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) – Review of study protocol and statistical analysis plan and start of RPDC

of 18 July 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 practice 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). By G-BA's declaratory resolution of 1 February 2024, the pharmaceutical company was notified of the adjustments to the study protocol (version 1.0, 9 October 2023) and the statistical analysis plan (SAP; version 1.0, 9 October 2023) 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 28 March 2024.

By e-mail dated 25 April 2024, the pharmaceutical company informed the G-BA about the resolutions of the DHR Steering Committee from December 2023 and April 2024 and pointed out two resolutions from April 2024 that were particularly relevant for the implementation of

the RPDC and whose contents were described differently in the revised study documents submitted on 28 March 2024.

The pharmaceutical company was therefore requested to submit an adapted version of the study protocol and statistical analysis plan that takes into account the resolutions of the DHR Steering Committee from April 2024.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP, which take into account the resolutions of the DHR Steering Committee from April 2024, to the G-BA in due time by 23 May 2024.

The revised drafts for a study protocol and an SAP were reviewed by the G-BA along with 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 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, 23 May 2024) and the statistical analysis plan (SAP; version 3.0, 23 May 2024) that are considered necessary.

The following adjustments, which the G-BA considered necessary for the start of routine practice data collection of etranacogene dezaparvovec, have not been fully implemented:

- In the study documents, the exclusion criteria "Presence of acute infections or uncontrolled chronic infections" was deleted, the exclusion criteria "Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy" and "Known intolerance/ hypersensitivity to any FIX concentrates and/or etranacogene dezaparvovec" are currently not part of the DHR data record.

- The required comparison and the supplements to the procedure for identifying and defining relevant confounders were carried out, but the exclusion of potentially relevant confounders on the grounds of a lack of evidence is considered inappropriate; moreover, these are not collected in the DHR.

Based on an overall analysis of the requirements stated in the study documents, the G-BA came to the conclusion that the implementation of the requirements for routine practice data collection and evaluations in the revised study protocol and statistical analysis plan, prepared by the pharmaceutical company subject to the condition that further adjustments deemed necessary are made, can be considered fulfilled to the extent that a start of the routine practice data collection of etranacogene dezaparvovec can be determined in the present case.

This decision is based on the subsequent reasons:

The German Haemophilia Registry (DHR) is suitable for the research question of the present routine practice data collection and was accordingly classified by the G-BA as a potential primary data source. However, the use of the suitable DHR registry as a data source is a special case, as the DHR is subject to legal requirements due to its establishment in the Transfusion Act (Act on the Regulation of Transfusion Science; Section 21a German Haemophilia Registry, prescription authorisation) and certain planned extensions to the data record could therefore not be carried out. However, the extension of the data record and the elimination of existing limitations of the DHR necessary for the present routine practice data collection has been implemented by the majority, so that the G-BA continues to classify the DHR as currently the best possible data source for the implementation of routine practice data collection. In addition, the uncertainties resulting from the adjustments not fully implemented in the DHR can be reduced by suitable measures, so that the G-BA is of the opinion that proper data collection can be implemented.
With regard to the exclusion criteria which are not currently collected in the DHR data record, it should also be noted that, according to the information in the study protocol, the pharmaceutical company is planning a 100% Source Data Verification (SDV) for the inclusion and exclusion criteria. The requirement that the planned SDV must also be guaranteed for inclusion or exclusion criteria specified in the study protocol and not collected in the DHR was added accordingly in the present declaratory resolution.
The exclusion criterion "Presence of acute infections or uncontrolled chronic infections" can be considered to be covered by the general exclusion criterion "Other concomitant disorders or conditions that would, in the opinion of the investigator, render the patient unsuitable for gene therapy" in view of the fact that acute infections or uncontrolled chronic infections are a contraindication for the administration of etranacogene dezaparvovec according to the product information. The deletion is therefore considered acceptable by the G-BA.
With regard to the confounders, the pharmaceutical company has basically carried out the comparison and supplements required by the G-BA; the G-BA therefore assumes that a sufficiently complete list of potentially relevant confounders has been identified. In the present declaratory resolution, the requirement has also been added that a missing collection of confounders to be classified as relevant in the study documents must be addressed as uncertainty and the consideration in the interpretation of the results must be described.
With regard to the definitions and operationalisation of the required specific AEs "severe liver disease", "malignant neoplasms" and "thromboembolic events", supplements were made to the study documents and certain variables were included in the DHR data record. The procedure is considered to be adequate by the G-BA.

Particularly taking into account the special situation described here, 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) Data source: Collection of baseline data

The fact that the baseline data are checked for timeliness on the index date is to be added to the study documents.

b) Data source: Completeness of the data

Financial incentives alone are not sufficient to increase the completeness of the documentation of data that is not subject to mandatory collection in the DHR.

Incentivising the enrolled patients in the PRO instruments is inappropriate in view of the mandatory open-label design of the study and should be deleted.

Information on how to deal with possible missing values for data not subject to mandatory collection, or how these could be avoided in the best possible way (e.g. intensification of monitoring), must be added to the study documents.

c) Data source: Source Data Verification

According to the information in the study protocol, a 100% source data verification is planned for the patient consent form, the inclusion and exclusion criteria, the baseline confounders and the primary endpoint. A 100% source data verification for the data field "Patient participates in RPDC and fulfils all necessary inclusion criteria and none of the exclusion criteria" must be ensured for all inclusion and exclusion criteria defined in the study protocol, including those that are not collected in the DHR.

Event-related monitoring visits in combination with the measures already listed in the previous version of the study documents appear to be suitable measures for avoiding missing values. However, the planned specification of event-related monitoring visits at 4 study sites is incomprehensible and must be adjusted accordingly.

d) Data source/ study design: Confounders

The exclusion of potentially relevant confounders must be justified in the study documents with regard to content. The existence of insufficient evidence is considered an inappropriate justification for excluding a potentially relevant confounder.

The missing collection of confounders classified as relevant must be addressed as uncertainty in the study documents and the consideration of this must be described in the interpretation of the results.

e) Study design: Discontinuation criteria

In the study documents, the sample size estimate based on a non-shifted null hypothesis is named as a criterion for futility check, but it remains unclear what specific procedure is envisaged. Subsequently, no information on specific discontinuation criteria can be found in the study documents. This is to be supplemented.

f) Data evaluation: Sensitivity analyses

For the sensitivity analysis requested by the G-BA, it is not necessary to divide the control group into patients with "Factor IX preparation (prevention)" and "Factor IX preparation (prevention + treatment on demand)". A sensitivity analysis taking into account the entire control group must be supplemented accordingly.

g) Data evaluation: Confounder adjustment

The description of the respective patient population (total, included in the analysis, excluded from the analysis) should be based on the baseline characteristics and not only on the confounders. This must be revised in the study documents.

h) 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).

The requirement of the G-BA was not implemented, so the corresponding supplements must still be made.

i) Data evaluation: Subgroup analyses

For the subgroup analysis of the factors of joint status and annualized bleeding rate (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.

These subgroup analyses are not necessary if no substantially justified cut-off value that allows a clear group subdivision according to the severity of the disease can be determined for joint status and ABR 12 months before the start of the study.

A subgroup analysis of the influence of the AAV5 antibody titre at baseline is planned in the study documents. In the current version of the study documents, the cut-off value was changed (AAV5 antibody positive vs negative) with the justification that this could be implemented in the data fields of the DHR. The justification is inappropriate, as a substantially justified cut-off value must be defined a priori. However, the subgroup analysis for the AAV5 antibody is redundant and should therefore be deleted.

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, patient-reported endpoints and joint function

As required by the G-BA, the specified tolerance ranges for the survey time points of the patient-reported outcomes (PROs) and joint function are not contiguous. Nevertheless, they are very wide at 5 months, particularly for the patient-reported endpoints. If the return time differs systematically between the study arms, this can lead to risk of bias. It can be assumed that feedback on the PROs and joint function will generally be received after the planned survey time point rather than before. For this reason, it is recommended selecting asymmetrical tolerance ranges with a shorter time frame before the planned survey time point (e.g. 2 weeks) and a longer time frame afterwards (e.g. 4 to 6 weeks).

b) Question according to PICO: Endpoint of pain

The patient-reported outcome (PRO) of pain should be collected using the Brief Pain Inventory – Short Form (BPI-SF). The evaluations of the scales of pain intensity (4 items) and impairment due to pain (7 items) planned according to the SAP are appropriate in accordance with the BPI-SF manual. For content-related reasons, however, it is recommended that item 3 of the pain intensity scale be subject to a separate evaluation.

c) Data source/ study design: Confounders

It is planned to include the dichotomised (≤ 50 years, > 50 years) age confounder in the PS model. No justification is given for the limit value. Furthermore, dichotomisation can lead to convergence issues and loss of information when calculating propensity scores. The inclusion of age as a continuous variable is therefore recommended.

d) Data source: Source Data Verification

According to the information in the study documents, the participating study sites are reminded by telephone call or e-mail to collect data in good time prior to each data cut-off. It is recommended that further measures be added to ensure that the documentation of the collected data is standardised for all patients soon after the respective survey.

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 2 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 August 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 etranacogene dezaparvovec have been implemented as specified in the resolution of 12 May 2023, 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 18 July 2024, the plenum decided on the outcome of the review regarding the submitted study protocol (version 3.0; 23 May 2024) and the statistical analysis plan (version 3.0; 23 May 2024).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	17 June 2024 4 July 2024	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	9 July 2024	Consultation on the result of the review of the study protocol and SAP
Plenum	18 July 2024	Resolution on the result of the review of the study protocol and SAP

Berlin, 18 July 2024

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

Prof. Hecken