Valoctocogen roxaparvovec (severe haemophilia A)
Requirement of Routine Practice Data Collection and Evaluations

Resolution of: 2 February 2023/ 21 September 2023/ 19 September 2024 valid until: unlimited
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Requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient valoctocogen roxaparvovec:

Therapeutic indication (according to the marketing authorisation of 24 August 2022):

Roctavian is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Therapeutic indication for the requirement of routine data collection and evaluations (resolution of 2 February 2023):

Treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors.

1. Requirements for routine practice data collection and evaluations

With reference to the justification for the requirement of routine practice data collection for the active ingredient valoctocogen roxaparvovec for the purpose of the benefit assessment, which forms the basis of the procedure-initiating resolution on the requirement of routine practice data collection of 3 February 2022, the following requirements arise:

1.1 Question according to PICO scheme

Population	Adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors
Intervention	▪ Valoctocogen roxaparvovec[a] The marketing authorisation and the dosage information in the product information of valoctocogen roxaparvovec must be taken into account.
Comparator	▪ Therapy according to doctor's instructions, taking into account recombinant or human plasma-derived blood coagulation factor VIII preparations and emicizumab[a]

	The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.

Outcome	Mortality
	▪ Deaths
	
	Morbidity
	▪ Pain measured with a validated instrument
	▪ Joint function measured with a validated instrument
	▪ Haemorrhage
	  ○ Major bleeding
	  ○ Life-threatening bleeding
	  ○ Joint bleeding
	  ○ Treated bleeding
	
	Health-related quality of life
	
	Side effects
	▪ Serious adverse events (operationalised as events leading to hospitalisation or death; overall rate)
	▪ Specific adverse events (with indication of the respective severity)
	  ○ Formation of factor VIII inhibitors
	  ○ Thromboembolic events
	  ○ Symptomatic liver damage
	  ○ Malignant neoplasms

Supplementary information on the question	Supplementary information on: ▪ Number of factor concentrates consumed as well as emicizumab, separated by on demand and prophylactic treatment ▪ Time of resumption of prophylactic treatment
[a] It is assumed that the patients in the therapeutic indication of valoctocogen roxaparvovec are eligible for prophylaxis (not for a treatment on demand). A treatment on demand alone is not considered an adequate comparator therapy. A treatment on demand must be possible in all study arms.	

1.2 Type and methods of data collection

Taking into account the question of the routine practice data collection and the methodological limitations of non-randomised comparisons, the following requirements are

placed on the study design and the data source for the present routine practice data collection.

1.2.1 Requirements for the study design

- Non-randomised, prospective comparison of valoctocogen roxaparvovec with the listed comparator preferably as a comparative registry study, if a comparative registry study is not feasible, as a comparative study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection).

1.2.2 Data source requirement

- Use of registries or a data platform to be set up specifically for the present routine practice data collection as a data source, which meet the requirements of routine practice data collection and fulfil at least the following quality criteria[1]:
  - Detailed registry description or description of the data platform (protocol)
  - Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders
  - Use of standard classifications and terminologies
  - Use of validated standard data collection tools (questionnaire, scales, tests)
  - Training courses on data collection and recording
  - Implementation of a consensus disease-specific core data set
  - Use of exact dates for the patient, the disease, important examinations and treatments/ interventions
  - Clearly defined inclusion and exclusion criteria for patients
  - Strategies to avoid selection bias in patient inclusion to achieve representativeness
  - Specifications to ensure completeness of data per data collection time point and completeness of data collection time points
  - Source data verification for 100% of patients per data collection site for the primary endpoint and for at least 10% of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection
  - When using a registry: Ensuring scientific independence and transparency
- Use of a registry or a data platform to be set up specifically for the present routine practice data collection, in which treatment of haemophilia A is carried out in accordance with German daily care or is sufficiently similar to care in Germany

[1] IQWiG Rapid Report A22-20: Concept for routine practice data collection – valoctocogen roxaparvovec.

1.2.3 Primary data source and integration of further data sources

For the study design in the form of a comparator registry study, the following specifications must be taken into account:

- Use of the German Haemophilia Registry (DHR) as primary registry, provided that the quality criteria mentioned in section 1.2.2 are fulfilled
- It is also possible to integrate other registries, taking into account all the data source requirements mentioned in section 1.2.2.

1.3 Duration and scope of data collection

Taking into account that first indications suggest that factor VIII activity under gene therapy weakens after 1 to 2 years, the following observation period should be implemented during the routine practice data collection:

- Observation period of at least 3 years

As an approximation of the appropriate number of cases for the routine practice data collection, three possible scenarios based on the endpoints bleeding-free and annual bleeding rate (ABR) are assumed in the result of an orienting sample size estimate:

- Endpoint bleeding-free:
  - Assuming a distribution of 1:5 between intervention and comparator group, 87.5 % responders under the intervention and 35 % responders under the comparator therapy:
    - 516 patients (intervention group n = 86, comparator group n = 430)
  - Assuming a distribution of 1:5 between intervention and comparator group, 80.5 % responders under the intervention and 35 % responders under the comparator therapy:
    - 1,554 patients (intervention group n = 259, comparator group n = 1,295)
- Endpoint ABR:
  - Assumption of a distribution of 1:5 between intervention and comparator group, ABR = 0.85 under the intervention and ABR = 3 under the comparator therapy:[2]
    - 397 patients (intervention group n = 67, comparator group n = 330)

On the basis of this orienting sample size estimate on the basis of estimated or theoretically established effect assumptions, exemplary case numbers result in an order of magnitude at which it can be assumed that routine practice data collection for the present research

[2] using a negative binomial model and assuming a dispersion of 1.5.

question is feasible in principle. The final sample size planning is part of the study documents to be prepared (statistical analysis plan, study protocol; see section 1.5).

1.4 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of 3 interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3.
  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan. In the process, a check for discontinuation due to futility must also be carried out for each interim analysis.

  On the 1st interim analysis:

  Based on this interim analysis, a final sample size estimate will be made using the more precise effect assumptions rendered possible. If necessary, this can also be carried out at this time on the basis of benefit endpoints other than those mentioned in the present resolution and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's concept[3].

The interim analyses shall be prepared on the basis of module 4 of the dossier template, providing the full texts and study documents

- Final evaluations for the purpose of the renewed benefit assessment

  The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies.

The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA.

1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection and evaluations.

When preparing the study protocol and statistical analysis plan, the pharmaceutical company shall address the necessary adaptations to the identified indication-specific registry. With regard to the implementation of the collection of patient-reported endpoints on health-related quality of life, for the approval of the study documents, it must be confirmed:

- To what extent an adaptation of the identified indication registry to the present requirements regarding the recording of patient-reported health-related quality of life is possible and within what period of time this can be done.

[3] IQWiG Rapid Report A22-20: Concept for routine practice data collection – valoctocogen roxaparvovec.

With regard to the evaluation of the data, the following information in particular must be presented in advance in the study protocol and statistical analysis plan:

- Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation
- Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies to deal with missing data
- Information on dealing with implausible data and outliers
- Prespecification of a sensitivity analysis for the separate evaluation of the data on valoctocogen roxaparvovec versus the data on recombinant or human plasma-derived coagulation factor VIII preparations as well as the data on emicizumab
- Prespecification of a sensitivity analysis for the evaluation of the patient population with known AAV5 antibody status
- Information on other planned sensitivity analyses
- Information on the standardisation of the start of patient observation
- Information on the identification, as well as the adequate, pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers
- Information on interim analyses taking into account the requirements under section 1.4 and the specifications under section 2.3
- Information on discontinuation criteria due to futility

2. Specifications for reviewing whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

2.1 Submission of a study protocol as well as the statistical analysis plan for coordination with the G-BA

The final drafts for a study protocol and for a statistical analysis plan prepared by the pharmaceutical company are to be submitted to the G-BA for approval by 2 July 2023 at the latest.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

Before submitting the requested documents to the G-BA, the pharmaceutical company has the option to request a consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The subject of such consultation is, in particular, the drafts for a study protocol as well as for a statistical analysis plan. In order to enable the pharmaceutical company to

adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA by 3 March 2023 at the latest.

If the G-BA determines during the first submission of the study protocol and statistical analysis plan that the requirements of routine practice data collection and evaluations are inadequately implemented, the pharmaceutical company is given the opportunity to revise the study documents once. The G-BA shall adopt a declaratory resolution in this regard in the procedure for routine practice data collection and evaluations, which shall set out the necessary need for adaptation of the study documents. The deadline for submission of the revised statistical analysis plan and study protocol is 4 weeks, unless otherwise specified in the declaratory resolution.

The G-BA may come to the conclusion that the routine practice data collection can be carried out on the basis of the submitted study protocol and statistical analysis plan under the condition that further adaptations to the study documents deemed mandatory for the implementation of the requirements from this resolution must be made. In this case, the final versions of the statistical analysis plan and the study protocol must be submitted to the G-BA for final review, usually 4 weeks after the resolution has been adopted.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

6 months, 18 months, 36 months and 54 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, the pharmaceutical company shall provide the G-BA in particular with the information on

- the number and the respective medicinal treatment of the patients included so far,
- patient-related observation periods, and
- any deviations regarding the expected number of recruits.

2.3 Submission of interim analyses

At the following time points after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, interim analyses shall be carried out and corresponding evaluations shall be submitted to the G-BA, taking into account the requirements specified in section 1.4:

- 18 months after the start of routine practice data collection
- 36 months after the start of routine practice data collection
- 54 months after the start of routine practice data collection

The G-BA carries out a review of the interim analyses with the involvement of the IQWiG.

3. Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations of data collected as part of the routine practice data collection must be submitted by 2 November 2029 at the latest.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5, Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5, Section 58 of the Rules of Procedure of the G-BA.