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: Valoctocogene roxaparvovec (haemophilia A) – Review of study protocol and statistical analysis plan and start of RPDC

of 18 July 2024

At its session on 18 July 2024, 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 valoctocogene roxaparvovec (haemophilia A):

I. It is stated 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 are considered fulfilled under the condition that the pharmaceutical company is obliged to make the following 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:

a) Question according to PICO: Inclusion and exclusion criteria

The list of variables for the inclusion and exclusion criteria must be added to the Annex of the SAP.

b) Question according to PICO: Outcome (bleeding)

The deletion of the options "suspected bleeding" and "unknown reason" from the information on the reason for treatment on demand for bleeding of any severity in the study documents is inappropriate.

Deletion is only appropriate in the case of severe and life-threatening bleeding; in other cases, the deletion must 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 study protocol shall define appropriate tolerance ranges for the collection of patient-reported outcomes (PROs) 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 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.

f) Data source: Completeness of the data

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

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 by the pharmaceutical company with regard to all inclusion and exclusion criteria defined in the study protocol.

The planned source data verification based on the source files, such as the patient record, is appropriate. However, the relevant contradictory information in the study documents should be standardised accordingly.

h) Data source/ study design: Confounders

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 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

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 routine practice data collection.

k) Data evaluation: shifted hypothesis boundary

The described presentation of the results for the comparison of valoctocogene roxaparvovec for control is insufficient. 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. An appropriate observation period must be defined, after which the patients are assigned to the comparator arm or the valoctocogene roxaparvovec arm.

The patients are to be analysed in terms of an intention-to-treat (ITT) evaluation, depending on the defined assignment, in the intervention arm or in the comparator 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.

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).

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 valoctocogene roxaparvovec.

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.

The use of stabilised weights must 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.

In the SAP, a clear hierarchy of eligible PS procedures and the test criteria for selecting the most robust method must be defined.

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

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

The described evaluation using mixed model repeated measures (MMRM) is inappropriate.

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.

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 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)

Information on the hierarchical procedure, on multiple imputation to replace missing values and on dealing with patients who switch treatment must be added.

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 must be added.

s) Data evaluation: Dealing with missing values

The exact procedure with regard to the described multiple imputation (MI) method using the Fully Conditional Specification (FCS) / Chained Equations (MICE) method must be specified.

The study documents must 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.

II. The routine practice data collection starts on 30 August 2024.

III. The revised study protocol and the revised SAP are to be submitted to the G-BA by 2 March 2026.

IV. The resolution will enter into force on the day of its publication on the website of the G-

BA on 18 July 2024.

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

Berlin, 18 July 2024

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

Prof. Hecken