Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Exagamglogene autotemcel (sickle cell disease);
requirement of routine practice data collection and evaluations

of 21 December 2023

At its session on 21 December 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Exagamglogene autotemcel as follows:

Exagamglogene autotemcel

Resolution of: 21 December 2023
Entry into force on: 15 January 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient exagamglogene autotemcel:

Therapeutic indication (according to ongoing marketing authorisation procedure):

Exagamglogene autotemcel is indicated for the treatment of severe sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the genotype ßS/ßS, ßS/ß0 or ßS/ß+, for whom haematopoietic stem cell transplantation is an option and for whom no HLA-compatible, related haematopoietic stem cell donor is available.

Therapeutic indication for the requirement of routine practice data collection and evaluations (resolution of 21 December 2023):

See therapeutic indication according to ongoing marketing authorisation procedure

1. Requirements for routine practice data collection and evaluations

With reference to the justification for the necessity of routine practice data collection for the active ingredient exagamglogene autotemcel for the purpose of the benefit assessment, which forms the basis of the procedure-initiating resolution on the requirement of a routine practice data collection of 1 June 2023, the following requirements arise:

1.1 Research question according to PICO scheme

Population	Patients 12 years of age and older with severe sickle cell disease with recurrent vaso-occlusive crises who have the genotype ßS/ßS, ßS/ß0 or ßS/ß+, for whom haematopoietic stem cell transplantation is an option and no HLA-compatible, related haematopoietic stem cell donor is available.
Intervention	▪ Exagamglogene autotemcel[a] The marketing authorisation and the dosage information in the product information of exagamglogene autotemcel must be taken into account.
Comparator	A patient-individual therapy under selection of[a]: ▪ hydroxycarbamide ▪ red blood cell transfusions

	▪ voxelotor ▪ High-dose therapy with allogeneic stem cell transplantation under consideration of: ▪ the nature and severity of the symptoms, ▪ the age, ▪ the availability of an HLA-compatible unrelated donor for an allogeneic stem cell transplantation, ▪ the risk of cerebrovascular events.

Outcome	Mortality
	▪ Deaths
	
	Morbidity
	▪ Pain (chronic and acute), measured with a validated instrument
	▪ Vaso-occlusive crises[b]
	  ▪ Priapism
	  ▪ Splenic sequestration
	  ▪ Acute chest syndrome
	  ▪ Pain crises
	▪ Chronic organ damage (e.g. renal failure, cerebrovascular complications)
	
	Health-related quality of life, measured with a validated instrument
	
	Side effects
	▪ Serious adverse events (SAEs), operationalised as adverse events which lead to hospitalisation or prolong an existing hospitalisation, or lead to death; overall rate
	▪ Specific adverse events (with information on the respective severity)

[a.] The treatment of concomitant symptoms or complications of sickle cell disease with e.g. analgesics, chelating agents for iron overload, antithrombotic therapy for vascular occlusions, prevention of infection should be documented accordingly in both study arms. [b.] For the assessment of vaso-occlusive crises (e.g. pain crises, acute chest syndrome, priapism, splenic sequestration), it must be ensured via operationalisation that vaso-occlusive crises are reliably collected.	

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 exagamglogene autotemcel with the listed comparator preferably as a comparator registry study or, if a comparative registry study is not feasible, as a comparator study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection).
- If necessary, endpoint-specific inclusion of retrospective data. Compliance of data, which is not collected in parallel and is used within a data source, with the data quality requirements specified in section 1.2.2 must be checked.
- For the enrolment in the study and the start of observation of the patients, the time of the treatment decision should be chosen based on an intention-to-treat principle.

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

[1] IQWiG: Concept for routine practice data collection A23-49– exagamglogene autotemcel (sickle cell disease).

- Use of a registry or a data platform to be set up specifically for the present routine practice data collection, in which treatment of sickle cell disease is carried out in accordance with German daily care or is sufficiently similar to care in Germany

1.2.3 Primary data source and integration of further data sources

- GPOH registry sickle cell disease, provided that the quality criteria specified in section 1.2.2 are met
- 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 the fact that it is currently not possible to estimate how long the therapeutic effect with regard to the prevention of vaso-occlusive crises will last after the use of exagamglogene autotemcel, the following duration of observation should be implemented during routine practice data collection:

- At least 3 years follow-up time

As an approximation of the appropriate sample size for the routine practice data collection, possible scenarios based on the endpoint of avoidance of vaso-occlusive crises[2] are assumed in the result of an indicative sample size estimate:

- Assuming a distribution of 1:1 between intervention and comparator groups, response rate = 93% under the intervention and response rate = 25% under the comparator therapy:
  - 86 patients
- Assuming a distribution of 1:2 between intervention and comparator groups, response rate = 93% under the intervention and response rate = 25% under the comparator therapy:
  - 75 patients (intervention group n = 25, comparator group n = 50)

Regardless of the result of the indicative sample size estimate, a sample size of at least 100 patients is required to enable adequate control of confounders for the routine practice data collection.

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 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) and can, if necessary,

[2] IQWiG: Concept for routine practice data collection A23-49– exagamglogene autotemcel (sickle cell disease). Section 5.5.2, Figure 1 and Annex D

also be carried out on the basis of endpoints other than those listed in the present resolution (e.g. reduction of vaso-occlusive crises) and taking into account a shifted hypothesis boundary based on the procedure in the IQWiG concept.

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 2 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 drawing up the study protocol and statistical analysis plan, the pharmaceutical company must deal with the necessary adjustments to the implementation of the collection of patient-reported outcomes (PROs) on symptomatology and health-related quality of life. With regard to the implementation of the collection of PROs, it must be shown for the approval of the study documents:

- whether an implementation of the collection of PROs is possible and within which period of time this can be realised (e.g. adjustment of the registry, required effort for

a methodologically appropriate collection of PROs), as well as possible effects of the necessary time period for implementation on the recruitment options for prospective data collection

The G-BA reserves the right to review whether, after submission of the study protocol and the statistical analysis plan, the requirement to assess health-related quality of life and the patient-reported assessment of pain is waived within the framework of a weighing decision in the specific case at hand, insofar as the effort for the implementation of the collection would be disproportionate.

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
- Information on planned sensitivity analyses
- Information on the start of observation of the patients
- 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
- Information on planned measures to increase the percentage of adults in the routine practice data collection

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 at the latest 5 months after adoption of the present resolution.

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 at the latest 4 weeks after adoption of the present resolution.

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

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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

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 at the latest 6 years after the adoption of the present resolution.

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.

II. The resolution shall enter into force on the date on which Exagamglogene autotemcel is first placed on the market.

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

Berlin, 21 December 2023

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

Prof. Hecken