Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on the Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Talquetamab (relapsed and refractory multiple myeloma, at least 3 prior therapies); requirement of routine practice data collection and evaluations

of 18 July 2024

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No. 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

2. Key points of the resolution

The active ingredient talquetamab received a conditional marketing authorisation for placing on the market (Article 14-a of Regulation (EC) No. 726/2004, as last amended by Regulation (EU) 2019/5) for the treatment of relapsed and refractory multiple myeloma after at least 3 prior therapies from the European Commission (EC) on 21 August 2023. The first listing in the directory services in accordance with Section 131, paragraph 4 SGB V, took place on 15 September 2023.

In addition, the active ingredient talquetamab was approved as a medicinal product for the treatment of rare diseases (orphan drug) under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

On the basis of the ongoing or completed studies on talquetamab considered for the marketing authorisation, the G-BA identified gaps in the evidence, particularly for the following aspects relevant to the early benefit assessment, which justify the requirement of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGBV for the active ingredient talquetamab:

- Data to assess the long-term (additional) benefit and harm of treatment with talquetamab for the approved patient population;
- comparator data of treatment with talquetamab versus existing therapeutic alternatives for the approved patient population

Various ongoing studies were identified during the study research. However, only single-arm studies are ongoing for this assessment relevant patient population and intervention. The

identified comparator studies each investigate a combination therapy of talquetamab with various active ingredients already approved for multiple myeloma and therefore do not suggest an improvement in the body of evidence for the present patient population and intervention (talquetamab as monotherapy). The information provided by the pharmaceutical company on planned studies also does not indicate that comparative evidence on monotherapy with talquetamab compared to existing therapeutic alternatives is to be expected.

Therefore, there are no direct comparator data available from the label-enabling studies compared to existing therapeutic alternatives for the treatment of adults with relapsed and refractory multiple myeloma and at least three prior therapies. Direct comparator data on monotherapy with talquetamab versus existing therapeutic alternatives for the treatment of adults with multiple myeloma and at least three prior therapies is also not expected from the ongoing and planned studies. Based on the current study planning, no improvement in the body of evidence can therefore be expected.

Taking into account the mentioned gaps in the evidence, the research question of the present routine practice data collection comprises the assessment of the benefit and harm profile of talquetamab in comparison with existing therapeutic alternatives as well as the assessment of the sustainability of the therapeutic success for 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.

By resolution of 19 October 2023, the G-BA initiates a procedure for the requirement of a routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient talquetamab.

A concept was drawn up in preparation for the resolution on the requirement of routine data collection and evaluations. The concept contains in particular requirements for:

1. the type, duration and scope of data collection,
2. the research question (PICO framework: patient/population, intervention, comparison, outcomes) that is to be the subject of the data collection and evaluations, including the patient-relevant endpoints to be recorded,
3. the data collection methods,
4. the evaluations by the pharmaceutical company according to Section 50, paragraphs 2 of the Rules of Procedure of the G-BA.

The G-BA decides whether to prepare the concept itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG) to do so. In the present case, the G-BA commissioned IQWiG to prepare the concept. The expert bodies according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V made a written submission in drawing up the concept. The submission took place in such a way that the expert bodies were given the opportunity in writing to comment on the requirements of routine practice data collection and evaluations

in accordance with the concept that had been drawn up. In addition, expert consultation was held.

In preparing the concept, ongoing and planned data collections were taken into account, especially those resulting from conditions or other ancillary provisions imposed by the marketing authorisation or licensing authorities. A review of the ongoing or planned studies on talquetamab commissioned by the regulatory authority has shown that the submission of further data from two other single-arm studies (PMR 4473-2 and NCT06066346) was commissioned by the regulatory authority, in addition to the pivotal, single-arm MonumenTAL-1 study. As the studies are not comparative in design, they are unsuitable for the necessary comparison with existing therapeutic alternatives as part of the benefit assessment.

In addition, the U.S. Food and Drug Administration (FDA) has commissioned a randomised controlled trial (RCT, PMR 4473-1 / MonumenTAL-3) to investigate talquetamab-based combination therapies in comparison with standard therapies. As this RCT does not include a comparison with talquetamab monotherapy in accordance with the marketing authorisation, no comparator data for the present intervention under evaluation are to be expected.

Based on the above-mentioned question, the G-BA, on the basis of IQWiG's concept and the submission of the expert bodies in drawing up the concept, decided by the present resolution on the requirements of routine practice data collection and evaluations, as well as on the specifications for the review of the obligation to perform and on the deadline for the submission of evaluations.

2.1 Requirements for routine practice data collection and evaluations

2.1.1 Question according to PICO scheme

Patient population

The target population for the active ingredient talquetamab comprises 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.

The therapy recommendations of the S3 guideline differentiate between the treatment setting of the first to third recurrence and from the fourth recurrence onwards. This is due to the very heterogeneous patient population in the advanced lines of therapy, for whom the substances used in the earlier lines of therapy are increasingly no longer an option and who therefore have a poorer prognosis.

Accordingly, in the present therapeutic indication of relapsed/refractory multiple myeloma, it is differentiated between two distinct patient populations, depending on the number of prior therapies (three prior therapies vs at least four prior therapies). However, in the present specific case of the requirement of routine practice data collection and evaluations, splitting

the research question depending on the number of prior therapies is considered inexpedient. On the one hand, this is due to the routine practice nature of the data collection, which means that data must be collected on all comparators of patient-individual therapy specified by the G-BA depending on their use in the healthcare context. On the other, there is a relevant overlap in the recommended therapy options for patients up to the third relapse compared to patients from the fourth relapse onwards. Therefore, the pharmaceutical company should collect and evaluate comparator data for the total population in accordance with the marketing authorisation for the present requirement of routine practice data collection and evaluations.

In order to be able to investigate possible effect modifications between patients with three prior therapies and at least four prior therapies, subgroup analyses should be carried out depending on the number of prior therapies (see Section 1.5 in the resolution).

Intervention

In accordance with the present requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V, the intervention includes the active ingredient talquetamab. The marketing authorisation and the dosage information in the product information of talquetamab (Talvey) must be taken into account.

Comparator therapy

The following criteria were applied:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

on 1. In addition to talquetamab, the following active ingredients are approved in the present therapeutic indication:

bortezomib, carfilzomib, carmustine, ciltacabtagene autoleucel, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, elranatamab, idecabtagene vicleucel, isatuximab, ixazomib, lenalidomide, melphalan, melphalan flufenamide, panobinostat, pomalidomide, prednisolone, prednisone, selinexor, teclistamab and vincristine.

on 2. A non-medicinal treatment is unsuitable as a comparator therapy in this therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Elranatamab – resolution of 4 July 2024
- Talquetamab – resolution of 7 March 2024
- Teclistamab – resolution of 15 February 2024
- Ciltacabtagene autoleucel – resolution of 17 August 2023
- Selinexor – resolutions of 16 March 2023
- Melphalan flufenamide – resolution of 16 March 2023
- Idecabtagene vicleucel – resolution of 16 June 2022
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolutions of 15 February 2018, 3 February 2022 and 15 September 2022
- Elotuzumab – resolutions of 1 December 2016 and 16 December 2021
- Isatuximab – resolutions of 4 November 2021
- Ixazomib – resolution of 21 April 2022
- Panobinostat – resolution of 17 March 2016
- Pomalidomide – resolutions of 17 March 2016 and 5 December 2019

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Among the approved active ingredients listed under 1), only certain active ingredients named below will be included in the comparator, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The evidence is limited for patients who have received three or at least four lines of prior therapy. A uniform treatment standard cannot be derived from the available evidence. National and international guidelines generally refer to patient-individual therapy which is influenced by various factors. According to the S3 guideline, the active ingredients and combinations of active ingredients used in prior therapies as well as

the type and duration of the response to the respective prior therapies and the general condition of the patients play a key role in the choice of therapy.

One criterion for patient-individual therapy is the duration of the response to the prior therapy. If the disease progresses under the respective prior therapy or if the duration of response after completion of the respective prior therapy is less than 12 months, it will not be considered again in the further course of treatment in accordance with the generally recognised state of medical knowledge. Accordingly, this therapy using the specific active ingredients or combinations of active ingredients in the further course of treatment may again be a suitable treatment option for relapsed patients in whom a response in the form of a complete remission (CR), a very good partial response (VGPR) or a partial response (PR) of more than 12 months after the end of therapy was achieved with a specific previous therapy.

For patients in the present therapeutic indication, it is assumed that they will generally continue to receive antineoplastic treatment. Best supportive care is therefore not considered a comparator therapy.

With regard to the relapsed/refractory disease situation after three or after at least four prior therapies, the S3 guideline initially states that a triplet therapy with two new substances (monoclonal antibody, immunomodulatory agent, proteasome inhibitor) and a steroid should be used for patients. With reference to the respective approved therapeutic indications of the active ingredients, the guideline on the therapy of the first to third relapse also states that all active product classes can generally be used and combined in an individual sequence with regard to the respective combination therapy. This is also done against the background that the therapeutic benefit of triplet therapies over doublet therapies is offset by increased therapy toxicity, meaning that they are not suitable for all patients.

Overall, all approved therapies and preferably all approved triplet therapies with two new substances and a steroid are therefore initially considered. With regard to the individual therapy options, the following limitations apply to the respective active ingredients and combinations of active ingredients in the present therapeutic indication:

The therapy options pomalidomide in combination with bortezomib and dexamethasone (PVd) and ixazomib in combination with lenalidomide and dexamethasone (IRd) are restricted to patients with a specific refractoriness to the active ingredients or combinations of active ingredients used in the previous treatments. The suitability of patients for the use of PVd and IRd as part of patient-individual therapy must be demonstrated based on the type and duration of response to the respective prior therapies in accordance with the specified limitations.

In addition to the triplet therapies, the dual combination of carfilzomib and dexamethasone is also determined as the comparator as part of patient-individual therapy. By G-BA resolution of 15 February 2018, a hint for a considerable additional

benefit of this combination therapy compared to bortezomib in combination with dexamethasone was identified in the benefit assessment for adults after at least one prior therapy.

In addition, the S3 guideline also refers to doublet therapies, classic cytostatic agents, bispecific antibodies and CAR-T cell therapies.

Dual combinations can also be considered for at least double-refractory subjects with at least four prior therapies who are ineligible for triplet therapy.

For at least triple refractory subjects with at least four prior therapies who are ineligible for triplet or doublet therapy, daratumumab, cyclophosphamide and melphalan, each as monotherapy, as well as cyclophosphamide in combination with dexamethasone and melphalan in combination with prednisone or prednisolone, are also suitable comparators as part of patient-individual therapy. Ineligibility for triplet or doublet therapy should be justified on the basis of the patients' refractoriness and comorbidity and taking into account the toxicity of the respective therapy.

The clinical experts emphasised the significance of newer therapy options for a therapy directed against the B-cell maturation antigen (BCMA) in medical treatment practice as part of the expert consultation as well as in the submission procedure. These include the CAR-T cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel and the bispecific antibodies teclistamab and elranatamab.

The CAR-T cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel are approved for the treatment of patients who have undergone at least three prior therapies. For idecabtagene vicleucel (resolution of 16 June 2022) as well as ciltacabtagene autoleucel (resolution of 17 August 2023), a hint for a non-quantifiable additional benefit was identified since the scientific data basis did not allow quantification. This was done against the background that no statement could be made about the extent of the additional benefit on the basis of the indirect comparisons presented for both therapy options.

The bispecific antibodies teclistamab and elranatamab are both therapy options for the treatment of subjects with at least three prior therapies. By resolution of 15 February 2024 or 4 July 2024, it was determined that an additional benefit of teclistamab or elranatamab is not proven, as no data were available to enable the assessment of an additional benefit.

In addition, selinexor and melphalan flufenamide have been approved as additional therapy options, with the potential significance of these therapy options in the present therapeutic indication being secondary to the treatment options directed against BCMA.

The active ingredient selinexor is approved for the treatment setting after at least one prior therapy in combination with bortezomib and dexamethasone, as well as in combination with dexamethasone after at least four prior therapies. For both

combination therapies, it was determined by resolutions of 16 March 2023 that an additional benefit compared to the appropriate comparator therapy is not proven.

Melphalan flufenamide is a therapy option for the treatment of subjects with at least three prior therapies. For melphalan flufenamide, the G-BA determined by resolution of 16 March 2023 that an additional benefit is not proven, as no suitable data were available to enable an assessment of the additional benefit.

The treatment options and their significance in the present therapeutic indication are subject to dynamic developments, in particular due to the establishment of numerous new treatment options, including in the previous lines of therapy, which affects the significance of treatment options in the present treatment setting. In this regard, new active ingredients or combinations of active ingredients are already being used in earlier lines of therapy, which has an impact on the significance of these active ingredients or combinations of active ingredients in later lines of therapy, taking into account any refractoriness that may occur. According to statements made by the clinical experts in the expert consultation, it is therefore to be assumed that the use of the newer therapy options that have already been approved will increase in the healthcare context. According to the clinical experts, bispecific antibodies and CAR-T cell therapies directed against BCMA in particular are considered a relevant therapy option after at least three prior therapies. In addition, the potential significance of newer treatment options, particularly for triple refractory patients for whom the use of a combination therapy consisting of two new substances (monoclonal antibody, immunomodulator, proteasome inhibitor) and a steroid is no longer possible, was pointed out.

For the present requirement of routine practice data collection and evaluations, the following therapy options are therefore additionally defined as comparators for the routine practice study:

- CAR-T cell therapies (idecabtagene vicleucel, ciltacabtagene autoleucel)
- Bispecific antibodies (teclistamab, elranatamab)

The G-BA determines the mentioned therapy options as a comparator for the routine practice study taking into account the required duration of the routine practice data collection, during which a new situation may arise with regard to the generally accepted state of medical knowledge in the therapeutic indication in question. In principle, this is to be considered separately from the determination of the appropriate comparator therapy, which only becomes legally binding with the resolution on the benefit assessment according to Section 35a, paragraph 3 SGB V.

Overall, the comparator is thus determined to be a patient-individual therapy by selecting the active ingredients and combinations of active ingredients mentioned in the resolution and 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 as the comparator therapy.

Outcome

Comparator data on the following endpoint categories shall be collected for the patient population required here for routine practice data collection in accordance with Section 35a, paragraph 3b, sentence 1 SGB V: Mortality, morbidity, health-related quality of life and side effects.

In the present therapeutic indication, overall survival, in particular, is of high relevance for patients. Against this background, the survey of overall survival in the registry study is of great importance for the comparison of talquetamab versus patient-individual therapy in the comparator arm.

In addition, patient-reported endpoints on morbidity as well as health-related quality of life are to be collected with specifically validated instruments at uniform data collection time points. The questionnaire of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30) in conjunction with the myeloma-specific additional module Multiple Myeloma 20 (-MY20) can preferably be used for this purpose, as well as the Brief Pain Inventory - short form (BPI-SF) for morbidity. The mentioned instruments have already been used in the MYRIAM registry for data collection.

The selection of appropriate instruments to collect patient-reported endpoints on symptomatology and health-related quality of life in the talquetamab routine practice data collection should be outlined during the development of the study protocol and statistical analysis plan.

Skeletal-related events (e.g. pathological fractures, spinal cord compression, the need for radiotherapy / surgery of the bone) may be relevant symptoms of the present disease. The extent to which symptomatic skeletal-related events can be collected as an additional morbidity endpoint should be examined.

The overall rates of serious adverse events (SAEs) should be mapped. In doing so, SAEs should be operationalised as adverse events (AEs) which lead to hospitalisation or prolong an existing hospitalisation, or lead to death.

Furthermore, the overall rate of therapy discontinuation due to adverse events should be collected. It should be noted here that the patient-individual therapy of the comparator also includes therapies which are administered in the form of a single infusion (CAR-T cell therapies) and cannot be discontinued. It should therefore be stated in the study documents that the significance of the endpoint "discontinuation due to AEs" should be discussed in relation to the percentage of CAR-T cell therapies in the comparator arm.

2.1.2 Type and methods of data collection

According to Section 35a, para. 3b SGB V, the Federal Joint Committee can demand indication-related data collection without randomisation for routine practice data collection.

For the present requirement of routine practice data collection, indication registries that meet the requirements for routine practice data collection and at least fulfil the quality criteria specified in the resolution shall be used as the data source. The minimum data quality requirements mentioned are based on the national and international quality criteria for registries mentioned in the IQWiG concept, whereby the focus was placed on the quality criteria for standardisation and validity of data collection, as well as for sample collection, which were considered particularly relevant for the present requirement.

In order to ensure the suitability of the data collected, the use of an indication registry is also required in which treatment of multiple myeloma is carried out in accordance with everyday German care or is sufficiently similar to care in Germany. The guarantee of care sufficiently similar to that in Germany, which is required when using (indication) registries, should make it possible to integrate data from other European countries without compromising data quality. If there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine practice data collection and evaluations.

Based on the available information, the MYRIAM registry of the International Organisation of Medical Oncology (iOMEDICO) may be suitable as a primary data source for a routine practice data collection, provided that the still existing limitations are eliminated. The adaptations required for the routine practice data collection refer in particular to the following aspects in accordance with the IQWiG concept[1]:

- Increase in the number of patients, in particular expansion of the data record for patients after at least three prior therapies
- Standardised survey of AEs at fixed survey time points
- Supplementing the measures to ensure the accuracy of the data (source data verification based on a sample of, e.g. 10% of the data records)

Provided that the quality criteria and requirements of routine practice data collection specified in this resolution can be implemented in the MYRIAM registry, this is to be used as the primary registry.

For the present requirement of routine practice data collection, it should be examined to what extent the data from other registries on talquetamab are suitable as a supplement to the MYRIAM registry (e.g. GMMG follow-up registry of the German-Speaking Multiple Myeloma Multicentre Group and OSHO Myeloma Registry of the East German Haematology and Oncology Study Group). Duplicate survey of patients in different registers should be avoided here.

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

A comparison of two therapies without randomisation poses in principle a potentially high risk of bias. Therefore, additional factors with a potentially high risk of bias such as the use of different data sources for the comparator group or data of different quality within one data source should be avoided.

For treatment with CAR T-cell therapies, T-cells are removed from the patients by means of leukapheresis and prepared individually for each patient. The production of the medicinal product can therefore take several weeks and the treatment is not available to patients immediately after indication. This delay in the start of therapy does not exist for talquetamab. Therefore, the time of treatment decision should be chosen as the time of enrolment in the sense of an intention-to-treat principle.

In summary, the study design required for talquetamab is a non-randomised, prospective comparison with the patient-individual therapy determined as comparator, which can be supplemented by retrospective data on an endpoint-specific basis if necessary, provided these meet the requirements. The routine practice data collection should preferably be carried out as a comparative registry study in the MYRIAM registry.

If a comparator registry study is therefore infeasible for the present requirement of routine practice data collection and evaluations due to the required adjustments to the MYRIAM registry, a comparator study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection) is required as an alternative. All requirements described in the resolution for the routine practice data collection and evaluations must be taken into account in the same way when using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection), unless specified otherwise.

2.1.3 Duration and scope of data collection

The duration and scope of routine practice data collection result from the estimated suitable patient-related duration of observation and the estimated required number of patients (sample size).

The aim of the routine practice data collection is to determine the long-term benefits and harms of treatment with talquetamab compared to the comparator therapy. A key therapeutic goal in multiple myeloma is to increase overall survival. It can be assumed that a clear effect on overall survival can be recognised after a duration of observation of 24 months. In order to observe possible effects on overall survival, patients should therefore be followed up for at least 24 months during the routine practice data collection.

As an approximation of the appropriate sample size for the routine practice data collection, an orienting sample size estimate was performed based on the endpoint of overall survival.

The orienting sample size estimate is subject to a high degree of uncertainty as it is based on a comparator group that only partially corresponds to the required comparator. Furthermore,

it cannot be estimated whether the patients in the LocoMMotion[2], MaMMoth[3] and MoMMent[4] studies considered for the sample size estimate were treated with the therapy options of the comparator in accordance with the generally recognised state of medical knowledge (in particular with regard to any existing refractoriness). However, it can be assumed that the pharmaceutical company has more precise information that can address these uncertainties as the studies mentioned are those conducted by the pharmaceutical company concerned. This information should be taken into account in the sample size estimate when preparing the study documents.

Overall, the G-BA estimates the existing high uncertainties not to be so serious that it is not possible to provide an orienting sample size estimate. On the basis of this estimate, the G-BA continues to assume that routine practice data collection is feasible in principle for the present research question.

In this case, the estimated sample size was not multiplied by a variance inflation factor (VIF) in accordance with the pharmaceutical company's approach in the submission procedure. It is unclear beforehand what value the c-statistic will assume and how high the overlap of patients in the propensity score method with weighting will be as a result. The uncertainty of the necessary assumptions is considered too high overall for them to be included a priori in the orienting sample size estimate.

Furthermore, taking into account the patient number available in the therapeutic indication and the numerous, including newer, therapy options covered by the comparator, it is considered feasible to achieve a sufficient sample size within a reasonable recruitment period despite the existing uncertainties.

In the submission procedure, it was pointed out that a recruitment ratio of 1:1 is considered infeasible due to the high number of components of the comparator's patient-individual therapy. 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).

2.1.4 Evaluations of the data collection for the purpose of the benefit assessment

The general requirements for the evaluation of comparator studies without randomisation must correspond to the planning of the evaluation of comparator studies with randomisation. The information given in the resolution must be taken into account when drawing up the study

[2] Mateos MV, Weisel K, De Stefano V et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 2022; 36(5): 1371-1376.

[3] Gandhi UH, Cornell RF, Lakshman A et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019; 33(9): 2266-2275.

[4] Einsele H, Moreau P, Bahlis N et al. Comparative Efficacy of Talquetamab vs. Current Treatments in the LocoMMotion and MoMMent Studies in Patients with Triple-Class-Exposed Relapsed/Refractory Multiple Myeloma. Adv Ther 2024; 41(4): 1576-1593.

protocol and statistical analysis plan prior to carrying out the routine practice data collection (see also section 2.1.5).

The evaluation of data from different data sources, i.e. different registries, should be done separately for each data source. Additional pooled analysis is possible after checking the suitability of data from different data sources. Information on the verification of suitability for pooled analysis should be set out accordingly in advance in the statistical analysis plan.

The pharmaceutical company shall perform the evaluations mentioned in the resolution (interim analyses and final evaluation) according to the specifications in the study protocol and the statistical analysis plan. The interim analyses shall be prepared on the basis of Module 4 of the dossier template with provision of the full texts and study documents, the final evaluations shall be prepared in a dossier in accordance with the provisions in Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA. The relevant times for conducting the interim analyses are the times specified in the resolution under section 2.3 and for submitting the final evaluations to the G-BA the time specified in the resolution under section 3.

The orienting sample size estimate is subject to uncertainties due to the small information base available and therefore represents a first hint of the required size of the study population. Against this background, the G-BA considers it expedient that a review is carried out by the pharmaceutical company during the course of the study, which may lead to an adjustment of the sample size. 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.

In addition to presenting the results of the entire patient population as the main analysis, subgroup analyses should be presented for patients with three prior therapies and with at least four prior therapies.

2.1.5 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. In this respect, the requirements for the information to be presented as described in the resolution shall be taken into account.

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

Taking into account the time frame required for drafting, the pharmaceutical company shall submit the final drafts of a study protocol and a statistical analysis plan to the G-BA for approval by 18 December 2024.

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.

In order to be able to clarify queries during the preparation of the final drafts for a study protocol as well as for a statistical analysis plan, the pharmaceutical company has the possibility - before submitting the requested documents to the G-BA - to request 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). 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.

According to Section 35a para. 3b, sentence 10 SGB V, the data obtained and the obligation to collect data must be reviewed by the G-BA at regular intervals, but at least every 18 months.

With regard to the information on the course of data collection (in particular information on the status of recruitment), the pharmaceutical company shall provide the G-BA with information on the number and the respective medicinal treatment of the patients included to date, on patient-related observation periods and on possible deviations with regard to the expected number of recruits at intervals of 18 months.

The subject of the continuous review of the data obtained is in particular whether the data collection is carried out or not, or can no longer be carried out.

The pharmaceutical company shall submit two interim analyses to the G-BA 18 and 36 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution. Within the framework of the first interim analysis, a review of the sample size estimate on the part of the pharmaceutical company is also to be carried out. The G-BA carries out a review of the interim analyses with the involvement of the IQWiG.

2.3 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 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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 of the Rules of Procedure of the G-BA and, accordingly, no bureaucratic costs.

4. Process sequence

In order to prepare a recommendation for a resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of AM-RL) according to Section 35a, paragraph 3b SGB V, the Subcommittee on Medicinal Products commissioned a working group (WG routine practice data collection (RPDC)) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions. In addition, the competent higher federal authority, the Paul Ehrlich Institute, was involved in the consultation to assess the requirement of routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V.

The recommended resolution on the initiation of a procedure for the requirement of a routine practice data collection was discussed on 10 October 2023 at the subcommittee session and the draft resolution was approved.

At its session on 19 October 2023, the plenum resolved to initiate a procedure for the requirement of a routine practice data collection.

In conjunction with the resolution of 19 October 2023 regarding the initiation of a procedure for the requirement of a routine practice data collection, the G-BA commissioned IQWiG to scientifically develop a concept for routine practice data collection and evaluations for the purpose of preparing a resolution.

Version 1.0 of IQWiG's concept was submitted to the G-BA on 27 March 2024. On 2 April 2024, the written submission of the expert bodies according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V was initiated. The deadline for making the written submission was 29 April 2024.

On 21 May 2024, the IQWiG submitted a new version of the concept on routine practice data collection to the G-BA. This version 1.1 dated 21 May 2024 replaces version 1.0 of the concept dated 27 March 2024. The assessment result was not affected by the changes in version 1.1 compared to version 1.0. In version 1.1, a reference to an indirect comparator study was corrected.

The expert consultation within the framework of the submission by the expert bodies took place on 27 May 2024.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 9 July 2024, and the draft resolution was approved.

At its session on 18 July 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	6 July 2023 3 August 2023 7 September 2023 5 October 2023	Consultation on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL), involvement of the higher federal authority
Subcommittee on Medicinal Products	10 October 2023	Concluding discussion of the draft resolution
Plenum	19 October 2023	Resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL)
WG RPDC	13 May 2024	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	27 May 2024	Implementation of the expert consultation
WG RPDC	6 June 2024 17 June 2024 4 July 2024	Consultation on IQWiG's concept and on the specifications for the review of the obligation to conduct and submit evaluations, evaluation of the submission procedure
Subcommittee on Medicinal Products	9 July 2024	Concluding discussion of the draft resolution
Plenum	18 July 2024	Resolution on the requirement of routine practice data collection (amendment of Annex XII of the AM-RL)

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Berlin, 18 July 2024

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

Prof. Hecken