

Justification

for 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:
Exagamglogene autotemcel (sickle cell disease) – Submission
of the study protocol and statistical analysis plan

From 3 September 2026

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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 from 30.04.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4 from 07.01.2019, 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 review 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 December 2023, the G-BA decided on the requirement of routine practice data collection and evaluations for the active ingredient exagamglogene autotemcel in accordance with Section 35a, paragraph 3b, sentence 1 SGB V. The requirement came into force on 15 January 2025 and was amended by the resolutions of 7 November 2024, prior to its entry into force, and of 18 September 2025, after its entry into force.

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 of a study protocol and a statistical analysis plan (SAP) (version 1.0, respectively) to the G-BA in due time in a letter dated 13 June 2025. The documents were reviewed by the G-BA with the involvement of the Institute for Quality and Efficiency in Health Care (IQWiG).

By the resolution of 18 September 2025, the G-BA determined that the requirements for routine practice data collection and evaluations set out in the study protocol and statistical analysis plan prepared by the pharmaceutical company and submitted to the G-BA for review (version 1.0) had been inadequately implemented and that corresponding adjustments must be made.

The pharmaceutical company submitted the revised drafts of a study protocol and an SAP to the G-BA in due time by 16 October 2025. The revised drafts of a study protocol and an SAP (version: 2.0) were reviewed by the G-BA with the involvement of IQWiG.

On the basis of this review, the G-BA came to the conclusion that the decision on whether the routine practice data collection can be carried out on the basis of the submitted study protocol and statistical analysis plan (version 2.0) could not be made appropriately at this time.

In this regard, the G-BA took into account the fact that the operator of the sickle cell disease registry established by the Society for Paediatric Oncology and Haematology (GPOH) did not consider it feasible to carry out routine practice data collection for exagamglogene autotemcel

using the GPOH sickle cell disease registry, taking into account the adjustments deemed necessary by the G-BA in the declaratory resolution of 18 September 2025.

Against this background, the G-BA examined which requirements for routine practice data collection could be amended with a view to reducing the workload, in order to enable data collection in the GPOH sickle cell disease registry whilst avoiding unnecessary duplication during data collection in the therapeutic indication of sickle cell disease. In a letter dated 10 February 2026, the G-BA informed the pharmaceutical company of the data collection requirements that may be adapted, provided that the routine practice data collection is carried out in the GPOH sickle cell disease registry. At the same time, the pharmaceutical company was informed of the amendments to the study documents that were still considered necessary and must be implemented in order to enable the start of routine practice data collection.

The G-BA have therefore decided to extend the period for the 2nd review of the study documents in order to give the pharmaceutical company the final opportunity to examine a potential collaboration with the GPOH sickle cell disease registry, taking into account proposals for reducing the workload, and to rectify the remaining deficiencies that must be resolved before the start of routine practice data collection. The letter dated 10 February 2026 set 21 May 2026 as the deadline for submitting the revised study documents.

The pharmaceutical company submitted the revised drafts of a study protocol and a statistical analysis plan to the G-BA in due time by 21 May 2026 (version 3.0, respectively). The revised drafts of a study protocol and a statistical analysis plan were reviewed by the G-BA along with IQWiG.

On the basis of this review, the G-BA came to the conclusion that 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 have been inadequately implemented.

The continuing deficiencies in the study documents relate to mandatory adjustments that are considered indispensable for the start of routine practice data collection. As these deficiencies have not been rectified by the pharmaceutical company, the routine practice data collection will not be carried out.

2.1 Remaining deficiencies in the study protocol and statistical analysis plan

The following remaining deficiencies prevent the start of routine practice data collection:

a) Question according to PICO: patient population

There are still no clear criteria to be used to assess the suitability or unsuitability for treatment with exagamglogene autotemcel or stem cell transplantation, as already stated in the declaratory resolution of 18 September 2025 (Section a). This may result in different assessment criteria being applied at each study site or even within each treatment arm, leaving it unclear exactly which patients were included in the routine practice data collection. In the absence of clearly predefined criteria for assessing suitability or unsuitability for treatment with exagamglogene autotemcel, the comparability of the patient populations enrolled between the intervention and comparator arms cannot be assessed as part of the new benefit assessment; consequently, it is not possible to interpret the data from the routine practice data collection. This prevents the start of routine practice data collection.

The pharmaceutical company added contraindications to the exclusion criteria, and these may be regarded as an exhaustive list.

In a letter dated 10 February 2026, with regard to the inclusion criterion "severe sickle cell disease with recurrent vaso-occlusive crises (VOCs)", the G-BA accepted the restriction to VOCs that have resulted in hospitalisation, taking into account the statements made by the pharmaceutical company and the registry operator regarding the impossibility of reliably measuring VOCs that do not result in hospitalisation.

The pharmaceutical company added the definition of vaso-occlusive crises (VOCs) to the study documents. However, it is not clear why, despite previous statements regarding the impossibility of reliably measuring VOCs that did not result in hospitalisation, these events are now to be included as part of the inclusion criteria for defining severe sickle cell disease.

b) Study design: baseline assessment

In a letter dated 10 February 2026, the G-BA informed the pharmaceutical company that the requirements set out in the declaratory resolution of 18 September 2025 (see Section n) regarding the baseline assessment of inclusion and exclusion criteria must be implemented before the start of routine practice data collection. These requirements relate to ensuring positivity in the context of the MACNU design planned by the pharmaceutical company.

An index date is determined by matching a subject from the comparator arm with a subject from the intervention arm. Both subjects must be sufficiently comparable; in other words, both must, in principle, be suitable for treatment with exagamglogene autotemcel. By the specified index date, up to two years may have elapsed since the baseline assessment; in addition, retrospective data is collected in the baseline assessment, which may date back even further.

In this regard, it must be ensured that patients in the comparator arm remain suitable for treatment with exagamglogene autotemcel after the index date. This should be implemented, for example, by an enquiry of the principal investigators during the annual routine examination to check whether patients' suitability for treatment with exagamglogene autotemcel has changed as of the index date.

The study documentation did not provide any information on how it is ensured that patients in the comparator arm remain suitable for treatment with exagamglogene autotemcel after the index date. As, according to version 3.0 of the study documents, there are still no plans to establish a regular, targeted enquiry of the principal investigators regarding changes in patients' suitability for exagamglogene autotemcel, changes may occur between the baseline assessment and the index date that challenge the patient's suitability for exagamglogene autotemcel. As the timeliness of the baseline data is not checked at regular intervals in accordance with version 3.0 of the study documents (for example, as part of the annual routine examination) and the baseline data collected may be several years old, there is further uncertainty regarding the comparability between the comparator arm and the intervention arm as of the index date. Due to the time lag between the baseline assessment and the index date, the baseline value may have changed, which could lead to exclusion from the RPDC (if the inclusion criterion "suitability for treatment with exagamglogene autotemcel" no longer applies to the subject in the comparator arm). Furthermore, according to the study documents (version 3.0), the age of the baseline value is not recorded, which makes it even more difficult to interpret the data.

This means it is not possible to ensure or verify that only those patients who meet the study's inclusion and exclusion criteria are included in the analysis of the routine practice data collection. Specifically, without regular monitoring, it cannot be ruled out with certainty that, on the index date, a subject in the comparator arm, when matched with a corresponding subject in the intervention arm, is no longer sufficiently comparable to the latter, meaning that a comparison of the two subjects in the analysis would be marred by significant deficiencies. This may mean that the data from the routine practice data collection cannot be interpreted as part of the new benefit assessment, thereby preventing the start of routine practice data collection.

c) Study design: confounders

In a letter dated 10 February 2026, the G-BA informed the pharmaceutical company that the conditions set out in the G-BA's declaratory resolution of 18 September 2025 (Section q) regarding the definition of confounders in the submitted study documents (version 2.0 of 16 October 2025) had not been implemented. The pharmaceutical company was informed that clear operationalisations for all confounders that can be assessed during the routine practice data collection must still be included in the study documents in order for the routine practice data collection to start. A table with the relevant operationalisation of the confounders from the pharmaceutical company's perspective has been added to the study documents (version 3.0). Apart from the confounders of age, HbF percentage, sex and number of vaso-occlusive crises, the only operationalisation specified is "yes/ no".

Operationalisation as "yes/ no" is inadequate to ensure consistent data collection. For example, with regard to the confounder of chronic pain, it is not clear whether the pharmaceutical company plans to operationalise this in accordance with the definition in the GPOH sickle cell disease registry (based on the daily intake of pain medication). Overall, there is a lack of clear definitions for the majority of confounders. As the confounders to be assessed have not been defined, it is not possible to ensure or verify that the relevant confounders are consistently assessed across the participating study sites. This may mean that the data from the routine practice data collection cannot be interpreted as part of the new benefit assessment, thereby preventing the start of routine practice data collection.

d) Study design: baseline assessment of the confounders

In a letter dated 10 February 2026, the G-BA informed the pharmaceutical company that the conditions set out in the declaratory resolution of 18 September 2025 (Section n) regarding the baseline assessment of confounders have not been implemented and must be amended before the start of routine practice data collection. No baseline assessment of the confounders on the index date was planned in versions 1.0 and 2.0 of the study documents. If it is not possible to carry out a baseline assessment of the confounders on the index date, it must be justified on the basis of the evidence that the relevant confounders remain stable throughout the baseline period.

In version 3.0 of the study documents, the pharmaceutical company extended the baseline period from 1 year to 2 years, in light of the definition of vaso-occlusive crises and the reference period cited in this regard. Whilst extending the baseline period may seem reasonable, it does increase uncertainty regarding the completeness and quality of the data.

In version 3.0 of the study documents, the pharmaceutical company did not provide any information on the extent to which the confounders remain stable during the

baseline period. It can be assumed that the variation in the timeliness of the data is greater as a result of the extension of the baseline period. In particular, where confounders are assessed by routine examinations carried out less frequently, there is a greater likelihood that the data is older and may not reflect the patient's current condition. The pharmaceutical company did not provide any information on how they intend to counteract the resulting uncertainties. The pharmaceutical company have no plans to document the time interval between the baseline assessment and the index date, nor do they specify how they intend to ensure the completeness of the retrospective data.

As the manifestation of the confounders as of the index date are therefore not assessed and thus remain unclear, the comparability of the patient populations with regard to the confounders cannot be verified or interpreted during analysis of the data from routine practice data collection. This may mean that the data from the routine practice data collection cannot be interpreted as part of the benefit assessment, thereby preventing the start of routine practice data collection.

In addition to the unfulfilled requirements listed above, the G-BA informed the pharmaceutical company in a letter dated 10 February 2026 that it is mandatory to implement the condition set out in the declaratory resolution of 18 September 2025 (see Section j) regarding the observation period for patients, who do not reach the 60-day time point (d60) following their last red blood cell transfusion as part of post-transplant management. It is therefore necessary to set an appropriate time point as a reference for d60 for these patients and to plan further approaches as sensitivity analyses. The exclusion of patients, who do not reach the d60 time point, for example, because they did not receive an infusion of exagamglogene autotemcel, contrary to the original intention, is inappropriate, as this contravenes the intention-to-treat principle. These requirements were not incorporated into the newly submitted study documents and were not further addressed by the pharmaceutical company. Consequently, in addition to the points set out above, it is questionable whether the pharmaceutical company intends to carry out an analysis of the routine practice data that is suitable for the new benefit assessment.

Points raised by the pharmaceutical company regarding the infeasibility of routine practice data collection

In addition to the study protocol and the statistical analysis plan (version 3.0, respectively), the pharmaceutical company submitted a supplement setting out the reasons why, in the pharmaceutical company's view, the routine practice data collection does not appear to be feasible overall.

Taking into account the reduction in workload addressed by the G-BA in their letter dated 10 February 2026, the GPOH sickle cell disease registry operator has confirmed that routine practice data collection can be carried out within the GPOH registry.

The pharmaceutical company cites the number of patients in Germany and the duration of the study on routine practice data collection as major obstacles to targeted and feasible routine practice data collection.

On patient numbers

In order to carry out the routine practice data collection for exagamglogene autotemcel, at least 100 patients are required in accordance with the G-BA's indicative sample size estimate set out in the resolution on requirements of 21 December 2023, so as to ensure appropriate adjustment for confounders.

According to the pharmaceutical company, the number of suitable patients available in Germany is too small to achieve the sample size required for routine practice data collection.

In a letter dated 10 February 2026, with a view to reducing the administrative burden and accounting for the described difficulties faced by the pharmaceutical company and the registry operator in recruiting adult patients, the G-BA asked the pharmaceutical company to restrict the age of patients to 12 - 21 years. This restriction allows exclusive assessment of the patients in the paediatric GPOH sickle cell disease registry.

The pharmaceutical company states that the required patient number (141) is above the lower limit of the expected patient number in Germany (130 to 330). Based on the pharmaceutical company's calculations, an estimated 92 to 101 patients are available in the GPOH sickle cell disease registry for routine practice data collection. Consequently, adjusting for confounders must be assumed infeasible, even for the overall patient group aged 12 and over. According to the pharmaceutical company, the age restriction to 21 years would reduce the number of available patients to such an extent that the patient number would fall below 100, thereby making it no longer possible to carry out an appropriate adjustment for confounders.

Having examined the information provided by the pharmaceutical company regarding patient numbers, the G-BA continues to assume that, in principle, routine practice data collection is feasible for the present research question.

In principle, it is understandable that the restriction to the age group of 12–21-year-olds reduces the number of patients who can be recruited. However, the calculations submitted by the pharmaceutical company are only partially verifiable. Overall, there are uncertainties in the calculation of patient numbers regarding the assumptions made for this purpose, for example, regarding the actual percentage of patients with severe sickle cell disease with recurrent VOCs and the percentage of patients who are eligible for treatment with exagamglogene autotemcel.¹ With regard to the calculation submitted by the pharmaceutical company, it is inappropriate to use the age-specific percentages for AOK-insured persons in Germany to estimate the number of patients potentially available in the GPOH sickle cell disease registry as it focuses on paediatric patients. It is not possible to conclusively assess to what extent the calculations made by the pharmaceutical company regarding the percentage of subjects aged ≤ 21 years in the therapeutic indication in Germany correspond to the actual population size, as the number of patients in Germany can only be estimated with a degree of uncertainty. In particular, it is unclear to what extent the assumptions made can be applied to the limited population aged up to 21 years. The pharmaceutical company did not provide any information in this regard.

Overall, given the number of patients (130 to 330) assumed for the therapeutic indication of exagamglogene autotemcel and the continuing uncertainties regarding the population that can actually be recruited, the assumption that the number of patients required to carry out the routine practice data collection cannot be achieved as a rule is inadequately justified. The calculations submitted by the pharmaceutical company do not lead to a different assessment, as the underlying assumptions and methodological derivations are not consistently verifiable, and the existing uncertainties are therefore unsuitable to invalidate the G-BA's previous assessment regarding the fundamental feasibility of routine practice data collection. The G-BA therefore continues to assume that a sufficient number of patients can be recruited as part of the routine practice data collection.

¹ [Justification for the resolution of 18 September 2025 on exagamglogene autotemcel to amend the patient numbers](#)

On the study duration

Taking into account the necessary preparatory work, the required recruitment phase and the further steps involved in implementing the routine practice data collection, the pharmaceutical company states that the new benefit assessment of exagamglogene autotemcel cannot take place before the expiry of market exclusivity in February 2034. Having examined the information provided by the pharmaceutical company regarding the duration of data collection, the G-BA continues to assume that, in principle, routine practice data collection for the present research question can be carried out within a reasonable period of time.

The arguments put forward by the pharmaceutical company are considered inadequate to conclusively rule out the possibility of a new benefit assessment being carried out before the expiry of market exclusivity. This may help to reduce the lead time prior to the recruitment phase. Furthermore, it is not clear why the pharmaceutical company is allotting additional time following data collection for source data verification, as this is already scheduled to take place along with data collection according to version 3.0 of the study documents. Furthermore, other adjustments are conceivable, such as reducing the minimum duration of observation from 3 years for each patient to a median of 3 years.

Conclusion

The pharmaceutical company is responsible for carrying out routine practice data collection and evaluations. Overall, the points raised by the pharmaceutical company regarding the feasibility of routine practice data collection in the supplement are inadequate to assume the lack of feasibility of routine practice data collection in terms of the required patient numbers and the duration of the data collection.

However, the further existing deficiencies in the study documents (version 3.0) are preventing the start of routine practice data collection. Consequently, it is established by this resolution that the routine practice data collection will not be carried out.

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

In order to check whether the G-BA's requirements for routine practice data collection and evaluations of the active ingredient exagamglogene autotemcel have been implemented as specified in the resolution of 18 September 2025, the pharmaceutical company submitted 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 3 September 2026, the plenum decided on the outcome of the review regarding the submitted study protocol (version 3.0; 21 May 2026) and the statistical analysis plan (version 3.0; 21 May 2026).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	20 October 2025 4 December 2025 8 January 2026 19 January 2026 5 February 2026 5 March 2026 16 March 2026 13 July 2026 6 August 2026 17 August 2026	Consultation on the study protocol and statistical analysis plan (SAP)
Subcommittee on Medicinal Products	10 February 2026 25 August 2026	Consultation on the result of the review of the study protocol and SAP
Plenum	3 September 2026	Resolution on the result of the review of the study protocol and SAP

Berlin, 3 September 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk