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

of 1 February 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 12 May 2023, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient etranacogene dezaparvovec 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 12 October 2023. The documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

On the basis of this review, the G-BA came to the conclusion that the requirements for routine practice data collection and evaluations in the study protocol and SAP prepared by the pharmaceutical company and submitted to the G-BA for review were insufficiently implemented.

The present declaratory resolution and the associated justification establish and justify the necessary need for adaptation of the study protocol (version 1.0 (original); 9 October 2023) and the statistical analysis plan (version 1.0 (original); 9 October 2023).

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

1. Question according to PICO: Patient population

   The pharmaceutical company plans to document only the inclusion of patients in the German Haemophilia Registry (DHR), as some of the inclusion and exclusion criteria cannot be documented in the DHR even in the future. This is inappropriate; all inclusion and exclusion criteria and patient characteristics must be recorded in the DHR.

   It is also not clear from the study documents which patient characteristics are to be collected to describe the population in the routine practice data collection. The patient characteristics describing the population must be added to the study documents accordingly and their mandatory collection in the DHR must be ensured.

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

   The pharmaceutical company plans to assess the pain endpoint with the Brief Pain Inventory - Short Form (BPI-SF), joint function with the Haemophilia Joint Health Score (HJHS) and health-related quality of life with the Haemophila-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A) twice a year. The endpoints of pain, joint function and health-related quality of life are to be evaluated as responder analyses. According to the study protocol, all patients are considered responders if they show a change in score of ≥ 15% compared to baseline at least twice. However, this operationalisation 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 documents describe survey intervals of 6 months for the PROs and joint function without specifying tolerance ranges. Suitable tolerance ranges that are not contiguous must therefore be defined in the study protocol. 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)

   Based on the information in the study documents, it remains unclear on the basis of which information the specific AEs are to be analysed or how the data described for the specific AEs are entered in the DHR. An appropriate definition in the DHR must be ensured for the evaluation of the specific AEs.

   If the evaluation of the specific AEs is to be based on the MedDRA (Medical Dictionary for Regulatory Activities) codes, it must be ensured that the MedDRA codes are documented in the DHR. In addition, for each specific AE, corresponding MedDRA codes (e.g. PT

[preferred term] list or standardised MedDRA query [SMQ]) relevant to the specific AE in question must be added to the study documentation.

4. Data source: General

   If it is not possible to implement the necessary changes in the DHR, the pharmaceutical company plans to contact the G-BA and discuss setting up an alternative data platform. There is no timeframe for this potential approach in the study documents, but the pharmaceutical company states that it will report on the status of the technical implementation of the changes in the DHR in the status reports 6 and 18 months after the start of the routine practice data collection. This approach is improper. The selection of the data source(s) must be determined before the start of the routine practice data collection. In addition, 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 study documents describe that the pharmaceutical company assumes that financial incentives will increase the number of patients. However, there are different statements as to whether only the participating study sites or also the enrolled patients should be incentivised. This information should be standardised.

   According to the study documents, only treatment centres in which at least 10 patients with haemophilia B are treated should participate in the routine practice data collection. In order to ensure the enrolment of a sufficient number of patients as far as possible, this limitation should be cancelled.

5. Data source: Completeness of the data

   The study documents show that some data fields for the collection of endpoints and confounders are already available in the DHR, but are not or not completely mandatory to fill out. The pharmaceutical company plans to increase the completeness of the documentation through financial incentives (*see section 4. Data source: General*). That is not sufficient. 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

   A monitoring plan for the Source Data Verification (SDV) is not available and will be prepared after commissioning a Contract Research Organisation (CRO) according to the information in the study documents. 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

   To identify the confounders relevant to the present research question, the pharmaceutical company submits a list of potentially relevant confounders compiled on the basis of a systematic literature research. For the literature research, information was extracted from secondary sources that did not contain a sufficient number of suitable primary studies and did not report the statistical evidence required to assess the confounders.

   Therefore, the pharmaceutical company should compare this list 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 adjust if necessary.

   In addition, the approach for assessing the confounders as important, less important or unimportant is inappropriate, as there is not always a justification for excluding the potential confounders categorised as unimportant and the approach for the potential confounder bleeding rate is inconsistent in terms of content.

   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. The respective justifications should also be described in a comprehensible manner and go beyond the keyword-like naming of individual keywords. The lack of sufficient evidence for categorising whether a potential confounder is a relevant confounder is an insufficient justification for excluding this potential confounder. The assumption of a strong correlation between comorbidities and age is also an insufficient justification.

   In addition, there are differences between the confounders identified by the DHR and the pharmaceutical company, which should be discussed and justified in the study documents. The pharmaceutical company also names 4 interactions between the confounders: Dosage of factor IX prophylaxis*ABR_12, age*joint status, joint status*factor IX residual activity and ABR_12*factor IX residual activity. However, it remains unclear whether the 4 interactions between the confounders mentioned are taken into account in the modelling of the propensity score. This must be saved in the study documents.

   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

   The pharmaceutical company plans to include all patients who fulfil the inclusion criteria in the routine practice data collection without naming a specific sample size. This is inappropriate; a (provisional) sample size must be stated in the study documents and included in the feasibility study.

   The study documents describe 2 approaches to sample size planning, which the pharmaceutical company carries out for different bleeding endpoints, each operationalised as an annualised bleeding rate (ABR). The European Public Assessment Report (EPAR) for etranacogene dezaparvovec is also cited for the assumptions on ABR in the treatment arms. However, the information in the EPAR is inconsistent with the information in the SAP and study protocol and should be adjusted accordingly.

9. Study design: Discontinuation criteria

   The study documents do not contain any information on specific discontinuation criteria due to futility; this should be added. Changes to the routine practice data collection must be made in agreement with the G-BA.

10. Study design: Interim analyses

    The pharmaceutical company states that both the sample size estimate and the futility check can only be carried out in the 2nd interim analysis, as this is considered infeasible due to the delayed availability of data at the time of the 1st interim analysis. This is inappropriate as a final sample size estimate and a futility check must be performed in accordance with the information in the resolution of 12 May 2023 at the time of the 1st interim analysis. It is the responsibility of the pharmaceutical company to submit data covering the period required by the G-BA. This should include data up to 4 months before the respective interim analysis.

11. Data evaluation: Sensitivity analyses

    The pharmaceutical company plans to conduct various sensitivity analyses for the primary, secondary and AE endpoints.

    The literature describes procedures for dealing with the situation when a new therapy is not started in both treatment groups at the start of observation, such as the prevalent new user design. The pharmaceutical company must define corresponding sensitivity analyses. However, it should be noted that potential time-dependent confounders must be collected continuously during the study.

12. Data evaluation: Confounder adjustment

    The study documents indicate that an initial test of the balance between the treatment arms is to be carried out without prior data adjustment. For this purpose, the standardised mean difference (SMD) of the confounders is to be calculated. If all SMDs are less than 0.1, a confounder adjustment and thus, the use of the propensity score (PS), is not necessary

from the perspective of the pharmaceutical company. This approach is inappropriate as a confounder adjustment must also be carried out in this case to compensate for any remaining imbalances. With regard to the trimming procedure mentioned in the study documents, the pharmaceutical company does not justify its approach and there are no corresponding literature references. The results of a study by Stürmer et al.[1] show that other trimming procedures lead to less biased effect estimates. The trimming procedure selected for the confounder adjustment must therefore be justified with regard to its suitability for the study of the routine practice data collection, e.g. on the basis of suitable literature. The study documents do not specify a criterion for when the investigations lead to a sufficient overlap. Rather, it is described that the analysis population obtained in this way can deviate greatly from the G-BA's target population. This approach is improper. Even if there are currently no established criteria for categorising overlap, the study documents must specify the minimum percentage of overlap that must be guaranteed. With regard to the approach for selecting the propensity score (PS) procedure, the approach on balance outlined in the flow chart is not completely congruent with the information in the text. The information must 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 method, it must either be carefully justified that the resulting analysis population is sufficiently similar to the original target population; otherwise, the sub-population of the target population to which the results refer must be described. The pharmaceutical company plans to make an in-depth description of the baseline characteristics per treatment arm of the patients excluded or included in the analysis population. This approach is incomplete. The baseline characteristics are to be compared for all patients included in the routine practice data collection.

13. Data evaluation: Dealing with missing values

It is unclear whether a replacement is planned for missing monthly data and what effects the respective approach will have. Therefore, the pharmaceutical company shall add what efforts are being made to minimise the rate of missing values in the date specification.

With regard to the handling of missing data, the pharmaceutical company states that it intends to perform multiple imputation for the confounder variables if there are more than 5% missing values. Multiple imputation using chained equations is planned. The method described is suitable in principle, but it is not clear from the description how the multiple imputation is to be specifically combined with the estimation of the PS and the subsequent effect estimation for the endpoints. This concerns the estimation of balance and overlap as well as the model selection for the PS procedure. The pharmaceutical

1 Stürmer T, Webster-Clark M, Lund JL et al. Propensity Score Weighting and Trimming Strategies for Reducing Variance and Bias of Treatment Effect Estimates: A Simulation Study. Am J Epidemiol 2021; 190(8): 1659-1670

company is planning different replacement strategies for the endpoints in the mortality, morbidity and health-related quality of life endpoint categories. However, it is not clear at what percentage of missing values a replacement is no longer considered meaningful and the resulting consequences. For all endpoints collected, meaningful replacement strategies for missing values shall therefore be presented and the corresponding methodology shall be pre-specified. No replacement strategy is provided for AE endpoints. This approach is inappropriate; replacement strategies must also be specified for the AE endpoints.

14. Data evaluation: shifted hypothesis boundary

The effect to be assumed between etranacogene dezaparvovec and the comparator is composed of the true difference between the two treatment options and the bias due to the non-randomised study design. Due to unknown confounders, a statement on the benefit or harm of an intervention can only be derived from a certain effect magnitude. The specific threshold results from the quality of the data. For the evaluation of the data obtained, it must therefore be stipulated that a shifted hypothesis boundary of 0.2 to 0.5 is taken into account depending on the quality of the data collection and evaluation. In addition, the significance of the data collected in the context of the routine practice data collection is determined by the quality of the data in the specific case, for example, by the knowledge of relevant confounders. Therefore, 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

For some endpoints, e.g. life-threatening bleeding, overall survival and specific AEs, it can be assumed that only a few events will occur. 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.

Overall, there is a lack of precise information on the planned test statistics. These are to be supplemented.

16. Data evaluation: Subgroup analyses

According to the information in the study documents, subgroup analyses are planned for the factors of age, sex, dosage (intensity of prophylaxis) 12 months prior to enrolment in the study, joint status, ABR 12 months prior to enrolment in the study, factor IX residual activity at the time of enrolment in the study and adeno-associated virus serotype 5 (AAV5) antibody titre at the time of enrolment in the study. For both the joint status and the ABR 12 months prior to enrolment in the study, the pharmaceutical company provides the median at baseline of the enrolled patient population as the cut-off value. This

approach is inappropriate; a substantively 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.

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

1. Question according to PICO: Outcome (adverse events)

   In addition to recording the AE endpoints required by the G-BA, the study documents also include the overall rate of AEs of any severity. As the results cannot generally be interpreted on the basis of all AEs, it is recommended that the collection be omitted.

   In addition, the pharmaceutical company plans to evaluate the AE endpoints by system organ class (SOC) / PT as well as the overall rates. Weighing up the effort and significance for the RPDC, an evaluation of the AE endpoints by SOC / PT is not recommended.

   The pharmaceutical company states that all AE endpoints are coded by a contract research organisation (CRO) using MedDRA. This is ideal for the specific AEs, but is not recommended for all SAEs (and AEs).

2. Data source: Reporting dates

   It is recommended that the documentation of the collected data be carried out uniformly for all patients directly after the respective visit, if possible, in order to avoid reporting delays, and that this be specified accordingly in the study documents.

3. Study design: Assignment to the treatment groups

   The planned approach regarding the allocation to the treatment groups according to Figure 1 in the study protocol and SAP and the associated description is appropriate. In some places in the study documents, however, the allocation to the treatment groups is described differently when switching from the comparator therapy to etranacogene dezaparvovec during the course of the observation. It is recommended to adapt the deviating descriptions.

4. Data evaluation: Confounder adjustment (PS model)

   If the PS model does not converge, the pharmaceutical company plans to use a logistic ridge regression. If the PS model still does not converge, it is planned to carry out naive comparisons. It is recommended to add what effects this has on the interpretation of the results.

5. Data evaluation: MMRM model

For continuous data, the pharmaceutical company plans to carry out analyses using mixed models for repeated measures (MMRM) in addition to the evaluation using responder analyses. It is recommended that a description of the covariates and the definition of Hedges' g be added.

6. Data evaluation: Before-after comparisons

   The pharmaceutical company is planning before-after comparisons as part of sensitivity analyses. It should be noted that in a before-after comparison, there are uncertainties as to whether the effects observed after the change in therapy are actually due to the intervention or to other patient-individual factors, partly due to methodological limitations. Therefore, the results of a before-after comparison cannot be interpreted in a valid way. Accordingly, before-after comparisons are not recommended for the benefit assessment in this therapeutic indication.

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

Taking into account the implementation time required in this case for the adaptation of the data source, the revised study protocol and the revised SAP must be submitted to the G-BA by 28 March 2024.

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. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient etranacogene dezaparvovec have been implemented as specified in the resolution of 12 May 2023, the pharmaceutical company submitted 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 1 February 2024, the plenum decided on the result of the review regarding the submitted study protocol (version 1.0 (original); 9 October 2023) and the statistical analysis plan (version 1.0 (original); 9 October 2023).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	5 January 2024 15 January 2024	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	23 January 2024	Consultation on the result of the review of the study protocol and SAP
Plenum	1 February 2024	Resolution on the result of the review of the study protocol and SAP

Berlin, 1 February 2024

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

Prof. Hecken