Gemeinsamer Bundesausschuss

# Justification

for 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, statistical analysis plan and interim analyses

From 2 July 2026

## 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 from 30.04.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4 from 07.01.2019, 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 review the data obtained and the obligation to collect data at regular intervals, at least every eighteen months.

## 2. Key points of the resolution

At their 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 requirements of the G-BA for the routine practice data collection and evaluations of the data obtained have been implemented, the pharmaceutical company submitted the revised versions of the study protocol and the statistical analysis plan (SAP) (version 4.0 of 27 February 2026) to the G-BA in due time on 2 March 2026. The study documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

It is noted that the pharmaceutical company have not fully implemented the requirements for the implementation of the routine practice data collection (RPDC) and evaluations in the submitted, revised versions of the study protocol and the statistical analysis plan (SAP) (version 4.0 of 27 February 2026) as stated in the declaratory resolution of 18 July 2024. Furthermore, the submitted, revised versions of the study protocol and the SAP as well as the review of the approach taken in the 1st interim analysis indicate that further adaptations are required. This declaratory resolution defines and justifies the further adjustments to the study protocol and the SAP (version 4.0 of 27 February 2026) that are considered necessary.

### 2nd1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

a) Interpretation of the data: Confounder

When classifying confounders as "insignificant", the available study documents still occasionally cites reasons for exclusion which are regarded as inappropriate

justification for excluding a potentially relevant confounder (presence of inadequate evidence). The exclusion of potentially relevant confounders must be justified in the study documents with regard to content. The missing collection of confounders classified as relevant (in the absence of an adequate reason for exclusion) must be addressed as uncertainty in the study documents and the consideration of this must be described in the interpretation of the results.

b) Study design: Discontinuation criteria

The pharmaceutical company has defined criteria for study discontinuation in accordance with the G-BA's requirements; however, due to uncertainties, no final assessment can be made. Criterion 1 needs to be clarified as to how the study is to be handled if the criterion is not met. It is also unclear how the expected patient numbers should specifically be calculated at the time of the 2nd interim analysis. Therefore, the 2nd criterion can also not be conclusively assessed. Furthermore, there is lack of justification for the 75% criterion. It should be noted that criterion 1 is not equally relevant for all endpoints, and this must be accordingly taken into account when deciding on study discontinuation. The criteria for study discontinuation should therefore be revised accordingly.

Changes that go beyond the conditions in the declaratory resolution of 18 July 2024

c) Start of monitoring for the endpoints of haemorrhage and Factor IX infusions:

Unlike previous versions, the current study documents state that the start of monitoring for the endpoints on haemorrhage and Factor IX infusions in the intervention arm has been postponed to day 21 following the infusion of etranacogene dezaparvovec. No adjustment was made to the comparator arm in the study documents, meaning that monitoring of these endpoints in the comparator arm commenced from the index date, as originally planned for both treatment groups. However, it must be ensured that analyses are carried out consistently for both treatment arms from the index date onwards. Postponement of the start of monitoring for the endpoints on haemorrhage and Factor IX infusions in the intervention arm to day 21 following the infusion of etranacogene dezaparvovec must therefore be cancelled.

d) Operationalisation of the responder analyses for the patient-reported endpoints and joint function:

In the previous version of the study documents (version 3.0 of 23 May 2024), the adjustment made to the operationalisation of the responder analyses for the patient-reported endpoints and joint function was deemed appropriate. However, the current version of the study documents (version 4.0 of 27 February 2026) still contains, in some instances, the original operationalisation of a responder (a patient who, on at least two occasions, shows a change in score by ≥ 15% of the scale range compared with baseline), which cannot be meaningfully interpreted. Any passages that still contain the original definition of a responder should be revised accordingly.

e) Evaluation of side effects:

In contrast to the study design, in the report on the 1st interim analysis, the pharmaceutical company provided no data in the methodology section regarding the collection and evaluation of specific adverse events (AEs) (formation of Factor IX inhibitors, thromboembolic events, symptomatic liver damage, malignant neoplasms).

The absence of specific AEs has not been justified. However, side effects must be collected and evaluated for the following interim analyses and the renewed benefit assessment, as required by the G-BA's resolution and as planned in the study documents (overall rate of SAEs and specific AEs, specifying the respective severity grade).

f) Presentation of pre-specified patient characteristics:

For the 1st interim analysis, the pharmaceutical company did not submit data for all the patient characteristics specified in the study documents. Although all patient characteristics are listed in the description of the methodology, there is lack of information on, for example, "History of Factor IX inhibitors" and "Known advanced liver fibrosis or cirrhosis" for characterisation of the currently enrolled patients. It is unclear why these characteristics – the presence of which leads to exclusion from the study – are not presented, particularly as they are included in the DHR data record. In particular, given that the individual inclusion and exclusion criteria for the RPDC cannot be fully recorded in the DHR, and that compliance with the inclusion criteria and non-compliance with the exclusion criteria are only documented using a single field, at least those inclusion and exclusion criteria that can be recorded individually must be presented for the following interim analyses and the renewed benefit assessment.

In addition to the adaptations that must be implemented as mandatory requirements, the G-BA make the following recommendations for further adaptation to the study protocol and the statistical analysis plan:

1. It is recommended continuing the recruitment until 6 months before the final data cut-off and including all patients enrolled in the analysis. In addition, sensitivity analyses that include only patients with a duration of observation of at least 3 years should be carried out in order to draw conclusions about the sustainability of the effects.

2. If it is not possible to implement a data cut-off independently of the annual data cut-off in the DHR at the end of the year, it is recommended shifting the dates of the data cut-offs for the 2nd interim analysis as well as the renewed benefit assessment to the end of the year respectively: For the revised deadline for the 2nd interim analysis on 30 April 2028, 31 December 2027 is therefore recommended as the data cut-off date; for the revised deadline for the renewed benefit assessment on 1 July 2030, 31 December 2029 is recommended as the data cut-off date.

3. In the report on the 1st interim analysis, the crude annualised bleeding rate data is based on 1 patient-year, whilst the accompanying footnote incorrectly states that the figures are based on 1,000 patient-years. For the following interim analyses, it is recommended disregarding the relevant footnote.

**2nd2 Deadline for submission of the revised study protocol and statistical analysis plan**

The revised study protocol and the revised SAP must be submitted to the G-BA by 30 April 2028.

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 6 June 2024, the pharmaceutical company submitted revised drafts of a study protocol and an 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 their session on 2 July 2026, the plenum decided on the outcome of the review regarding the submitted study protocol and the SAP (version 4.0 of 27 February 2026).

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| WG RPDC | 18 May 2026<br>4 June 2026<br>15 June 2026 | Consultation on the review of study documents (study protocol and SAP) and the interim analysis |
| Subcommittee on Medicinal Products | 23 June 2026 | Consultation on the review of study documents (study protocol and SAP) and the interim analysis |
| Plenum | 2 July 2026 | Adoption of the resolution on the review of study documents (study protocol and SAP) and the interim analysis |

Berlin, 2 July 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk