Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee (G-BA) on the Finding in the Procedure of Routine Practice Data Collection and Evaluations according to Section 35a, paragraph 3b SGB V:
Talquetamab (multiple myeloma, at least 3 previous therapies) – submission of study protocol and statistical analysis plan

of 17 April 2025

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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.

According to Section 35a, paragraph 3b, sentence 10 SGB V in conjunction with Chapter 5 Section 60 Rules of Procedure of the G-BA (VerfO), the G-BA reviews the data obtained and the obligation to collect data at regular intervals, at least every eighteen months.

2. Key points of the resolution

At its session on 18 July 2024, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient talquetamab in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

By this resolution, the pharmaceutical company was instructed to prepare a study protocol and a statistical analysis plan (SAP) before carrying out the routine practice data collection and evaluations and to submit it to the G-BA by 18 December 2024 at the latest. The pharmaceutical company did not submit drafts of a study protocol and a statistical analysis plan to the G-BA.

To justify the non-submission of the study documents, the pharmaceutical company submitted explanations including a sample size estimate, taking into account the comparators ciltacabtagene autoleucel, idecabtagene vicleucel, teclistamab and elranatamab included in the patient-individual therapy.

The pharmaceutical company's presentation results in >500 different scenarios in which the care percentage of the above-mentioned comparators is between 10% and 40%. For the estimation of the duration and feasibility of the routine practice data collection, the pharmaceutical company exclusively refer to what they consider a "medium scenario", which assumes a sample size of 3,448 patients with an HR of 0.44. In this scenario, the pharmaceutical company arrives at a recruitment period of 10 years for the routine practice data collection via various steps.

After examining the new sample size scenarios resubmitted by the pharmaceutical company and further explanations, the G-BA continue to assume - on the basis of the indicative estimates of the sample size used in the resolution on requirements - that routine practice data collection is feasible in principle for the present research question. The sample sizes submitted by the pharmaceutical company cannot be conclusively assessed. In particular, it cannot be ruled out that lower sample sizes may also result, leading to significantly shorter

recruitment periods for the routine practice data collection. This is justified in particular by the following aspects:

The statements made by the pharmaceutical company completely ignore the uncertainty addressed by the G-BA in the resolution on requirements of 18 July 2024 as to whether the use of the therapy options of the comparator arm in the underlying LocoMMotion[1], MaMMoth[2] and MoMMent[3] studies was in accordance with the generally recognised state of medical knowledge (in particular with regard to any existing refractoriness). The studies mentioned are studies by the pharmaceutical company concerned, which is why it was assumed that the pharmaceutical company should have specific information on this aspect. There is no contextualisation of the uncertainties addressed in the resolution on requirements with regard to the new sample site estimates resubmitted by the pharmaceutical company or there is no justification of the extent to which specific data on the addressed uncertainties are available to the pharmaceutical company.

The pharmaceutical company does not justify why they limit their considerations on the recruitment period exclusively to one scenario. In particular, they give no reason why this scenario is more likely than any other of the >500 scenarios they list. However, for some of the scenarios identified by them, the sample sizes is much lower and, as a result, recruitment periods are significantly shorter. Furthermore, the underlying assumptions of the pharmaceutical company regarding the future care percentages of the four additionally named comparators are subject to uncertainties. It should also be taken into account here that the G-BA generally have the option of extending the duration of the routine practice data collection and thus, the recruitment period if, in the course of the submission of the status reports or interim analyses, a slower recruitment than initially assumed becomes apparent or the final sample size planning by the pharmaceutical company results in an increase in the required patient number.

Based on the scenarios listed by the pharmaceutical company, it is not evident with sufficient certainty that recruitment of the number of patients required to implement the routine practice data collection within a reasonable period of time is ruled out, taking into account the available number of approx. 1,210 - 1,310 patients in the therapeutic indication.

Therefore, taking into account the patient number available in the therapeutic indication and the numerous, including newer, therapy options covered by the comparator, the G-BA continue to consider achievement of a sufficient sample size within a reasonable recruitment period to be feasible despite the existing uncertainties.

The other aspects addressed by the pharmaceutical company with regard to a selection bias and the percentage of missing values also do not exclude the feasibility of routine practice data collection. Using the inclusion criteria of the routine practice data collection, it must be ensured that both talquetamab and all of the comparator options named by the G-BA are basically suitable for the patients participating in the data collection (positivity). In a non-randomised comparator study, differences in the baseline characteristics are also to be expected, including the type and number of previous therapies. As long as they are relevant confounders, these factors must be adjusted accordingly in the evaluation. The

1 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.

2 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.

3 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.

pharmaceutical company does not justify why the situation for the comparison of talquetamab with the comparator specified in the resolution on requirements of 18 July 2024 differs from other situations. Evaluation strategies for dealing with missing data can also be addressed in the statistical analysis plan.

Accordingly, the pharmaceutical company should have fulfilled their obligation to prepare a statistical analysis plan and study protocol prior to conducting the routine practice data collection. However, the present resolution states that the routine practice data collection will not be carried out as the pharmaceutical company did not fulfil this obligation.

This result shall be communicated to the National Association of Health Insurance Funds for the purpose of a decision pursuant to Section 130b, paragraph 3, sentence 9 SGB V.

3. Process sequence

According to the resolution of 18 July 2024 on the requirement of routine practice data collection and evaluations for the active ingredient talquetamab, the pharmaceutical company should have submitted the final drafts of a study protocol and a statistical analysis plan to the G-BA for approval by 18 December 2024.

The pharmaceutical company did not submit drafts of a study protocol and a statistical analysis plan to the G-BA.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At its session on 17 April 2025, the plenum decided that the routine practice data collection will not be carried out.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	6 February 2025 17 February 2025 3 April 2025	Advice on the review of the pharmaceutical company's obligation to submit the study protocol and SAP
Subcommittee on Medicinal Products	8 April 2025	Consultation on the outcome of the review of the pharmaceutical company's obligation to submit the study protocol and SAP
Plenum	17 April 2025	Resolution on the review of the pharmaceutical company’s obligation to submit the study protocol and SAP

Berlin, 17 April 2025

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

Prof. Hecken