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) – Submission of study protocol and statistical analysis plan

of 4 April 2024

At its session on 4 April 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 requirements for routine practice data collection and evaluations are insufficiently implemented in the study protocol and statistical analysis plan prepared by the pharmaceutical company and submitted to the G-BA for review. The following adjustments deemed necessary shall be made to the study protocol (version 1.0 (original); 31 July 2023) and the statistical analysis plan (version 1.0 (original); 10 August 2023):

1. Question according to PICO: Patient population

   The inclusion and exclusion criteria must be supplemented by the data quality requirements specified in the G-BA resolution.

   The inclusion criterion "Visit defined as a baseline visit must be between 6 weeks before and 3 weeks after the first application of the SMA medication" must be deleted.

   With regard to the exclusion criterion "Prior treatment of patients with risdiplam, nusinersen or onasemnogene abeparvovec before inclusion in the registry", it must be ensured that patients who have only received prior treatment with risdiplam or nusinersen in the form of bridging therapy are not also excluded.

2. Question according to PICO: Outcome

   If evaluations are planned for endpoints at several points in time, the evaluation that takes into account the longest possible observation period should always be presented as the primary analysis.

   A data collection plan must be added to provide an overview of the planned data collection time points during the course of the observation.

3. Question according to PICO: Outcome, morbidity

   In order to reduce the number of endpoints describing motor function, relevant pre-specified endpoints should be selected in the study protocol and the endpoints should be hierarchised.

   The age-appropriate use of instruments to assess motor function should be examined, particularly in the planned use of HFMSE and RULM in patients with type 2 and type 3 SMA. The study protocol must specify and ensure that age-appropriate instruments are used to assess motor function, particularly for operationalisations in which changes from baseline are assessed.

4. Question according to PICO: Outcome, Bayley III

   The score to be analysed (scaled scores, composite scores, percentile ranks, and growth scores) must be specified in the study documents.

   For all operationalisations, the time of evaluation is to be determined depending on the time since the start of treatment.

5. Question according to PICO: Outcome, CHOP-INTEND

   With regard to the evaluations of the percentage of patients with a score of ≥ 40, the extent to which a score of 40 represents a suitable response threshold should be added to the study documents. In addition, the selected operationalisation must ensure that the entire observation period is covered.

6. Question according to PICO: Outcome, 6-minute walk

   It must be demonstrated that the selected response threshold (improvement or deterioration in the distance walked by > 30 m) is a clinically relevant change, otherwise continuous analyses must be defined.

   If the endpoint is to be used for the benefit assessment, an evaluation of the walking distance at month 36 after the start of treatment should be defined without taking the baseline values into account.

7. Question according to PICO: Outcome, achievement of motor milestones

   The endpoint "standing without support" and an endpoint for maintenance of motor function should be added.

   With regard to the operationalisation of the percentage of patients who reach a milestone at an age-appropriate point in time, time-to-event analyses or analyses of the percentage of patients who have reached a motor milestone at a point in time to be defined (e.g. 12 months, 24 months and 36 months after the start of treatment) should be carried out.

8. Question according to PICO: Outcome, bulbar function

The operationalisation of the percentage of patients who show age-appropriate scores, defined as age equivalents, in the expressive language and receptive language subscales must be adjusted, e.g. as a change compared to baseline.

9. Question according to PICO: Outcome, further complications of the disease

   Age-appropriate, valid instruments should be used to assess the symptoms of pain or fatigue, if these are present. A corresponding review must be carried out.

   A justification should be added as to why the assessment of scoliosis is limited to the occurrence of severe events.

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

    If the duration of observation is comparable, evaluations of the percentage of patients with an event in the AE endpoints should be performed.

    The endpoint "number of unplanned hospitalisations" is dispensable and should be deleted.

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

    A description of the operationalisation of the SAEs should be added. It should be made clear that an approximation of AEs that lead to hospitalisation or a prolongation of hospitalisation or AEs that lead to death is selected as operationalisation. The corresponding documentation fields in the SMArtCARE registry must be completed.

12. Data source/ study design: General

    For endpoints, inclusion criteria and confounders, all relevant data fields with the corresponding operationalisation must be specified in the study documents in the registry. In addition, the current version of the coding manual must be submitted for supplementary information.

13. Data source: Inclusion of further registries

    If other registries are to be included, the inclusion of the respective registries must be specified in advance and the suitability of the respective registries must be examined in accordance with the criteria specified by the G-BA in the resolution on requirements.

14. Data source: Confounder

    For patients with type 3 SMA, a systematic literature research is required to identify any further potential confounders.

    In addition, the way in which the selected confounders are included in the propensity score (PS) calculation model (e.g. continuous or dichotomous) and what influence the classification into "less important" and "very important" has on the modelling of the PS must be described.

15. Data source: Reporting dates

The reporting dates in the selected data source must ensure that the data from the routine practice data collection are available for timely submission of the interim analyses specified in the resolution of 21 July 2022 and of the dossier for the new benefit assessment. This requirement must be saved in the study documents.

16. Data source: Completeness of the data

    The planned plausibility checks to ensure the quality and completeness of data collection must be executed.

    Information on the consequences of the planned Source Data Verification (SDV) should be added.

17. Study design: Index date

    The index date, i.e. the date for the start of observation, should be defined as the day of the treatment decision (or a best possible approximation) in accordance with the procedure for target trial emulation.

18. Study design: Assignment to the treatment groups

    Since bridging therapy (e.g. until gene therapy is used) is not designed for further treatment, it should be noted that patients who have received bridging therapy are assigned to the subsequent therapy.

19. Study design: Sample size planning

    The sample size planning presented cannot be conclusively assessed.

    The sample size planning for patients with type 2 SMA and with type 3 SMA based on the RULM must be adjusted, as the operationalisation of the RULM is inappropriate (*see Outcome, Morbidity*).

    The assumptions for the presented sample size planning for patients with type 1 SMA and the assumptions for the effect magnitude for patients with type 1 and type 2 SMA are incomprehensible. The assumptions must be substantiated in more detail and adjusted if necessary.

    If disproportionately high sample sizes result for the initially selected endpoint despite a review of the underlying assumptions, the pharmaceutical company must examine or carry out further possible sample size planning on the basis of other benefit endpoints and, if necessary, also on the basis of harm endpoints.

    Due to the high level of uncertainty in estimating an adequate sample size in this procedure, the study documents must also include a review of the assumptions made during the course of data collection.

    The distribution ratios of the treatment arms on which the respective sample size planning is based must be added.

20. Study design: Discontinuation criteria

The pharmaceutical company must specify how to proceed for the populations for which no sample size planning has yet been carried out.

It should also be added to the study protocol that any decision to discontinue the RPDC (and to change the sample size estimate) will be made in consultation with the G-BA.

21. Study design: Duration of observation

    For the RPDC study, all patients must be followed up for at least 36 months, regardless of any change in treatment.

    For the endpoint "unplanned hospitalisations", the fact that the follow-up ends with the change of treatment should be deleted.

22. Study design: Information on the data collection process

    If possible, descriptive analyses of data on prospectively enrolled patients should also be submitted for the required information on the course of data collection 6 months after the start of the study.

23. Data evaluation: Estimand

    It should be noted in the study documents that the primary estimand of the RPDC study corresponds to the Treatment Policy Strategy and includes the evaluation according to the intention-to-treat (ITT) principle for all patient-relevant endpoints. With regard to the evaluation of adverse events, reference is also made to point 29.

24. Data evaluation: Responder analyses

    Information on the planned test statistics for the planned responder analyses and the model to be used for the calculation must be added.

25. Data evaluation: continuous evaluations

    The missing information on the effect measure and the test statistics for the planned Mixed Model for Repeated Measures (MMRM) 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).

26. 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 must be added to the study documents.

27. Data evaluation: Subgroup analyses

    The different assessment of the planned subgroup feature of age ("age at enrolment in the study" and "age at diagnosis") is to be standardised for all populations to be investigated and applied to all populations.

A substantive rationale for categorising the subgroups on the basis of the median must be added.

In addition, information on the planned methodology for the subgroup analyses and on how to interpret the results should be added.

28. Data evaluation: Propensity score method

    When dealing with extreme weights, the planned procedure must be justified by relevant literature. In the absence of relevant literature, the procedure must be adapted, e.g. by truncating extreme weights.

    A detailed description of the testing of the analysis population and target population according to PS weighting must be added by the pharmaceutical company.

29. Data evaluation: adverse events (AEs)

    It should be noted in the study documents that, in addition to the planned evaluation using a hypothetical strategy, evaluations using a treatment policy strategy will also be conducted for the AE endpoints.

30. Data evaluation: Dealing with missing values

    The planned replacement of the month for patients with an event potentially leads to bias and is inappropriate. This provision should therefore be deleted. Instead, the pharmaceutical company shall add what efforts are being made to minimise the rate of missing values in the date specification.

    It is planned not to impute missing values and not to use a variable as a confounder if more than 40% of the data for the respective variable is missing. The resulting consequences for the evaluations and interpretation of the data must be discussed by the pharmaceutical company.

31. Data evaluation: Missing information

    The pharmaceutical company must complete the following missing information in accordance with the requirements of the resolution on requirements:

    - Dealing with implausible data and outliers
    - Information to check the extent to which the data on nusinersen and onasemnogene abeparvovec collected in parallel, as well as data not collected in parallel, are suitable for pooled analysis
    - Information to check the extent to which any data comparing risdiplam versus nusinersen and onasemnogene abeparvovec from different data sources are suitable for a pooled analysis

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 revised study protocol and the revised SAP are to be submitted to the G-BA by 2 May 2024.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 April 2024.

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

Berlin, 4 April 2024

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

Prof. Hecken