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: Valoctocogen roxaparvovec (severe haemophilia A) – submission of study protocol and statistical analysis plan

of 21 September 2023

At its session on 21 September 2023, 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 valoctocogen roxaparvovec (Val-Rox; severe haemophilia A):

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); 29 June 2023) and the statistical analysis plan (version 1.0 (original); 29 June 2023):

1. Question according to PICO: Patient population

   The exclusion criteria should be supplemented by the presence of active infections (acute or uncontrolled chronic) and the presence of known significant liver fibrosis or cirrhosis.

2. Question according to PICO: Outcome

   The study protocol must specify that all endpoints in both study arms are collected from the index date.

3. Question according to PICO: Outcome, mortality

   The survey of overall mortality is to be added to table 8 of the study protocol.

4. Question according to PICO: Outcome, bleeding

   In the case of severe and life-threatening bleeding, the reason for treatment on demand should be specified as far as possible; the selection of "suspected haemorrhage" and "unknown reason" information should be deleted for this case.

   The operationalisation of severe and life-threatening bleeding must be clearly stated in the study protocol.

5. Question according to PICO: Outcome, joint function

   The information on the assessment of joint function is to be standardised in the study protocol. An annual assessment is considered sufficient.

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

   The study protocol shall define appropriate tolerance ranges for the collection of patient-reported outcomes (PROs) and joint function that are non-contiguous. In addition, appropriate measures to avoid missing values shall be described in the study protocol.

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

   The survey of serious AEs (SAEs) is to be defined in relation to all events leading to hospitalisation or death (overall rate) and not to be restricted to those events that are related to the treatment of haemophilia.

   For specific AEs, the study protocol shall specify the recording of events leading to hospitalisation or death in addition to the overall rate.

   For the specific AE "thromboembolic events", the recording of all events regardless of any relation to the treatment of haemophilia is to be specified in the study protocol.

   The definition of the specific AE "severe liver damage" must be stored in the SAP and study protocol in a form that ensures the recording of symptomatic liver damage.

   For the specific AE "malignant neoplasms", the study protocol must specify the measures or definitions used to ensure uniform documentation of these events.

   It should be specified that the endpoints on side effects are collected in both study arms until the end of the study.

8. Question according to PICO: Outcome, supplementary information

   For the endpoint "time of resumption of prophylactic treatment", it is to be specified that any resumption of prophylactic treatment is documented.

9. Data source/ study design: General

   All relevant data to be collected and associated evaluations must be defined a priori and described in the study protocol and SAP before the start of the routine practice data collection. It should be deleted from the study documents that definitions, operationalisations or evaluations are only determined on the basis of the observed data or in the course of the routine practice data collection.

10. Data source: Collection of baseline data

    It must be specified in the study protocol that all inclusion and exclusion criteria with clear operationalisation are collected on the index date. For patients who switch to treatment with Val-Rox in the course of the study and are assigned to the Val-Rox arm according to the treatment group assignment below, it must be specified that the baseline data are collected again on the index date (date of application of Val-Rox).

    In the study protocol, the information that only patients for whom data have already been documented in the registry for at least 12 months are accessed for the collection of baseline data should be deleted.

    It must be specified in the study protocol that the age of the patients and the AAV5 status are clearly recorded in the data source. In addition, it is to be ensured that any AAV5 status collected is recorded for patients in both study arms. This is to be specified in the study protocol.

11. Data source: Definitions and operationalisation

    In the study protocol and statistical analysis plan, all data to be collected (including exposures, clinical events, endpoints, confounders) must be defined a priori with their corresponding operationalisation. For operationalisation, standard classifications are to be used as far as possible. The collection of the required data must be ensured in the selected data source before the start of the routine practice data collection.

12. Data source: Confounders

A systematic literature search for potentially relevant confounders must be carried out before the start of the routine practice data collection and supplemented with the involvement of experts.

The section on the identification and definition of confounders in the study protocol must be thoroughly revised. 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. If it is not possible to collect certain parameters, this uncertainty must be addressed in the study protocol and its consideration in the interpretation of the results must be described.

13. Data source: Reporting dates

The reporting dates in the selected data source must ensure that the data from the routine practice data collection are available for timely submission of the interim analyses specified in the resolution of 2 February 2023 and of the dossier for the new benefit assessment. This requirement must be saved in the study documents.

14. Data source: Completeness of the data

The study protocol must describe the measures taken to train the treating physicians for appropriate data collection.

In addition, the study protocol must address measures that are carried out to ensure the completeness of the data for each patient.

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.

15. Data source: Source Data Verification

The technical process of source data verification must be described clearly and comprehensibly in the study protocol. The study monitoring plan must be attached to the study protocol or submitted separately for the re-examination of the study documents.

16. Study design: Estimand

For the routine practice data collection, the treatment policy strategy is to be stored as the primary estimand.

17. Study design: Recruitment

The study protocol shall describe the measures taken to bring about the transfer of a higher percentage of patients from the collective report to the individual report.

18. Study design: Assignment to the treatment groups

    Information must be added to the study protocol on how patients in the comparator arm will be handled if they switch to treatment with Val-Rox. In this regard, an appropriate observation period must be defined, after which the patients are assigned to the comparator arm or the Val-Rox arm. Patients who switch to treatment with Val-Rox shortly after the scheduled recruitment period should also be considered.

19. Study design: Sample size planning

    In the study protocol, the information on the methodology of sample size estimate is to be corrected according to the explanations in the SAP.

    In addition, the measures taken to recruit a sufficiently high number of patients under treatment with factor VIII preparations into the routine practice data collection shall be described.

20. Study design: Discontinuation of study participation

    Discontinuation of study participation solely on the basis of the clinical assessment of the treating physician is to be deleted from the study documents. Specific criteria are to be defined on the basis of which the patients are to be discontinued from the study.

21. 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.

22. Study design: Interim analyses

    The planned interim analysis 6 months after the start of the routine practice data collection is to be deleted. The interim analyses are to be carried out according to the time points stored in the resolution of 2 February 2023 18 months, 36 months and 54 months after the start of the routine practice data collection.

23. Evaluation of the data: 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).

24. Data evaluation: Evaluation population

In the statistical analysis plan, the information that only patients for whom complete data are available on all variables to be included in the propensity score procedure are included in the evaluation should be deleted. Measures must be established to ensure the completeness of the data as well as clear criteria on how to deal with missing values in the analysis.

25. 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 Val-Rox 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).

    Furthermore, sensitivity analyses for the separate evaluation of the data on Val-Rox versus the data on factor XIII preparations and on emicizumab are to be pre-specified.

26. Data evaluation: Subgroup analyses

    The statistical tests for subgroup analyses shall be described in the SAP. In accordance with the module templates for the benefit assessment, the execution of further subgroup analyses on disease severity and age, among other things, is to be examined.

    Inconsistent data regarding the observation of the AAV5 status characteristic between study protocol and SAP are to be standardised (subgroup analyses vs sensitivity analyses).

27. Data evaluation: Propensity score method

    In the statistical analysis plan, the information that all previously identified relevant confounders are taken into account in the regression model for estimating the PS is to be stored. An appropriate alternative strategy shall be stored for the case of non-convergence of the regression model. It is to be specified that a discussion of the results is to take place, in particular, also taking into account the balanced nature of the variables not included in the model.

    The main analysis for confounder adjustment using the Standardised Mortality Ratio Weighting (SMRW) is to be deleted and a suitable analysis method relating to the Average Treatment Effect (ATE) (e.g. inverse probability of treatment weighting (IPTW)) is to be registered. The handling of extreme weights shall be clearly specified in the SAP.

    It shall be determined when sufficient overlap is assumed in the planned overlap investigations (visual examination of the density curve and histograms of the propensity scores, c-statistics).

The underlying methodology for dealing with imbalances must be presented in a comprehensible and transparent manner. The reasons for the suitability of the chosen methodology shall be described in the SAP, as well as the criteria for the model selection for the final analysis.

In the SAP, a clear hierarchy of eligible propensity score methods and the test criteria for selecting the most robust method shall be defined. In this context, specific information on the verification of sufficient overlap and balance shall be provided. It is necessary to add what consequences arise if no propensity score procedure that achieves sufficient overlap and balance is identified.

In the SAP, it should be clarified that the estimate of the propensity score represents the probability of a patient receiving an intervention and this is independent of the endpoint under consideration.

It shall be specified in the SAP that sensitivity analyses with different propensity score methods are performed for all relevant endpoints and not only for the primary endpoint.

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

28. Evaluation of the data: binary endpoints

    For binary endpoints with a comparative duration of observation, the relative risk shall be defined as an effect estimator.

29. Data evaluation: Bleeding

30. The information on the negative-binominal model for the evaluation of bleeding must be completed in the SAP, taking into account all events observed between the index date and the end of the study, as well as the specification of an offset. In addition, the application of the zero-inflated negative binomial model must be clearly specified in the SAP. Data evaluation: Patient-Reported Outcomes (PROs)

    The generalised mixed models for repeated measures provided for the PROs shall be described in detail in the SAP. A value of at least 15% of the scale range is to be defined as the response criterion. In addition, the evaluation in the form of progression curves for the interpretation of the responder analyses must be defined in the SAP.

31. Evaluation of the data: adverse events (AE)

    For the AEs, an evaluation shall be determined regardless of the number of events that occurred. The statistical procedure for the evaluation of the AE shall be fully described in the SAP. An analysis shall be defined for the AE in which patients who switched to treatment with Val-Rox in the comparator arm and continue to be assigned to the

comparator arm are not censored at the time of switching. In addition, a further analysis with censoring is to be determined for these patients at the time of switching. For patients who continue to be assigned to the intervention arm when they receive factor VIII therapy again, no censoring should take place for the analysis.

32. Data evaluation: Dealing with missing values

    The information on how to deal with missing values should be clarified and standardised in the study documents. Meaningful replacement strategies for missing values shall be presented and the corresponding methodology shall be pre-specified.

    The planned replacement of the month potentially leads to significant risks of bias and is not appropriate. This provision should therefore be deleted. Instead, the pharmaceutical company shall add what efforts are being made to minimise the rate of missing values in the date specification.

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 19 October 2023.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 21 September 2023.

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

Berlin, 21 September 2023

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

Prof. Hecken