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: Etranacogene dezaparvovec (haemophilia B) – submission of study protocol and statistical analysis plan

of 1 February 2024

At its session on 1 February 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 etranacogene dezaparvovec (haemophilia B):

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); 9 October 2023) and the statistical analysis plan (version 1.0 (original); 9 October 2023):

1. Question according to PICO: Patient population

   It is not appropriate to only document the inclusion of patients in the German Haemophilia Registry (DHR) on the assumption that some of the inclusion and exclusion criteria cannot be documented in the DHR even in the future.

   All inclusion and exclusion criteria and patient characteristics must be recorded in the DHR.

   In addition, the pharmaceutical company must supplement the patient characteristics to describe the population in the study documents and ensure their mandatory collection in the DHR.

2. Question according to PICO: Outcome, patient-reported outcomes (PROs) and joint function

   The planned operationalisation of a responder as patients who show a change in score of ≥ 15% at least twice compared to baseline cannot be interpreted meaningfully.

If responder analyses are to be considered for the benefit assessment, significant responder analyses, e.g. at the end of observation, must be defined.

The study protocol should define appropriate tolerance ranges for the survey time points of PROs and joint function that are non-contiguous. In addition, appropriate measures to avoid missing values shall be described in the study protocol.

Should uniform survey time points not be possible within the DHR, an external centre should be considered for the collection of PROs and joint function.

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

   An appropriate definition in the DHR must be ensured for the evaluation of specific AEs.

   If the evaluation of the specific AEs is to be based on the MedDRA codes, it must be ensured that the MedDRA codes are documented in the DHR. In this case, the corresponding MedDRA codes that are relevant for the specific AE in question must also be added to the study documents for each specific AE.

4. Data source: General

   When using the DHR as a data source, all necessary adjustments for the collection of the required data must be ensured before the start of the routine practice data collection. This must be recorded in the study documents.

   The selection of the data source(s) must be determined before the start of the routine practice data collection.

   The contradictory information in the study documents regarding the incentivisation of the participating study sites alone or additionally of the enrolled patients should be standardised.

   With regard to the participating treatment sites, the limitation that only sites in which at least 10 patients with haemophilia B are treated should be deleted.

5. Data source: Completeness of the data

   Within the framework of the selected data source, it must be ensured that the relevant data for the routine practice data collection are not only optional but mandatory data fields when entering the data into the data source. Accordingly, it must be specified in the study protocol that collection of all relevant data fields for the implementation of the routine practice data collection is mandatory.

   It should be deleted from the study documents that the completeness of the documentation of the relevant data for the routine practice data collection, which is not yet fully mandatory, should only be increased through financial incentives.

6. Data source: Source Data Verification

   The source data verification for the secondary endpoints must be specified in the study protocol so that at least 10% of randomly selected patients (but at least one subject) are included for each data collection site. The study monitoring plan must be attached to the study protocol or submitted separately for the re-examination of the study documents.

7. Data source/ study design: Confounders

   The list compiled by the pharmaceutical company on the basis of a systematic literature research does not ensure the identification of all potential confounders. The previous list of potential confounders should therefore be compared with the baseline characteristics of the non-comparator primary studies (before-after comparisons) for the active ingredient etranacogene dezaparvovec and the factor IX preparations previously subjected to early benefit assessment (based on the information in the respective dossiers) and adjusted if necessary.

   For the categorisation of a confounder as "unimportant", i.e. for the exclusion of a potential confounder, sufficient justification must be provided on the basis of the literature and the assessments by the clinical experts. If there is any doubt as to whether a confounder is relevant with regard to the present study of the routine practice data collection, this should also be included in the evaluation.

   In addition, the existing differences between the confounders identified by the DHR and those identified by the pharmaceutical company, as well as the exclusion of confounders considered unimportant, should be justified in each case and the procedure with regard to the potential confounder of bleeding rate should be standardised.

   In addition, it must be stated in the study documents that the interactions between the confounders named by the pharmaceutical company are taken into account in the modelling of the propensity score.

   It must be ensured that all relevant confounders identified a priori in the selected data source are collected appropriately from the beginning of the routine practice data collection.

8. Study design: Sample size planning

   A (provisional) sample size must be specified in the study documents and included in the feasibility study. A justified adjustment of the (provisional) sample size can be made as part of the interim analysis.

   The information on the annualised bleeding rate (ABR) in the statistical analysis plan (SAP) and study protocol cited in connection with the indicative sample size estimates for various bleeding endpoints is inconsistent with the cited source and should be adjusted accordingly.

9. Study design: Discontinuation criteria

   Discontinuation criteria due to futility must be added to the study protocol and SAP. Changes to the routine practice data collection must be made in agreement with the G-BA.

10. Study design: Interim analyses

    A final sample size estimate and a futility check are to be carried out in accordance with the information in the resolution of 12 May 2023 at the time of the 1st interim analysis. This should include data up to 4 months before the respective interim analysis.

11. Data evaluation: Sensitivity analyses

    Sensitivity analyses must be defined by the pharmaceutical company using procedures that can be applied if a new therapy is not started in both treatment groups at the start of observation (e.g. prevalent new user design).

12. Data evaluation: Confounder adjustment

    The study documents must state that a confounder adjustment is also carried out in the case of a first non-adjusted (positive) verification of the balance between the treatment arms in order to compensate for any remaining imbalances.

    The trimming procedure selected for the confounder adjustment must be justified with regard to its suitability for the study of the routine practice data collection, e.g. on the basis of appropriate literature.

    It must be determined when sufficient overlap is assumed in the planned overlap investigations.

    The information on the approach for selecting the propensity score (PS) procedure, on the consideration of balance, is not congruent in the graphical illustrations and in the text of the study documents and should therefore be standardised.

    For the main analysis for confounder adjustment, a suitable analysis method relating to the average treatment effect (ATE) (e.g. inverse probability of treatment weighting (IPTW)) must be defined.

    After successful application of a PS procedure, a detailed description of the patient population resulting from the application of the respective PS procedure is required, including a comparison of this patient population with the original target population of the routine practice data collection. In this context, the baseline characteristics must be compared for all patients included in the routine practice data collection.

13. Data evaluation: Dealing with missing values

    The pharmaceutical company shall add what efforts are being made to minimise the rate of missing values in the date specification.

For all endpoints collected, meaningful replacement strategies for missing values shall be presented and the corresponding methodology shall be pre-specified.

The handling of missing values shall be explained in the study documents.

14. Data evaluation: shifted hypothesis boundary

    In the study protocol and SAP, it is to be specified, taking into account the non-randomised study design, that a shifted hypothesis boundary of 0.2 to 0.5 is used for the evaluation and interpretation of the results data, depending on the quality of the data collection and evaluation.

    In addition, a section should be added to the study protocol and SAP that addresses the interpretation of the results of the data, taking into account the non-randomised study design and using an appropriate shifted hypothesis boundary (in the range between 0.2 and 0.5).

15. Data evaluation: Endpoints

    More detailed information on the planned test statistics must be included in the study documents.

    The analytical methods described by the pharmaceutical company may lead to biased effect estimates for endpoints where only a few events occur. Adequate analysis procedures for this possible data basis must be specified in SAP.

16. Data evaluation: Subgroup analyses

    For the subgroup analysis of the factors joint status and ABR 12 months prior to enrolment in the study, a justified cut-off value must be defined a priori in each case, which does not depend on the study 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 revised study protocol and the revised SAP are to be submitted to the G-BA by 28 March 2024.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 February 2024.

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

Berlin, 1 February 2024

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

Prof. Hecken