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) – Review of Study Protocol and Statistical Analysis Plan and Start of routine practice data collection

of 20 July 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 authorised 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 practice data collection and evaluations for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagen autoleucel) in accordance with Section 35a, paragraph 3b, sentence 1 SGB V. The clarifying provisions of the Act to Combat Supply Shortages and Improve the Supply of Medicines (ALBVVG) do not result in any changes with regard to the comparators determined in the resolution on requirement.

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. The documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG). 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. The revised draft study protocol and SAP were reviewed by the G-BA along with IQWiG.

On the basis of this review, the G-BA came to the conclusion that the implementation of the requirements for routine practice data collection and evaluations in the study protocol and statistical analysis plan prepared by the pharmaceutical company and submitted to the G-BA for review is to be considered fulfilled under the condition that further adjustments to the study documents deemed necessary are made. This declaratory resolution defines and justifies the further adjustments to the study protocol (version 2.0, 13 April 2023) and the statistical analysis plan (SAP; version 2.0, 13 April 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

The pharmaceutical company describes in section 2.2.3.1 of the study protocol that it is currently being discussed whether the patient will receive a telephone call before submitting the questionnaire, explaining verbally the procedure for collecting the patient-reported endpoints, so as to increase the response rate of the patient-reported endpoints. For the final review of the study protocol and SAP, the process of collecting patient-reported endpoints must be finalised. It must therefore be defined whether the telephone call to the patient described above is made or not. In addition, all further necessary measures related to the process of collecting patient-reported endpoints are to be finalised.

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

Compared to version 1.0 of the study protocol, the information on the tolerance range for the collection of patient-reported endpoints was changed from months to days. At the same time, however, the tolerance ranges have also been significantly extended. For example, for the survey time point of one month after the start of the study, the time frame was extended from 1 month ± 3 days to day 31 (day 28 to day 61). The tolerance range of survey time point of month 3 (now day 92) starts on day 62. In the view of the G-BA, the extended time frames are inappropriate. Therefore, the changes in the table "Procedure for the Collection of HRQoL using Patient Questionnaires" in section 2.2.3.3 of the study protocol (version 2.0) regarding the tolerance ranges for the time of the respective PRO survey are to be reversed and saved according to table 2 in version 1.0 of the study protocol.

c) Question according to PICO: Outcome, specific adverse events (AEs)

In the specific AEs defined in the study protocol (table 6 and section 2.2.4.5) and in the SAP (section 8.5.3.1), the encephalopathy event is missing as a component of the neurological events. This is to be supplemented.

The study protocol describes that the specific criterion for a CTCAE grade ≥ 3 should be collected for those of the designated specific AEs for which there is a specific definition of

severity grade in the CTCAE catalogue. For those of the specific AEs for which there is no such specific definition of severity grade, it is to be ascertained whether the criterion "significant impairment of the activity of daily living" is fulfilled. The type of survey presented in table 6 of the study protocol thus does not provide for a separate assessment as to whether the event is one with CTCAE grade ≥ 3 or whether the event meets the criterion of "significant impairment of the activity of daily living". This does not fully correspond to the need for adjustment required by the G-BA in the declaratory resolution of 16 March 2023, but the aggregated survey is assessed by the G-BA as sufficient in the context of the routine practice data collection. However, in order to ensure proper data collection, the G-BA considers it necessary that the principal investigators are provided with appropriate information material that clarifies the designated specific AEs for which specific definitions are available and how the CTCAE grades ≥ 3 are defined. This must be specified accordingly in the study protocol.

For the specific AEs with information on severity grade, the table in section 2.2.4 of the study protocol does not clearly show that the severity grade is to be determined by the CTCAE grade. This is to be specified.

The definition of severe specific AEs listed in section 2.2.4 of the study protocol and section 8.5.3.1 of the SAP implies that a severe specific AE is defined solely by the criterion "significant impairment of activities of daily living". This is considered inappropriate as the requirement of the G-BA is " [...] including specific AEs that lead to a significant impairment of the activity of daily living or with CTCAE grade ≥ 3". A definition which clarifies that a severe specific AE is not defined solely by the criterion of "significant impairment of the activities of daily living" must therefore be saved.

d) Study design: Recruitment of the study population

The selection of countries for the routine practice data collection made by the pharmaceutical company in the study protocol is not conclusively comprehensible. The study protocol does not specify the exact criteria used to assess a sufficiently similar standard of care. This must be clarified. The reasons why collaborating centres are not included in the routine practice data collection with regard to the criteria for a standard of care sufficiently similar to the EMCL register is therefore also incomprehensible. A corresponding justification is to be saved in the study protocol.

The pharmaceutical company describes in the study protocol that the search for suitable study sites for the routine practice data collection has not yet been completed and, for example, the participation of the study site in the Netherlands is still under discussion. Before starting the routine practice data collection, the search for suitable study sites must be completed. For the final review of the study protocol and statistical analysis plan, the final participating study sites must therefore be presented in the study protocol.

e) Data source: Confounders

Within the study protocol, the manifestations of the morphology confounder are inconsistent with the manifestations of the morphology baseline characteristic reported

in table 5. For the morphology confounder, the pharmaceutical company defines the classic, blastoid, pleomorphic, CLL-like and unknown manifestations. At baseline, in contrast, the classic, blastoid, pleomorphic, unknown and other manifestations are to be collected for morphology. This needs to be aligned.

f) Data evaluation: Propensity score method

With regard to the criteria for sufficient balance, it should be clarified in section 8.2.2 of the SAP in the first sentence of the penultimate paragraph that this is the case of multiple imputation and that the median refers to the results of the multiple imputation per confounder and not to the median across all confounders. In the case of a complete case analysis, the description of the criteria must be supplemented. In addition, an error in section 8.2.2 point 3 needs to be corrected. It should read "Sufficient balance is given by a median of <0.25 for each confounder." not ">0.25".

g) Data evaluation: Dealing with missing data

There is no information on the efforts made to minimise the rate of missing values in the date specification. This must be supplemented.

The restriction to "complete case datasets" in case of too many missing values without further classification is inappropriate. It should therefore be added to the SAP that, in the case of restriction to complete case datasets, a comprehensive justification must be provided as to the extent to which the results are still transferable to the initial population when restricted to the patient population with complete confounder data.

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.

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 17 August 2023 for final 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.

3. Start of the routine practice data collection

The routine practice data collection starts on 21 August 2023.

4. Process sequence

In order to check whether the requirements of the G-BA for routine data collection and evaluations for the active ingredient autologous anti-CD19-transduced CD3+ cells have been implemented as specified in the resolution of 21 July 2022, 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 its session on 20 July 2023, the plenum decided on the outcome of the review regarding the submitted study protocol (version 2.0; 13 April 2023) and the statistical analysis plan (version 2.0; 13 April 2023).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	1 June 2023 19 June 2023 6 July 2023	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee Medicinal products	11 July 2023	Consultation on the outcome of the review of the study protocol and SAP
Plenum	20 July 2023	Resolution on the outcome of the review of the study protocol and SAP

Berlin, 20 July 2023

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

Prof. Hecken