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:
Valoctocogene roxaparvovec (haemophilia A) – 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 2 February 2023, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient valoctocogene roxaparvovec 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 30 June 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 21 September 2023, the pharmaceutical company was notified of the adjustments to the study protocol (version 1.0, 29 June 2023) and the statistical analysis plan (SAP; version 1.0, 29 June 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 19 October 2023. 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 decision on whether the routine practice data collection can be carried out on the basis of the submitted study protocol and statistical analysis plan could not be made appropriately at this time.

The G-BA took into account the fact that the (previous) deadlines for changes to the data record of the German Haemophilia Registry (DHR) at the Paul Ehrlich Institute and the necessary implementation time may represent possible limiting factors for ensuring the necessary adjustments to the overall data record of the DHR registry.

The G-BA has therefore decided to extend the period for the 2nd review of the study documents in order to give the pharmaceutical company the last opportunity to ensure that the necessary adjustments are made to the overall data record of the DHR registry and to rectify all remaining defects that are relevant for the start of routine practice data collection. The pharmaceutical company is responsible for rectifying the remaining defects and ensuring that all relevant data is collected in the selected primary data source.

By letter of 23 January 2024, the pharmaceutical company was explicitly informed only of those remaining defects that must be remedied before the decision of the G-BA on the start of routine practice data collection of valoctocogene roxaparvovec (Val-Rox) and the operational start of the data collection.

The G-BA's declaratory resolution of 21 September 2023 for the active ingredient valoctocogene roxaparvovec is generally decisive for remedying the inadequate implementation of the requirements for routine practice data collection and evaluations in the study protocol and statistical analysis plan prepared by the pharmaceutical company.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP to the G-BA in due time by 26 April 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, 26.04.2024) and the statistical analysis plan (SAP; version 3.0, 26.04.2024) that are considered necessary.

The changes made by the pharmaceutical company do not fully address the necessary adjustments identified by the G-BA by letter of 23 January 2024, which must be rectified for the start of the routine practice data collection of valoctocogene roxaparvovec (Val-Rox).

The following adjustments, which the G-BA considered necessary for the start of routine practice data collection of valoctocogene roxaparvovec (Val-Rox), have not been fully implemented:

- In the study documents, the exclusion criteria were supplemented by the presence of acute infections or uncontrolled chronic infections, but the exclusion criterion is currently not part of the data record of the German Haemophilia Registry (DHR)

- The study protocol indicates that for specific baseline data (e.g. information on comorbidities), information that was already collected in the DHR before the index date will be used in some cases.

- The procedure for identifying and defining relevant confounders was revised, but the justification for excluding a potentially relevant confounder based on the lack of a suitable survey instrument is considered inappropriate; in addition, the HIV status at baseline mentioned as a potential confounder is 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 valoctocogene roxaparvovec 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 criterion (presence of acute infections or uncontrolled chronic infections) that is 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.

From the point of view of the G-BA, the use of information on baseline data, some of which was already collected in the DHR before the index date, may be relevant for the possibly changing status of the comorbidities to be collected. The requirement that the baseline data relating to comorbidities be checked for their timeliness on the index date has therefore been included in the present declaratory resolution.
With regard to the confounders, the G-BA 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) Question according to PICO: Inclusion and exclusion criteria

   The additions to the exclusion criteria in the study protocol and in the SAP are appropriate, but the list of variables for the inclusion and exclusion criteria in the Annex to the SAP was not supplemented as required. This is pending.

b) Question according to PICO: Outcome (bleeding)

   In the study protocol, the options "suspected bleeding" and "unknown reason" were deleted from the information on the reason for treatment on demand for bleeding of any severity.

   However, deletion is only appropriate in the case of severe and life-threatening bleeding; in other cases, deletion should be reversed.

   In the case of severe and life-threatening bleeding, the reason for treatment on demand must be ascertained as specifically as possible, for instance, by adding the data field "traumatic bleeding".

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

The tolerance ranges for the collection of the PROs continue to be contiguous, and the planned tolerance range of ± 3 months for the survey time points of the PROs and the joint function is too wide. This approach is inappropriate.

The study protocol shall define appropriate tolerance ranges for the collection of patient-reported endpoints and joint function that are non-contiguous.

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

The replacement of the term adverse events (AEs) by the term medical events should be reversed.

e) Data source: Collection of baseline data

The study protocol indicates that for the baseline data, information that was already collected in the DHR before the index date will be used in some cases. This concerns information on demographics and disease status, e.g. severity of haemophilia and comorbidities.

The fact that the baseline data, especially with regard to comorbidities, are checked for timeliness on the index date is to be added to the study documents as the status of the respective comorbidities may vary.

f) Data source: Completeness of the data

According to the preliminary draft of the Clinical Operations Plan (COP), only selected study sites are to be monitored. With regard to the further measures for the planned training of treating physicians and participating staff by qualified monitors, it also remains unclear whether they are only to be carried out in selected study sites or in all participating study sites.

It must be made clear in the study documents that the measures described in the Clinical Operations Plan (COP) for training doctors and investigators and for ensuring the completeness of the data are implemented in all study sites.

g) Data source: Source Data Verification

According to the information in the study protocol, a 100% source data verification of all data fields related to the inclusion and exclusion criteria and the primary endpoint is planned. 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.

The planned source data verification based on the source files, such as the patient record, is appropriate. However, the study documents contain contradictory information in this regard; section 10.5 currently still states that the data entered in the DHR should serve as the source file. The information must be accordingly standardised.

h) Data source/ study design: Confounders

The exclusion of potentially relevant confounders must be justified in the study documents with regard to content. The absence of a suitable survey instrument is not considered sufficient justification for categorising a confounder as irrelevant.

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.

i) Study design: Estimand

In the study documents, an estimand is described according to the treatment policy strategy, not as the primary estimand, but on an equal footing with the hypothetical estimand. For the RPDC, the treatment policy strategy is to be stored as the primary estimand.

j) Study design: Status report

The deletion of the status report to the G-BA is to be reversed 6 months after the start of the RPDC.

k) Data evaluation: shifted hypothesis boundary

The described presentation of the results for the comparison of valoctocogene roxaparvovec for control is insufficient. For the RPDC, it is not relevant whether a p value for an effect estimate falls below a specified probability of error; the upper 95% confidence interval limit of the relative risk (RR) with regard to the rate ratio, or its inverse, is decisive in comparison to a shifted null hypothesis. It must be made clear that corresponding results are presented and what is meant by this when analyses are based on observed data.

A corresponding section on the interpretation of the results, taking into account the non-randomised study design, is to be submitted subsequently.

l) Data evaluation: Treatment switching, assignment to the treatment groups

In the study documents, it is planned that patients who switch from the comparator arm to treatment with valoctocogene roxaparvovec after the end of the recruitment phase are not included in the analyses. The approach is inappropriate. According to the requirements of the G-BA, a strategy in the sense of an Intention-To-Treat (ITT) evaluation is to be pursued in the present setting, whereby patients who switch from the comparator therapy to valoctocogene roxaparvovec in the course of the observation should be assigned to the study arms, depending on the observation period under the comparator therapy. Accordingly, an appropriate observation period must be defined, after which the patients are assigned to the comparator arm or the valoctocogene roxaparvovec arm.

m) Data evaluation: Evaluation population

The lack of implementation in the description of the estimation of the propensity scores (PS) is inappropriate, and the description of the replacement procedure is also inadequate *(see point s*).

It must be ensured that a suitable procedure for taking missing values into account is adequately applied when estimating the PS; the corresponding procedure must be specified in the study documents.

n) Data evaluation: Sensitivity analyses

For the endpoints in the mortality, morbidity and health-related quality of life categories, sensitivity analyses shall be defined in which patients who have switched to treatment with valoctocogene roxaparvovec in the comparator arm and continue to be assigned to the comparator arm are censored at the time of switching. In addition, sensitivity analyses must be defined 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).

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

It should be clarified that the sensitivity analysis of the various therapies in the comparator arm is the evaluation of data on valoctocogene roxaparvovec separately from the data on factor XIII preparations and emicizumab.

o) Data evaluation: Subgroup analyses

The adjustments to the statistical methods described by the pharmaceutical company are inappropriate.

With regard to the likelihood ratio test, it should be specified that the different factor XIII prophylaxis treatments should be compared with each other.

In the planned subgroup analyses, the disease severity characteristic and the likelihood ratio test must be added to the section on AAV5 status.

The conditions under which subgroup analyses are to be conducted must also be added.

p) Data evaluation: Propensity score method

The description of the PS procedure is inappropriate.

It remains unclear whether stabilised weights are used or whether their use is optional. The fixed value of 5 was selected as the criterion for truncation without further justification. The use of stabilised weights must therefore be specified and it must be explained why the choice of truncation is appropriate in the present setting.

The information on trimming must be specified and a definition of extreme stabilised weights must be added. Information on the criteria for the time after which the overlap is considered sufficient must be added.

The algorithm for selecting the PS procedure is inappropriate.

The primary procedure is the estimation of the average treatment effect (ATE) using inverse probability of treatment weighting (IPTW); PS matching (PSM) is presented as a sensitivity analysis. It is therefore not a hierarchical procedure. Due to the shortcomings mentioned, it cannot be ruled out that PS matching (PSM) is used as the primary procedure. It is incomprehensible why a 1:1 or 1:2 distribution ratio between intervention and control is sufficient to favour PSM as the primary procedure over IPTW when selecting the procedure.

In the event that IPTW and PSM do not achieve sufficient overlap and model quality, the planned multivariable regression analysis with adjustment with confounders is inappropriate.

Statements on the necessity for a detailed description of the patient population resulting from the application of the respective propensity score procedure, including the need for a comparison of this patient population with the original target population of the RPDC must be added.

q) Data evaluation: patient-reported outcomes (PROs)

The described evaluation using mixed model repeated measures (MMRM) is inappropriate. By using the last observed value, the results are potentially subject to a high risk of bias and cannot be interpreted, as the time points will differ between patients due to different observation times. Therefore, either an analysis of a difference at a fixed point in time, such as the difference in the change from the start of the study to month 36, or an analysis of the mean difference in the change compared to the start of the study over the entire study period must be performed.

The analyses for the instruments *Haemophilia Joint Health Score (HJHS), Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A) and Brief Pain Inventory – short form (BPI-SF)* must be carried out according to the PS procedure (or multiple regression analysis), which is caused by the hierarchical selection procedure (*see point p*).

An operationalisation must be added for the standardised mean difference (SMD). The multiple imputation procedure provided for in SAP, which still needs to be specified, must be added.

The responder analyses provided for the HJHS are inappropriate. The definition of an event is unclear as it is not sufficiently defined to which scales (individual items and/or total score) the definition refers. The unclear definition of an event and must be clarified accordingly. An improvement/ deterioration defined as 1 event in at least 1 of the joints is inappropriate here.

A representation of the mean observed values as progression curves must be added.

r) Data evaluation: adverse events (AEs)

The statistical evaluations are not described precisely enough. The pharmaceutical company only mentions IPTW for confounder adjustment, thus not any hierarchy of possible procedures. Furthermore, multiple imputation to replace missing values in confounders is not mentioned. The pharmaceutical company does not provide any information on how to deal with patients who switch treatment.

Information on the hierarchical procedure (*see point p*), on multiple imputation to replace missing values and on dealing with patients who switch treatment should therefore be added.

A sensitivity analysis of patients switching from the control arm to the intervention arm is not described. A sensitivity analysis in which the patients who switch from the control arm to the intervention arm and continue to be assigned to the comparator arm are censored at the time of switching should therefore be added.

s) Data evaluation: Dealing with missing values

The described method of multiple imputation (MI) using the Fully Conditional Specification (FCS) / Chained Equations (MICE) method to replace missing values is suitable in principle. However, it is not clear from the description how the MI is to be specifically combined with the estimation of the PS and the subsequent effect estimation for the endpoints. Furthermore, the number of imputations is not specified. The exact procedure with regard to the described method of MI using FCS/ MICE must therefore be specified.

Ignoring a relevant confounder with more than 40% missing data in the adjustment is inappropriate. The study documents must therefore describe how to deal with a considerable loss of information in the evaluations and under what conditions it makes sense to attempt to adjust for confounders.

In addition, the handling of missing information on endpoints must be described.

t) Data evaluation: Evaluation of the specific AEs

It must be added to the study documents that the specific AEs "malignant neoplasms" and "thromboembolic events" are analysed comparatively, regardless of the cause.

For the specific AEs, it must be added that all events leading to hospitalisation or death (overall rate) are included in the evaluation.

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: 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.

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 valoctocogene roxaparvovec have been implemented as specified in the resolution of 2 February 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; 26.04.2024) and the statistical analysis plan (version 3.0; 26.04.2024).

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