Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on the Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Exagamglogene autotemcel (sickle cell disease); requirement of routine practice data collection and evaluations

of 21 December 2023

Contents

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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.

2. Key points of the resolution

The EMA's centralised marketing authorisation procedure for the active ingredient exagamglogene autotemcel started in January 2023. The active ingredient exagamglogene autotemcel was granted orphan designation by the EMA on 9 January 2020 (EU/3/19/2242).

The marketing authorisation and initial listing in the directory services in accordance with Section 131, para. 4 SGB V were still pending at the time the resolution was passed.

On the basis of additional ongoing or completed studies on exagamglogene autotemcel underlying the marketing authorisation application, the G-BA identified gaps in the evidence, particularly for the following aspects relevant to the early benefit assessment, which justify the necessity of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient exagamglogene autotemcel:

- Data to assess the long-term (additional) benefit and harm of treatment with exagamglogene autotemcel for the patient population included in the marketing authorisation application;
- comparator data of treatment with exagamglogene autotemcel versus existing therapeutic alternatives for the patient population covered by the marketing authorisation application

Only single-arm studies were identified during the study research. On this data basis, it can be assumed that no comparator data are currently available for treatment with exagamglogene autotemcel compared to existing therapeutic alternatives for the patient population applied

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for the marketing authorisation and that no improvement in the body of evidence can be expected, taking into account the current study planning.

Taking into account the aforementioned gaps in the evidence, the research question of the present routine practice data collection comprises the assessment of the benefit and harm profile of exagamglogene autotemcel in comparison to existing therapeutic alternatives as well as the assessment of the sustainability of the therapy success for patients 12 years of age and older with severe sickle cell disease with recurrent vaso-occlusive crises who have the genotype βS/βS, βS/β0 or βS/β+, for whom haematopoietic stem cell transplantation is an option and no human leukocyte antigen (HLA)-compatible, related haematopoietic stem cell donor is available.

By resolution of 1 June 2023, the G-BA initiates a procedure for the requirement of a routine practice data collection according to Section 35a, para. 3b, sentence 1 SGB V for the active ingredient exagamglogene autotemcel.

A concept was drawn up in preparation for the resolution on the requirement of routine practice data collection and evaluations. The concept contains in particular requirements for:

1. the type, duration and scope of data collection,
2. the research question (PICO framework: patient/population, intervention, comparison, outcomes) that is to be the subject of the data collection and evaluations, including the patient-relevant endpoints to be collected,
3. the data collection methods,
4. the evaluations by the pharmaceutical company according to Section 50, paragraph 2 of the VerfO.

The G-BA decides whether to prepare the concept itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG) to do so. In the present case, the G-BA commissioned the IQWiG to prepare the concept. The expert bodies according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V made a written submission in drawing up the concept. The submission took place in such a way that the expert bodies were given the opportunity in writing to comment on the requirements of routine practice data collection and evaluations in accordance with the concept that had been drawn up. In addition, expert consultation was held.

In preparing the concept, ongoing and planned data collections were taken into account, especially those resulting from conditions or other ancillary provisions imposed by the marketing authorisation or licensing authorities. The pharmaceutical company stated in the written submission and in the expert consultation that a prospective Post Authorisation Safety Study (PASS) is planned in dialogue with the EMA and the FDA and is to be conducted, among others, in the transplant-specific procedure registry of the European Group for Blood and Marrow Transplantation (EBMT). In this study, subjects treated with exagamglogene autotemcel will be followed up for up to 15 years using registry data. The comparator arm consists of subjects who receive an allogeneic stem cell transplantation, which is possible from

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both HLA-compatible and haploidentical donors. The PASS concept had not yet been finalised at the time of the expert consultation.

In sickle cell disease, only the transplantation of HLA-compatible stem cells is the therapy standard for stem cell transplantation. These are primarily related donors; in rare cases, HLA-compatible, unrelated donors may also be considered. According to the clinical experts and the available guidelines, the transplantation of donated haploidentical stem cells is an experimental procedure that is currently being investigated in clinical studies.

Patients for whom an HLA-compatible, related donor is available are excluded from the therapeutic indication of the ongoing marketing authorisation procedure for exagamglogene autotemcel. Accordingly, for the majority of the patient population relevant for the routine practice data collection, a curatively intended allogeneic stem cell transplantation is not considered as a comparator therapy, but rather other non-curatively intended therapy options (e.g. hydroxycarbamide).

Patient-individual therapy with the selection of hydroxycarbamide, red blood cell transfusions, voxelotor and high-dose therapy with allogeneic stem cell transplantation when an HLA-compatible, unrelated donor is available, as defined by the G-BA as a comparator for the present routine practice data collection, is not found in the comparator arm of the PASS. Furthermore, it is unclear to what extent information on all relevant confounders for a non-randomised comparison is available from the PASS and whether the patient-relevant endpoints required for the benefit assessment are collected in the PASS.

Based on this, the G-BA classifies the PASS planned in collaboration with the regulatory authorities as unsuitable to adequately improve the existing body of evidence for the patient population covered by the applied marketing authorisation for the purpose of the benefit assessment.

Based on the above-mentioned question, the G-BA, on the basis of IQWiG's concept and the submission of the expert bodies in drawing up the concept, decided by the present resolution on the requirements of routine practice data collection and evaluations, as well as on the specifications for the review of the obligation to perform and on the deadline for the submission of evaluations.

2.1 Requirements for routine practice data collection and evaluations

2.1.1 Research question according to PICO scheme

Patient population

According to the ongoing marketing authorisation procedure, the target population for the active ingredient exagamglogene autotemcel comprises patients 12 years of age and older with severe sickle cell disease with recurrent vaso-occlusive crises who have the genotype βS/βS, βS/β0 or βS/β+, for whom haematopoietic stem cell transplantation is an option and no human leukocyte antigen (HLA)-compatible, related haematopoietic stem cell donor is available. For the present requirement of routine data collection and evaluations according to

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Section 35a, paragraph 3b, sentence 1 SGB V, the pharmaceutical company shall collect and evaluate comparator data for the patient population defined according to the marketing authorisation.

According to the statements made by the clinical experts in the submission procedure, haploidentical stem cell donations are not defined as HLA-compatible. The patient population applied for the marketing authorisation excludes patients for whom an HLA-compatible, related donor is available. The patient population thus includes patients for whom suitable HLA-compatible, unrelated and suitable haploidentical stem cells are available for donation. With regard to haploidentical stem cell donation, please refer to the comments below on the comparator/comparator therapy of the routine practice data collection.

In a comparator study without randomisation, the comparability of the study populations or the fulfilment of positivity for the treatment options to be compared must be given. Due to the specific conditions of the patients, which must be given for a therapy with exagamglogene autotemcel, the criteria for the suitability for a therapy with exagamglogene autotemcel should be applied in the definition of the inclusion and exclusion criteria of the routine practice data collection and evaluations.

Intervention

In accordance with the present requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V, the intervention includes the active ingredient exagamglogene autotemcel. The marketing authorisation and the dosage information in the product information for exagamglogene autotemcel (Casgevy) must be taken into account.

Comparator therapy

The following criteria were applied:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

On 1. Medicinal products with the active ingredients hydroxycarbamide and voxelotor as well as red blood cell concentrates are approved for the present therapeutic indication.

On 2. Allogeneic stem cell transplantation is generally considered as a non-medicinal treatment in this therapeutic indication. With regard to the application of the treatment method of allogeneic stem cell transplantation, the requirements under Section 137c SGB V apply. No method assessment has yet been carried out for this treatment method in the present indication.

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On 3. In the mentioned therapeutic indication, the following resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V is available:

- Voxelotor: resolution of 3 November 2022

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Comparator Therapy"). There is a written statement of the German Society for Haematology and Medical Oncology (DGHO) and the Society for Paediatric Oncology and Haematology (GPOH) respectively.

In the absence of a related HLA-compatible stem cell donor, therapy options are discussed according to the available evidence, depending on patient-individual factors, in particular to alleviate or prevent symptoms or complications. The guideline of the American Society of Hematology (ASH)[1] recommends acute or chronic treatment with red blood cell transfusions, depending on the risk of cerebrovascular events, in particular. This is in line with the written statements of the DGHO/GPOH on the question of comparator therapy, which also recommend hydroxycarbamide for the prevention of the (vaso-occlusive) pain crises frequently associated with sickle cell disease. From the available evidence, the Cochrane review by Rankine-Mullings et al. (2022), systematic reviews and the ASH guideline indicate a corresponding significance of hydroxycarbamide for the prevention of strokes and reduction of pain episodes.

According to the written statement of the DGHO/GPOH, voxelotor is recommended as another medicinal product to influence the course of the disease for the treatment of haemolytic anaemia due to sickle cell disease. By G-BA's resolution of 3 November 2022, a hint for a non-quantifiable additional benefit was identified since the scientific data did not allow quantification. Voxelotor, if applicable in combination with hydroxycarbamide, showed no assessment-relevant differences compared to placebo, if applicable in combination with hydroxycarbamide, in the endpoint categories of mortality, morbidity and side effects. Data on health-related quality of life were not available.

The clinical experts pointed out the significance of voxelotor in medical treatment practice during the expert consultation. Despite the lack of measurable influence on vaso-occlusive crises, voxelotor has an influence on the level of anaemia and on the frequency of transfusions, so that some patients received this active ingredient in their care.

[1] DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv 2020;4(8):1554-1588.

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For the present requirement of routine practice data collection and evaluations, voxelotor is defined as an additional component of the patient-individual therapy for the comparator of the routine practice study.

The G-BA determines voxelotor as part of the patient-individual therapy of the comparator for the routine practice study, taking into account the required duration of the routine practice data collection, during which a new situation may arise with regard to the generally accepted state of medical knowledge in the therapeutic indication in question. In principle, this is to be considered separately from the determination of the appropriate comparator therapy, which only becomes legally binding with the resolution on the benefit assessment according to Section 35a, paragraph 3 SGB V.

Weighing up the risks of continuing symptomatic therapy, allogeneic stem cell transplantation may also be considered for patients who are eligible for a haematopoietic stem cell transplantation but for whom no related, HLA-compatible stem cell donor is available. In this constellation, the transplantation of donated haploidentical stem cells or donated HLA-compatible, unrelated stem cells would be conceivable. Haploidentical stem cell donation is currently regarded as an experimental procedure and is being investigated in an ongoing clinical study in comparison with HLA-compatible stem cell donation (NCT04201210). The results of this study have not yet been published. The transplantation of donated haploidentical stem cells is therefore not named as part of the patient-individual therapy in the comparator arm.

Allogeneic stem cell transplantation with an HLA-compatible, unrelated stem cell donation represents a possible, relevant therapy option in specific cases and is therefore determined as part of the patient-individual therapy in the comparator arm.

In summary, no therapy option is generally preferable to all other therapy options according to the generally accepted state of medical knowledge for patients 12 years of age and older with severe sickle cell disease with recurrent vaso-occlusive crises who have the genotype βS/βS, βS/β0 or βS/β+, for whom haematopoietic stem cell transplantation is an option and no HLA-compatible, related haematopoietic stem cell donor is available. Rather, the treatment decision is made on the basis of the patient-individual criteria. Against this background, the G-BA determines a patient-individual therapy under selection of hydroxycarbamide, red blood cell transfusions, voxelotor and high-dose therapy with allogeneic stem cell transplantation, taking into account the type and severity of symptoms, age, availability of an HLA-compatible, unrelated donor for allogeneic stem cell transplantation and the risk of cerebrovascular events as comparator therapy. Some of the treatment options mentioned have lower percentages of care.

Furthermore, it is assumed that concomitant symptoms or complications of sickle cell disease are adequately treated, such as analgesics, chelating agents for iron overload,

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antithrombotic therapy for vascular occlusions, prevention of infection. These concomitant therapies should be documented in both treatment arms as part of a routine practice data collection.

Outcome

Comparator data on the following endpoint categories shall be collected for the patient population required here for routine practice data collection in accordance with Section 35a, paragraph 3b, sentence 1 SGB V: mortality, morbidity, health-related quality of life and side effects.

In this therapeutic indication, the avoidance/ freedom from vaso-occlusive crises (VOCs) is especially of high relevance for patients. Against this background, the collection of VOCs, in particular acute chest syndrome, pain crises, priapism and splenic sequestration in the registry study is of great importance for the comparison of exagamglogene autotemcel versus patient-individual therapy in the comparator arm. The specific operationalisation of the "VOC" endpoint must be defined by the pharmaceutical company in the study protocol (SP) and in the statistical analysis plan (SAP) and must be carried out in such a way that it can be reliably measured. From the G-BA's point of view, an operationalisation as a composite endpoint including the individual components mentioned could be considered for this. With regard to pain crises, a definition can be chosen in which pain events that lead to hospitalisation or treatment in the accident and emergency department are collected. The endpoints of priapism and splenic sequestration should be included in the composite endpoint regardless of hospitalisation/ treatment in the accident and emergency department. With regard to the individual component of acute chest syndrome, it is assumed that this event is generally associated with hospitalisation or treatment in the accident and emergency department. For the endpoint of avoidance of VOCs, an observation period of at least 3 years per patient is required. With regard to the observation period to be considered in the evaluation for the endpoint of avoidance of VOCs, the pharmaceutical company must justify in the study documents from which point in time post infusion with exagamglogene autotemcel it can be assumed that VOCs have been avoided.

The clinical experts stated in the written submission procedure that not only the complete avoidance of VOCs but also the reduction of VOCs is clinically relevant. Besides the endpoint described above, the pharmaceutical company can therefore also test an additional endpoint that validly records a reduction in the frequency of these events instead of a complete avoidance of VOCs. A median observation period of 3 years can also be selected for the reduction in the frequency of VOCs, whereby the observation should start from the time of the treatment decision and last at least 1 year. In addition, the observation period must take into account the time required until administration of the gene therapy and the onset of the therapeutic effect.

The observation periods are to be defined uniformly between the study arms of the routine practice data collection.

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As patients age, chronic organ damage is also a key characteristic of sickle cell disease. The G-BA therefore considers the collection of chronic organ damage (e.g. renal failure, cerebrovascular complications) to be relevant in the context of the routine practice study.

In view of the burdensome symptomatology of this disease, which can have a significant impact on patients' quality of life, the improvement of symptomatology and quality of life assumes high significance and the collection of patient-reported endpoints is generally considered relevant.

With regard to symptomatology, the patient-reported collection of chronic and acute pain is considered appropriate. This should be done with an instrument that is validated for patient-reported pain data collection.

Health-related quality of life should also be collected using a validated instrument.

If no indication-specific measurement instrument can be identified to assess health-related quality of life or pain, generic instruments can also be used. The selection of appropriate instruments to collect patient-reported endpoints on symptomatology and health-related quality of life in the exagamglogene autotemcel routine practice data collection should be outlined during the development of the study protocol (SP) and statistical analysis plan (SAP).

As part of the submission procedure, the experts stated that it would not be possible to implement uniform data collection time points for the collection of patient-reported endpoints in patients with sickle cell disease, particularly in the comparator arm. According to the information provided by the pharmaceutical company and the registry operator, visits of patients are currently irregular, as they depend on the individual course of the disease. In addition, the collection of patient-reported endpoints would change the legal character of the data collection to an interventional study. Furthermore, it was stated that the collection of patient-reported endpoints was difficult due to the linguistically heterogeneous patient population, as a validated translation of the questionnaires into numerous languages would be necessary.

From the G-BA's point of view, there is currently no standardised view on the extent to which the collection of patient-reported endpoints justifies the interventional character of a study. For example, there are already ongoing routine practice data collections in which the collection of patient-reported endpoints has not led to an interventional character of the data collection. Irrespective of this, the requirements for routine practice data collection in accordance with Section 35a paragraph 3b SGB V do not fundamentally exclude the conduct of an interventional study.

Currently, it is not possible to estimate the extent to which the data collection time points of the patient-reported endpoints will differ between the two study arms and whether this is likely to result in a relevant bias in the results of patient-reported endpoints. The pharmaceutical company must take measures to ensure that data collection time points are as uniform as possible. If it is not possible to implement uniform data collection time points based on the visits of patients in both study arms, the pharmaceutical company should consider choosing a procedure for the collection of patient-reported endpoints that is

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independent of the visit times in routine care (e.g. by delivering the questionnaires directly to the patients at uniform times).

In the view of the G-BA, the linguistic heterogeneity of the existing patient population does not fundamentally prevent the collection of patient-reported endpoints, but should be taken into account when selecting a suitable measurement instrument.

In the overall assessment, the G-BA has however taken into account in the present case that none of the identified registries is yet suitable as a primary data source for a routine practice data collection without extensive adjustments. Based on the available information, it is unclear in which time frame the collection of patient-reported outcomes (PROs) on symptomatology and health-related quality of life can be implemented. The time required to implement the collection of patient-reported endpoints may result in limitations in terms of feasibility since the G-BA believes that the registry needs to be adapted as soon as possible to implement the routine practice data collection.

With regard to the implementation of the collection of health-related quality of life and the patient-reported pain data, the pharmaceutical company must show:

- whether it is possible to implement the collection of PROs and within what time frame this can be realised (e.g. adaptation of the registry, effort required for a methodologically appropriate collection of PROs),
- the extent to which the time required for the implementation affects the recruitment opportunities of the prospective data collection.

The G-BA reserves the right to review whether, after submission of the study protocol and the statistical analysis plan, the requirement to assess health-related quality of life and the patient-reported assessment of pain is waived within the framework of a weighing decision in the specific case at hand, insofar as the effort for the implementation of the collection would be disproportionate.

In addition to the collection of symptomatology and health-related quality of life, the collection of data on deaths is also considered necessary, as the individual symptomatology of the patients can have an influence on life expectancy.

Taking into account the comments on the collection of data on adverse events made in the submission procedure, the G-BA defines the following endpoints for the side effects for the routine practice study:

The overall rates of serious adverse events (SAEs) should be mapped. In doing so, SAEs should be operationalised as AEs which lead to hospitalisation or prolong an existing hospitalisation, or lead to death. In addition, defined specific adverse events should be collected, with indication of the respective severity. According to the explanations made by the pharmaceutical company, no specific AEs have yet been defined for exagamglogene autotemcel. When drawing up the study protocol and statistical analysis plan, the pharmaceutical company must check which specific AEs are appropriate for the present routine practice data collection. The selection of the specific AEs must be justified. Moreover,

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specific aspects that may need to be considered in the implementation of routine practice data collection and evaluations due to a different side effect profile of the intervention and comparator can be addressed by the pharmaceutical company when preparing the study protocol and statistical analysis plan.

The specific AEs should address both exagamglogene autotemcel and the comparator therapy and ideally be coded using the MedDRA system. In relation to the comparator arm, a relevant specific AE in the present therapeutic indication may be, for example, graft-versus-host disease in allogeneic stem cell transplantation of donated HLA-compatible, unrelated stem cells.

2.1.2 Type and methods of data collection

According to Section 35a, para. 3b SGB V, the Federal Joint Committee can demand indication-related data collection without randomisation for routine practice data collection.

For the present requirement of a routine practice data collection, indication registries that meet the requirements for routine practice data collection and at least fulfil the quality criteria specified in the resolution shall be used as the data source. The minimum data quality requirements mentioned are based on the national and international quality criteria for registries mentioned in the IQWiG concept, whereby the focus was placed on the quality criteria for standardisation and validity of data collection, as well as for sample collection, which were considered particularly relevant for the present requirement.

In order to ensure the suitability of the data collected, the use of an indication registry is also required in which treatment of severe sickle cell disease is carried out in accordance with German daily care or is sufficiently similar to care in Germany. The guarantee of sufficiently similar care in Germany, which is required when using (indication) registries, should make it possible to integrate data from other European countries without compromising data quality. If there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine practice data collection and evaluations.

Based on the available information, the sickle cell disease registry of the GPOH (Society for Paediatric Oncology and Haematology) may be suitable as a primary data source for routine practice data collection, provided that the still existing limitations are eliminated. The adaptations required for the routine practice data collection refer in particular to the following aspects in accordance with the IQWiG concept[2]:

- Increase in the patient number, especially the number of adults
- Introduction of mandatory data fields to be documented on inclusion and exclusion criteria as well as relevant endpoints and concomitant medication, including exact date specifications

[2] IQWiG: Concept for routine practice data collection A23-49– exagamglogene autotemcel (sickle cell disease).

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- Reliable operationalisation of vaso-occlusive crises
- Implementation of the assessment of adverse events
- Assessment of patient-reported endpoints on symptomatology and health-related quality of life
- Collection and reporting time points at regular intervals (several times a year), which should be as uniform as possible
- Systematic identification of relevant confounders and expansion of the data set to include relevant confounders that were not previously collected
- Supplementing the measures to ensure the accuracy of the data (introduction of source data verification based on a sample of, e.g. 10% of the data records)

Provided that the quality criteria and requirements of routine practice data collection specified in this resolution can be implemented in the GPOH sickle cell disease registry, this is to be used as the primary registry.

In the submission procedure, the registry operator explained that the inclusion of more adults in the GPOH sickle cell disease registry had not been feasible to date. However, it was also made clear that the inclusion of more adults in the register in the future was not ruled out in principle. The provision of support staff to the relevant doctors for data documentation was listed as a possible strategy in this regard. The pharmaceutical company must show in the study documents what measures are planned to ensure the inclusion of adults in the routine practice data collection.

Please refer to the comments in section 2.1.1 with regard to the requirement of standardised data collection time points, the legal nature of the data collection and the implementation of the collection of patient-reported endpoints. In particular, the registry also requires regular data collection and reporting time points (several times a year), which ensure that the endpoints defined for the routine practice study are collected properly on the one hand and ensure that an evaluation of the data is available for the defined interim analyses and the new benefit assessment on the other.

For the present requirement of a routine practice data collection, it should be reviewed to what extent the data from other registries on exagamglogene autotemcel are suitable and can act as a supplement to the GPOH sickle cell disease registry (e.g. RADeep). No German study sites are involved in the European Haemoglobinopathy Registry (EHR). If the data are sufficiently transferable to the German healthcare context and the requirements for the routine practice data collection are met, an extension of the routine practice data collection with data from the EHR can be verified.

A comparison of two therapies without randomisation poses in principle a potentially high risk of bias. Therefore, additional factors with a potentially high risk of bias such as the use of different data sources for the comparator group or data of different quality within one data source should be avoided.

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For treatment with exagamglogene autotemcel, stem cells are removed from the patients by means of apheresis and subject to patient-individual preparation. The production of the medicinal product can therefore take several weeks and the treatment is not available to patients immediately after indication. This delay in the start of therapy only exists for the treatment options of the specific comparator in specific cases. Therefore, the time of treatment decision should be chosen as the time of enrolment in the sense of an intention-to-treat principle. In this regard, please refer to the above statements on the endpoints in section 2.1.1. Procedures such as the prevalent new user design are described in the literature, which can be used in the case constellation if a new therapy is not initiated in both treatment groups at the start of observation. The aim of these procedures is to reduce any bias caused by an incorrect choice of observation start. Statistical methods for evaluating data from this study design take into account data prior to the index date. Methods for statistical analysis are described in the literature and should be considered by the pharmaceutical company when preparing the study documentation.

During the submission procedure, the relevance of including legacy data was brought out. Taking into account the previous set-up of the GPOH sickle cell disease registry, it can be assumed that the retrospective data show deficiencies, among other things, with regard to the collection of endpoints on morbidity, health-related quality of life and side effects, the collection of clinically relevant confounders and the possibility of implementing the intention-to-treat (ITT) principle. Furthermore, although few adults have been included in the registry to date, they represent a relevant component of the therapeutic indication of exagamglogene autotemcel, which is currently in the marketing authorisation procedure, and should be recruited in a representative number for the routine practice data collection. From the G-BA's point of view, however, endpoint-specific inclusion of retrospective data may be possible. To this end, the pharmaceutical company must check in advance whether the endpoint-specific, retrospective data meet the stated data quality requirements. Accordingly, prospective comparator data collection, possibly supplemented by endpoint-specific retrospective data, is the primary option for exagamglogene autotemcel.

In summary, the study design required for exagamglogene autotemcel is a non-randomised, prospective comparison with the comparator determined as appropriate, which may be supplemented by retrospective data on an endpoint-specific basis, provided these data meet the requirements. The routine practice data collection should preferably be carried out as a comparative registry study in the GPOH sickle cell disease registry.

If a comparator registry study is therefore infeasible for the present requirement of routine practice data collection and evaluations due to the required comprehensive adjustments to the GPOH sickle cell disease registry, a comparative study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection) is required as an alternative. All requirements described in the resolution for the routine practice data collection and evaluations must be taken into account in the same way when using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection), unless specified otherwise.

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2.1.3 Duration and scope of data collection

The duration and scope of routine practice data collection result from the estimated suitable patient-related duration of observation and the estimated required number of patients (sample size).

The aim of the routine practice data collection is to determine the long-term benefits and harms of treatment with exagamglogene autotemcel compared to the comparator therapy. The present research question concerns a disease in which the function of haemoglobin is altered by a gene mutation. Exagamglogene autotemcel can be used to modify the body's own haematopoietic stem cells and progenitor cells by CRISPR-Cas9 gene editing so that they produce more HbF, which is not affected by the gene mutation. A key therapeutic goal in sickle cell disease is to avoid or reduce the frequency of VOCs. How long the therapeutic effect of exagamglogene autotemcel lasts cannot be estimated on the basis of the data available to date. In order to observe the sustainability of the therapeutic effect of exagamglogene autotemcel, patients should therefore be followed up for at least 3 years for the endpoint of avoidance of VOCs.

As an approximation of the appropriate sample size for the routine practice data collection, an indicative sample size estimate was performed based on the endpoint of avoidance of VOCs. Against the background of the curative therapeutic approach of exagamglogene autotemcel, the percentage of patients in whom no VOC is observed during the observation period (hereinafter referred to as responders) is considered a meaningful operationalisation of the endpoint.

In the submission procedure, it was put forth that patients' willingness to undergo therapy with exagamglogene autotemcel is considered high due to the curative approach and the limited therapy options in the comparator arm as well as the possibly insufficient treatment success with the comparator therapy. At the same time, according to the statements made by the pharmaceutical company, it cannot be ruled out that the number of patients treated will be limited due to the administrative effort involved in providing exagamglogene autotemcel, particularly in the initial period after the placing on the market of the medicinal product. In this respect, a 1:1 and 1:2 distribution between intervention and comparator groups was assumed in the indicative sample size estimate.

Taking into account the limited data basis on the number of responders to exagamglogene autotemcel and the comparator therapy, a response rate of 93% was assumed for exagamglogene autotemcel and a response rate of 25% for the comparator arm.

Assuming a response rate of 93% in the intervention and 25% in the comparator therapy, this results in a sample size of 75 patients with a 1:2 distribution and 86 patients with a 1:1 distribution. However, it should be noted that an adequate confounder control is not possible for sample sizes < 100 subjects, so that at least 100 patients must be recruited for the routine practice data collection. The scenarios were calculated assuming a significance level $\alpha = 5\%$, 2-tailed test, power at least 80% and shifted null hypothesis RR = 2.0.

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The exemplary sample sizes presented are of a magnitude where it can be assumed that routine practice data collection is feasible in principle for the question at hand. The final sample size planning is part of the preparation of the statistical analysis plan and the study protocol by the pharmaceutical company and can, if necessary, also be carried out on the basis of endpoints other than those listed in this resolution (e.g. reduction of VOCs) and taking into account a shifted hypothesis boundary in accordance with the procedure in the IQWiG concept.

2.1.4 Evaluations of the data collection for the purpose of the benefit assessment

The general requirements for the evaluation of comparator studies without randomisation must correspond to the planning of the evaluation of comparator studies with randomisation. The information given in the resolution must be taken into account when drawing up the study protocol and statistical analysis plan prior to carrying out the routine practice data collection (see also section 2.1.5).

The evaluation of data from different data sources, i.e. different registries, should be done separately for each data source. Additional pooled analysis is possible after checking the suitability of data from different data sources. Information on the verification of suitability for pooled analysis should be set out accordingly in advance in the statistical analysis plan.

The pharmaceutical company shall perform the evaluations mentioned in the resolution (interim analyses and final evaluation) according to the specifications in the study protocol and the statistical analysis plan. The interim analyses shall be prepared on the basis of Module 4 of the dossier template with provision of the full texts and study documents, the final evaluations shall be prepared in a dossier in accordance with the provisions in Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA. The relevant times for conducting the interim analyses are the times specified in the resolution under section 2.3 and for submitting the final evaluations to the G-BA the time specified in the resolution under section 3.

The indicative sample size estimate is subject to uncertainties due to the small information base available and therefore represents a first hint of the required size of the study population. Against this background, the G-BA considers it expedient that a review is carried out by the pharmaceutical company during the course of the study, which may lead to an adjustment of the sample size. If necessary, this can also be carried out at this time on the basis of benefit endpoints (e.g. reduction of VOCs) other than those mentioned in the present resolution and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's concept[2].

2.1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection and evaluations. In this respect, the requirements for the information to be presented as described in the resolution shall be taken into account.

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2.2 Specifications for reviewing whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan for approval by the Federal Joint Committee before carrying out the routine practice data collection and evaluations. Taking into account the time frame required for drafting, the pharmaceutical company shall submit the final drafts of a study protocol and a statistical analysis plan to the G-BA for approval at the latest 5 months after adoption of the present resolution.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

In order to be able to clarify queries during the preparation of the final drafts for a study protocol as well as for a statistical analysis plan, the pharmaceutical company has the possibility - before submitting the requested documents to the G-BA - to request consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). In order to enable the pharmaceutical company to adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA at the latest 4 weeks after adoption of the present resolution.

According to Section 35a para. 3b, sentence 10 SGB V, the data obtained and the obligation to collect data must be reviewed by the G-BA at regular intervals, but at least every 18 months.

With regard to the information on the course of data collection (in particular information on the status of recruitment), the pharmaceutical company shall provide the G-BA with information on the number and the respective medicinal treatment of the patients included to date, on patient-related observation periods and on possible deviations with regard to the expected number of recruits at intervals of 18 months.

The subject of the continuous review of the data obtained is in particular whether the data collection is carried out or not, or can no longer be carried out.

The pharmaceutical company shall submit 2 interim analyses to the G-BA 18 and 36 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution. Within the framework of the first interim analysis, a review of the sample size estimate on the part of the pharmaceutical company is also to be carried out. The G-BA carries out a review of the interim analyses with the involvement of the IQWiG.

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2.3 Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations must be submitted at the latest 6 years after the adoption of the present resolution.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5, Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5, Section 58 of the Rules of Procedure of the G-BA.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

In order to prepare a recommendation for a resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of AM-RL) according to Section 35a, paragraph 3b SGB V, the Subcommittee on Medicinal Products commissioned a working group (WG routine practice data collection (RPDC)) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the National Association of Statutory Health Insurance Funds, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions. In addition, the competent higher federal authority, the Paul Ehrlich Institute, was involved in the consultation to assess the requirement of a routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V.

The recommended resolution on the initiation of a procedure for the requirement of a routine practice data collection was discussed on 23 May 2023 at the subcommittee session and the draft resolution was approved.

At its session on 1 June 2023, the plenum resolved to initiate a procedure for the requirement of a routine practice data collection.

In conjunction with the resolution of 1 June 2023 regarding the initiation of a procedure for the requirement of a routine practice data collection, the G-BA commissioned IQWiG to scientifically develop a concept for routine practice data collection and evaluations for the purpose of preparing a resolution.

IQWiG's concept was submitted to the G-BA on 30 August 2023. On 6 September 2023, the written submission of the expert bodies according to Section 35a, paragraph 3b, sentences 7

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and 8 SGB V was initiated. The deadline for making the written submission was 4 October 2023.

The expert consultation within the framework of the submission by the expert bodies took place on 23 October 2023.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 12 December 2023, and the draft resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	6 April 2023 4 May 2023	Consultation on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL), involvement of the higher federal authority
Subcommittee Medicinal products	23 May 2023	Concluding discussion of the draft resolution
Plenum	1 June 2023	Resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL)
WG RPDC	16 October 2023	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	23 October 2023	Implementation of the expert consultation
WG RPDC	2 November 2023 20 November 2023 7 December 2023	Consultation on IQWiG's concept and on the specifications for the review of the obligation to conduct and submit evaluations, evaluation of the submission procedure
Subcommittee on Medicinal Products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Resolution on the requirement of routine practice data collection (amendment of Annex XII of the AM-RL)

Berlin, 21 December 2023

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

Prof. Hecken

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