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:
Autologous anti-CD19-transduced CD3+ cells (relapsed or refractory mantle cell lymphoma) – final review of study protocol and statistical analysis plan

of 16 November 2023

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 its session on 21 July 2022, the G-BA decided on the requirement of routine data collection and evaluations for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel) in accordance with Section 35a, paragraph 3b, sentence 1 SGB V.

In order to check whether the G-BA's requirements for routine practice data collection and evaluations have been implemented, the pharmaceutical company submitted drafts for a study protocol and a statistical analysis plan (SAP) to the G-BA in due time in a letter dated 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 statistical analysis plan (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 statistical analysis plan (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. The revised study documents were reviewed by the G-BA with the involvement of IQWiG.

Based on this review, the G-BA came to the conclusion that the adjustments to the study protocol and the statistical analysis plan that were further considered necessary by the declaratory resolution of 20 July 2023 were not fully implemented in the revised version of the study protocol and the statistical analysis plan submitted, which is why there is still a need for adjustments in this regard.

In addition, there is a need for adjustment with regard to the resolution adopted on 16 November 2023 to amend the requirement of routine practice data collection and evaluations for brexucabtagene autoleucel in the indication relapsed or refractory mantle cell lymphoma.

This declaratory resolution defines and justifies 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 are considered necessary.

2.1 Necessary adjustments to study protocol and statistical analysis plan

On the necessary adjustments in detail:

a) Question according to PICO: Outcome, patient-reported endpoints

With regard to the planned procedure, including the timeline for following up patients for the collection of patient-reported endpoints who have not returned their questionnaire to the data trustee on time, it is not clear why longer intervals are chosen for the follow-up surveys of patient-reported endpoints. This approach is inappropriate and must be adapted in accordance with the information on the baseline collection.

The 5th step of the baseline collection describes documenting the day on which the questionnaire is received by the data trustee. This step is described as "day x + 90 days" for the data collection time points from month 12 onwards. This information is implausible and must be corrected.

Maintaining the wide tolerance ranges for the individual time points for the collection of patient-reported endpoints is inappropriate. Time-differentiated returns between the study arms can lead to a bias of the results. The larger the tolerance range, the greater the risk of this bias. At later data collection time points (month 12, 24 and 36), the tolerance ranges are over 6 months. This approach is inappropriate and is not sufficiently justified by the possibility of increasing the response rate. The tolerance ranges must be defined in accordance with Table 2 of version 1.0 of the study protocol.

b) Data evaluation: Dealing with missing data

A comparative description of the two populations is necessary for justification of the transferability of the results to the baseline population based on the complete cases. The pharmaceutical company plans to present this description. However, the pharmaceutical

company does not comment on the required comprehensive justification (e.g. necessity, design). A comprehensive justification for the use of a complete case dataset must be added.

c) Question according to PICO: Comparator

By G-BA's resolution of 16 November 2023 to amend the requirement of routine practice data collection and evaluations for brexucabtagene autoleucel in the indication relapsed or refractory mantle cell lymphoma, the comparator of the routine practice data collection was adjusted. The active ingredient venetoclax was added as a suitable therapy option in the context of patient-individual therapy and the therapy option R-CHOP/R-DHAP was removed from the therapy options considered suitable. This adjustment was considered appropriate and necessary due to the further development of the generally recognised state of medical knowledge (for justification, see justification for the amendment resolution of 16 November 2023).

The active ingredient venetoclax must therefore be added to the study documents for the comparator of routine practice data collection and the therapy option R-CHOP/R-DHAP must be deleted.

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, particularly with regard to the patient-reported endpoints.

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

d) Study design: Recruitment of the study population

The pharmaceutical company does not provide any further justification for the estimate that there are uncertainties regarding a sufficiently similar standard of care for study sites in Croatia and Ireland compared to Germany. This is therefore not conclusively comprehensible. Since foreign study sites are used in particular to recruit patients for the comparator arm, differences in the standard of care can lead to a "selection bias". However, this could be addressed by sensitivity analyses excluding study sites from individual countries. It is therefore recommended that if the study sites from Croatia and Ireland are not included in the routine practice data collection, the justification for the exclusion of these study sites should be made clear in the study documents.

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 February 2025 for the first interim analysis.

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.

Changes to the statistical analysis plan and the study protocol made by the pharmaceutical company following the final review must be recorded in a separate addendum to the study protocol or SAP.

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 21 July 2022, last amended by resolution of 16 March 2023, the pharmaceutical company submitted the revised study protocol and the revised 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 its session on 16 November 2023, the plenum decided on the outcome of the review regarding the submitted study protocol (version 3.0; 16 August 2023) and the statistical analysis plan (version 3.0; 16 August 2023).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	16 October 2023 2 November 2023	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	7 November 2023	Consultation on the result of the review of the study protocol and SAP
Plenum	16 November 2023	Resolution on the result of the review of the study protocol and SAP

Berlin, 16 November 2023

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

Prof. Hecken