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:
Brexucabtagene autoleucel (relapsed or refractory mantle cell lymphoma) – Review of study protocol and statistical analysis plan

of 18 June 2025

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.

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 their session on 21 July 2022, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient brexucabtagene autoleucel in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

In order to check whether the requirements of the G-BA for the routine practice data collection and evaluations of the data obtained have been implemented, the pharmaceutical company submitted the revised versions of the study protocol and the statistical analysis plan (SAP) to the G-BA in due time on 21 December 2022. By G-BA's declaratory resolution of 16 March 2023, the pharmaceutical company was notified of the adjustments to the study protocol (version 1.0, 21 December 2022) and the SAP (version 1.0, 21 December 2022) that were considered necessary.

The pharmaceutical company submitted the revised drafts for a study protocol and an SAP to the G-BA in due time by 13 April 2023. By declaratory resolution of 20 July 2023, the pharmaceutical company was notified of the adjustments to the study protocol (version 2.0, 13 April 2023) and the SAP (version 2.0, 13 April 2023) that were further considered necessary, and the start of the routine practice data collection was fixed on 21 August 2023.

The pharmaceutical company submitted the revised study protocol and the SAP to the G-BA for final review by the deadline of 17 August 2023. By declaratory resolution of 16 November 2023, the pharmaceutical company was notified of the adjustments to the study protocol (version 3.0, 16 August 2023) and the statistical analysis plan (SAP; version 3.0, 16 August 2023) that were further considered necessary.

The pharmaceutical company submitted the revised study protocol and the SAP to the G-BA by the deadline of 21 February 2025. The revised drafts for a study protocol and an SAP were reviewed by the G-BA along with the Institute for Quality and Efficiency in Health Care (IQWiG).

Based on this review, the G-BA came to the conclusion that the adjustments to the study protocol and the SAP that were further considered necessary in the declaratory resolution of 16 November 2023 and in the amendment resolution of 16 November 2023 were appropriately implemented in the revised version of the study protocol and the SAP submitted.

The submitted, revised versions of the study protocol (version 4.0 of 17 February 2025) and the SAP (version 4.0 of 17 February 2025) require further adaptation.

This need for adaptation results from changes made by the pharmaceutical company in the present 3rd version of the study documents that go beyond the need for changes set out in the declaratory resolutions, thus entailing consequential changes.

This declaratory resolution defines and justifies the adjustments to the study protocol (version 4.0, 17 February 2025) and the statistical analysis plan (SAP; version 4.0, 17 February 2025) that are considered necessary.

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

a) Data evaluation: Definition of the baseline value

In the 4th version of the study documents, the baseline value was defined as the last non-missing value before or up to the index date (if available). If this is not available, the last non-missing value up to the date of infusion of brexucabtagene autoleucel or the first administration of the comparator therapy is used. This definition is only partially appropriate. If the baseline value (the last non-missing value before or up to the index date) is not available, the first non-missing value after the index date must be assumed as the baseline value. It must be ensured that the baseline collection is prior to any treatment. Prior to infusion with brexucabtagene autoleucel, leukapheresis, if applicable bridge therapy and lymphodepletion take place, which is why it is not appropriate to collect the baseline value up to the date of infusion with brexucabtagene autoleucel.

In order to be able to take into account a possible time lag between baseline collection and the index date when interpreting the results, the distribution of the time deviations of the respective baseline collection from the index date should be presented transparently for each treatment group.

This procedure must be recorded in the study documents.

b) Data evaluation: Non-severe specific adverse events (AEs)

In the 4th version of the study documents, the collection of any specific AEs with indication of the respective severity grade was deleted, so that only specific AEs that lead to a significant impairment of the activity of daily living or AEs with CTCAE grade ≥ 3 are collected. This deletion is inappropriate. Specific AEs must be evaluated regardless of their severity grade and specific AEs that lead to a significant impairment of the activity of daily living or with CTCAE grade ≥ 3 must also be evaluated.

The deletion must be reversed in the study documents.

c) Data evaluation: Patient-reported outcomes, death as a clinically relevant deterioration

In the 4th version of the SAP, an addition was made to the definition of the time to clinically relevant deterioration (confirmed once). The event of death is rated as a clinically relevant deterioration. This addition is inappropriate in the context of the evaluation of patient-reported outcomes relating to symptomatology and health-related quality of life. Evaluations in which deaths are not rated as an event must be presented. In the context of the evaluation of patient-reported outcomes with regard to symptomatology and health-related quality of life, deaths can at best be rated as confirmation of a previously measured deterioration.

The addition must be reversed in the study documents.

d) Data evaluation: Patient-reported outcomes, evaluation

In the 4th version of the SAP, it was added that a questionnaire is considered completed if at least one item has been filled out. This addition is inappropriate. The number of patients for whom analysable data is available must be shown for each scale. The questionnaires must be evaluated in accordance with the manuals. According to the manuals for the two EORTC questionnaires, the score of a scale should only be calculated if at least 50% of the items have been completed.

The addition must be reversed in the study documents.

In order to avoid inconsistencies, the pharmaceutical company must check whether the need for changes in the study protocol described here leads to corresponding subsequent changes in the SAP and vice versa.

The G-BA points out that a lack of implementation of the above-described adjustments considered necessary may significantly limit the interpretability of the data from routine practice data collection in the context of the new benefit assessment.

In addition to the mandatory adaptations, the G-BA makes the following recommendations for further adaptations of the study protocol and the SAP:

e) Data evaluation: Patient-reported outcomes, MMRM analyses

In certain data bases and in case of an adequate data collection structure, MMRM analyses can be a suitable methodological approach for different therapy concepts such as single therapy with CAR-T cells compared to continuous therapy in cycles for the evaluation of patient-reported outcomes. The G-BA therefore recommends that, in addition to the evaluation as responder analyses, a possible added value of the evaluation as an MMRM analysis should also be examined depending on the specific data basis.

2.2 Deadline for submission of the revised study protocol and statistical analysis plan

The revised study protocol and the revised SAP are to be submitted to the G-BA by 21 August 2026 for review.

When submitting the revised version of the SAP and the study protocol, the pharmaceutical company must ensure that the changes made can be completely and clearly understood. For this purpose, a version of the documents must usually be submitted in which the changes have been marked in detail, as well as a current version of the documents without marking the changes. Amendments that do not result from the need for adjustment set out in this resolution and the justification shall be justified separately.

As part of the new benefit assessment, the G-BA reserves the right to conclusively assess effects on the RPDC study that arise due to changes to the study protocol submitted for the first time or the statistical analysis plan submitted for the first time by the pharmaceutical company and that do not comply with the requirements of the G-BA in accordance with the declaratory resolutions in the procedure of routine practice data collection for the active ingredient brexucabtagene autoleucel in the therapeutic indication of relapsed or refractory mantle cell lymphoma.

3. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient brexucabtagene autoleucel have been implemented as specified in the resolution of 16 November 2023 and in the amendment resolution of 16 November 2023, the pharmaceutical company submitted revised drafts of a study protocol and an SAP to the G-BA. The documents were reviewed by the G-BA with the involvement of IQWiG.

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

At their session on 18 June 2025, the plenum decided on the outcome of the review regarding the submitted study protocol (version 4.0 of 17 February 2025) and the SAP (version 4.0 of 17 February 2025).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	2 May 2025 19 May 2025 5 June 2025	Advice on reviewing study documents (study protocol and SAP)
Subcommittee on Medicinal Products	11 June 2025	Advice on reviewing study documents (study protocol and SAP)
Plenum	18 June 2025	Resolution on the review of study documents (study protocol and SAP)

Berlin, 18 June 2025

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

Prof. Hecken