Talquetamab (multiple myeloma, at least 3 prior therapies)
Requirement of Routine Practice Data Collection and Evaluations

Resolution of: 18 July 2024
Entry into force on: 18 July 2024
Federal Gazette, BAnz AT 27 09 2024 B4

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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 talquetamab:

Therapeutic indication (according to the marketing authorisation of 21 August 2023):

Talvey is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Therapeutic indication for the requirement of routine data collection and evaluations (resolution of 18 July 2024):

see therapeutic indication in accordance with the marketing authorisation

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 talquetamab 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 19 October 2023, the following requirements arise:

1.1 Question according to PICO scheme

Population	Adults with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Intervention	▪ Talquetamab The marketing authorisation and the dosage information in the product information of Talvey must be taken into account.

Comparator	A patient-individual therapy under selection of: - carfilzomib in combination with lenalidomide and dexamethasone - elotuzumab in combination with lenalidomide and dexamethasone - elotuzumab in combination with pomalidomide and dexamethasone - daratumumab in combination with bortezomib and dexamethasone - daratumumab in combination with lenalidomide and dexamethasone - daratumumab in combination with carfilzomib and dexamethasone - daratumumab in combination with pomalidomide and dexamethasone (only for subjects who are refractory to lenalidomide) - isatuximab in combination with carfilzomib and dexamethasone - isatuximab in combination with pomalidomide and dexamethasone - pomalidomide in combination with bortezomib and dexamethasone (only for subjects who are refractory to an anti-CD38 antibody and lenalidomide) - ixazomib in combination with lenalidomide and dexamethasone (only for subjects who are refractory to bortezomib, carfilzomib and an anti-CD38 antibody) - carfilzomib in combination with dexamethasone - panobinostat in combination with bortezomib and dexamethasone (only for subjects with at least four prior therapies) - pomalidomide in combination with dexamethasone (only for at least double-refractory subjects with at least four prior therapies who are ineligible for triplet therapy) - lenalidomide in combination with dexamethasone (only for at least double-refractory subjects with at least four prior therapies who are ineligible for triplet therapy) - bortezomib in combination with pegylated liposomal doxorubicin (only for at least double-refractory subjects with at least four prior therapies who are ineligible for triplet therapy) - bortezomib in combination with dexamethasone (only for at least double-refractory subjects with at least four prior therapies who are ineligible for triplet therapy)

	- daratumumab monotherapy (only for at least triple refractory subjects with at least four prior therapies who are ineligible for triplet or doublet therapy) - cyclophosphamide as monotherapy or in combination with dexamethasone (only for at least triple refractory subjects with at least four prior therapies who are ineligible for triplet or doublet therapy) - melphalan as monotherapy or in combination with prednisolone or prednisone (only for at least triple refractory subjects with at least four prior therapies who are ineligible for triplet or doublet therapy) - ciltacabtagene autoleucel (only for subjects who are refractory to lenalidomide) - idecabtagene vicleucel - teclistamab monotherapy - elranatamab monotherapy taking into account the general condition, the active ingredients and combinations of active ingredients used in the prior therapies and the type and duration of the response to the respective prior therapies The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Outcome	Mortality ▪ Deaths Morbidity ▪ Patient-reported symptomatology, measured with a validated instrument 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 ▪ Discontinuation due to adverse events (overall rate)

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 talquetamab 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).
- 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 the 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

[1] IQWiG A23-100: AbD concept – Talquetamab (multiple myeloma), version 1.1

- 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 multiple myeloma 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

- MYRIAM registry, 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

Considering the assumption that a clear effect on overall survival can be recognised after 24 months, the following duration of observation should be implemented during routine practice data collection:

- 24 months

As an approximation of the appropriate sample size for routine practice data collection, the following sample sizes are assumed in the result of an orienting sample size estimate, based on the endpoint of overall survival:

- Assumption of a 1:1 distribution between intervention and comparator groups, estimated event percentage = 35% under the intervention and estimated event percentage = 70% under the comparator therapy; in each case at month 24, hazard ratio = 0.36
  - 536 patients
- Assumption of a 1:1 distribution between intervention and comparator groups, estimated event percentage = 45% under the intervention and estimated event percentage = 80% under the comparator therapy; in each case at month 24, hazard ratio = 0.37
  - 570 patients

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). If a different recruitment ratio between the intervention and comparator arms is to be assumed against the background of the specific comparator, the pharmaceutical company can also assume a different distribution between the intervention and control arms for the calculation of the sample size (e.g. 1:2).

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 two 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[1].

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.

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 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 subgroup analyses for patients with three prior therapies and with at least four prior therapies

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 18 December 2024 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 15 August 2024 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.

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

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 30 September 2030 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.