Gemeinsamer Bundesausschuss

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 and statistical analysis plan and start of RPDC

of 19 September 2024

At its session on 19 September 2024, 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 stated 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 considered fulfilled under the condition that the pharmaceutical company is obliged to make the following further adjustments to the study protocol (version 3.0, 25.06.2024) and the statistical analysis plan (SAP; version 3.0, 25.06.2024) that are considered necessary:

a) Question according to PICO: Patient population

It should be added to the study documents that all baseline characteristics are collected on the index date.

For the inclusion criteria, the relevant data fields with the corresponding operationalisation must be added to the study documents in the registry.

b) Question according to PICO: Outcome, morbidity

In the planned procedure for age-appropriate use of the HFMSE (Hammersmith Functional Motor Scale-Extended) and RULM (Revised Upper Limb Module) measurement instruments for SMA types 2 and 3, it can be assumed that no baseline values are available, particularly for a relevant percentage of patients with SMA type 2, and that no evaluations will be carried out as a result. 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 patients with SMA type 2 and SMA type 3, the endpoints for maintaining the sitting and standing milestones must be added.

d) Question according to PICO: Outcome, bulbar function

The planned operationalisation or evaluation of the percentage of patients who achieve age-appropriate scores in the expressive language and receptive language subscales of the Bayley III is inappropriate. In accordance with the guidelines for the follow-up of the SMArtCARE registry, the planned single survey at the age of 24 months 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. The component "AEs leading to death" is to be completed 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. However, 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.

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

For the secondary endpoints, it must be specified that in the case of evaluations at several points in time, the evaluation that takes into account the longest possible observation period is always presented as the primary analysis.

In the study documents, the index date is to be specified as the start of observation for the evaluations of the motor milestones (time-to-event analyses).

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.

In the evaluation of continuous endpoints, patients who have missing values, although the respective instrument is suitable for them, are 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 missing information on test statistics for the planned Mixed Model for Repeated Measures (MMRM) must be added.

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

The planning of heterogeneity analyses with regard to the therapy options in the comparator arm in the data evaluation as sensitivity analyses should further be added to the study documents.

It should be added in the study documents that sensitivity analyses are carried out not only for the primary endpoints as well as for all other patient-relevant endpoints.

n) Data evaluation: Subgroup analyses

For the categorisation of the subgroups on the basis of the median, a content-based cut-off value that does not depend on the study results must be specified a priori. Otherwise, the concerned 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.

A sensitivity analysis that includes patients with missing values for the corresponding subgroup feature (missing or unknown) as a subgroup should be added.

o) Data evaluation: Propensity score method

The planned procedure of excluding patients with a propensity score greater than 0.95 or less than 0.05 from the evaluations using Inverse Probability of Treatment Weighting (IPTW) and fine stratification weights is inappropriate and should be adjusted.

p) Data evaluation: Dealing with missing values

The procedure regarding missing confounders due to excessive percentages of missing values is inappropriate, as it remains unclear whether the adjustment is sufficient and thus, whether a method using a propensity score can be applied. 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.

II. The routine practice data collection starts on 30 October 2024.

III. The revised study protocol and the revised SAP are to be submitted to the G-BA by 30 March 2026.

IV. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 September 2024.

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

Berlin, 19 September 2024

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

Prof. Hecken