In patients with SMA type 2 and SMA type 3, this leads to contradictory information for the primary endpoint: although an estimand is planned in accordance with the treatment policy strategy, the ITT principle may be violated. In the evaluation of continuous endpoints, patients who have missing values, although the respective instrument is suitable for them, are therefore to be taken into account in the analyses in accordance with the ITT principle.

In the study documents, information on the RULM should be added in the section on secondary endpoints, as these are currently only listed under the primary endpoints.

l) Data evaluation: continuous evaluations

The study documents also lack information on the test statistics as the parameter estimates from an MMRM (Mixed Model for Repeated Measures) allow different effect estimates. Differences in the changes from baseline between the treatment arms at specific time points can be estimated, but also differences in the changes averaged over the course of the study. The effect estimates can lead to pertinently different results. The missing information on the test statistics must further be added.

It is described that the Cohen's d effect size is used for evaluation of continuous endpoints by means of effect estimates and standard deviations for the mean values from an MMRM. No standard deviations result from an MMRM, only standard errors for the parameters of the MMRM to be estimated. It therefore remains unclear how the pooled standard deviation for Cohen's d is approximated for observed values. The exact definition of the Cohen's d effect size in connection with the planned MMRM analysis must be added.

With regard to the continuous evaluations for the 6MWT endpoint, it must be specified that the relevance of the results is interpreted on the basis of the scale of the instrument (i.e. in this case, on the basis of the distance walked).

m) Data evaluation: Sensitivity analyses

With regard to the commissioned planning of heterogeneity analyses with regard to the therapy options in the data evaluation in the comparator arm as sensitivity analyses, separate evaluations for the intervention versus the therapy options in the control arm are described in the study documents. This is inappropriate as no heterogeneity analyses are described. One approach would be to analyse the data as part of a three-arm study and apply appropriate statistical methods. The planning of the aforementioned heterogeneity analyses must further be added accordingly.

Sensitivity analyses should also be conducted not only for the primary endpoints, but also for all other patient-relevant endpoints. This must be adjusted accordingly.

n) Data evaluation: Subgroup analyses

Furthermore, no substantive rationale is given for the categorisation of the subgroups on the basis of the median; this concerns the subgroup features "CHOP-INTEND at baseline" and "HFMSE at baseline". A substantively justified cut-off value which does not depend on the study results must be defined a priori. Otherwise, these subgroup features are dispensable and should be deleted

The description of the planned methodology for the subgroup analyses is incomplete as information on the specific modelling is missing. This is to be accordingly supplemented.

Patients with missing values for the corresponding subgroup feature (missing or unknown) are excluded from the analysis as planned. In this respect, a sensitivity analysis that includes these patients as a subgroup should be added.

o) Data evaluation: Propensity score method

For the evaluations using Inverse Probability of Treatment Weighting (IPTW) and fine stratification weights, patients with a propensity score greater than 0.95 or less than 0.05 should be excluded from the analysis. No justification or literature reference is given. The approach is inappropriate. An approach with fixed threshold values is not recommended as it is not sufficiently certain whether potential confounding is adequately taken into account due to the fixed values. Instead, procedures with relative threshold values (e.g. lower or upper 5% percentile) based on the observed distributions of the propensity scores should be used. This must be adjusted accordingly.

p) Data evaluation: Dealing with missing values

The procedure regarding missing confounders due to excessive percentages of missing values is inappropriate. It is only intended to describe the data basis. Possible consequences of the exclusion of confounders for the interpretation of the results are not mentioned. It therefore remains unclear whether the adjustment is sufficient and thus, whether it is possible to apply a propensity score-based method. If it is not possible to use a propensity score-based method, a naïve comparison without adjustment can be used for the benefit assessment. In this case, the consequences must be considered and described when interpreting the results.

In order to avoid inconsistencies, the pharmaceutical company must check whether the need for changes in the study protocol described here leads to corresponding subsequent changes in the SAP and vice versa.

In addition to the mandatory adaptations, the G-BA makes the following recommendations for further adaptations of the study protocol and the SAP:

a) Question according to PICO: Outcome

In order to provide an overview of the planned survey time points during the observation period, the pharmaceutical company has added specific information on the collection of the individual endpoints in the study documents. However, a survey plan would still be advisable for a better overview, also in view of the large number of planned endpoints.

b) Question according to PICO: Outcome, adverse events (AEs)

The planned endpoint on the number of AEs leading to unplanned hospitalisation was adjusted in the study documents and now refers to all hospitalisations. However, this endpoint is still irrelevant for the benefit assessment. Deletion of the endpoint is therefore recommended.

c) Data source: Completeness of the data/ Source Data Verification

The required information on the consequences drawn from the planned Source Data Verification (SDV) is still missing. It is recommended that these be added; in the event of anomalies, for example, specific training modules could be offered or the monitoring measures in study sites with anomalies could be expanded.

d) Data source: Reporting dates

It is questionable whether the addition in the study documents that data should be entered into the eCRF as soon as possible can ensure timely submission of the data for interim analyses or new benefit assessments. It is recommended to add to the study documents that it is ensured that for the data cut-offs for the interim analyses, all data collected up to that point are available. Safeguarding can be supported by study monitors, for example.

e) Study design: Information on the data collection process

It was added to the study documents that, if possible, analyses of prospectively enrolled patients will also be submitted for the first status report 6 months after the start of the study. It is also recommended to adjust the time for the planned data cut-off. This is still planned for this analysis at the start of the study (and therefore with a lead time of 6 months). Since only descriptive analyses are required for the follow-up survey, a shorter latency period should be sufficient to enable data on prospectively enrolled patients to be presented for the first follow-up survey.

f) Data evaluation: Responder analyses

The information on the planned test statistics for the planned responder analyses was supplemented as instructed. However, the effect sizes ARR and RR are not estimated using a logistic regression, i.e. a regression with the logit function as the link function; this requires the identity (ARR) or the log function (RR) as the link function. A corresponding supplementation is recommended.

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

The revised study protocol and the revised SAP are to be submitted to the G-BA by 30 March 2026 for final 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 adjustment set out in this resolution and the justification shall be justified separately.

3. Start of the routine practice data collection

The routine practice data collection starts on 30 October 2024.

4. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient risdiplam have been implemented as specified in the resolution of 21 July 2022, the pharmaceutical company submitted revised drafts of a study protocol and a 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 its session on 19 September 2024, the plenum decided on the outcome of the review regarding the submitted study protocol (version 3.0; 26.04.2024) and the statistical analysis plan (version 3.0; 26.04.2024).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	1 August 2024 19 August 2024 5 September 2024	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	10 September 2024	Consultation on the result of the review of the study protocol and SAP
Plenum	19 September 2024	Resolution on the result of the review of the study protocol and SAP

Berlin, 19 September 2024

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

Prof. Hecken