Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Exagamglogene autotemcel (sickle cell disease with recurrent vaso-occlusive crises; ≥ 12 years; no HLA-matched related stem cell donor available)

of 3 July 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect

that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient exagamglogene autotemcel on 15 January 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 14 January 2025.

Exagamglogene autotemcel for the treatment of sickle cell disease is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

Exagamglogene autotemcel concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 April 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA have adopted their resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G25-05) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance

with the General Methods [1] was not used in the benefit assessment of exagamglogene autotemcel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Exagamglogene autotemcel (Casgevy) in accordance with the product information

Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Therapeutic indication of the resolution (resolution of 3 July 2025):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of exagamglogene autotemcel is assessed as follows:

Patients 12 years of age and older with severe sickle cell disease and recurrent vaso-occlusive crises for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-identical related stem cell donor is not available

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

Justification:

The pharmaceutical company presented the results of the pivotal phase I/II/III CLIMB-SCD-121 study and the CTX001-131 extension study for the benefit assessment of exagamglogene autotemcel for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-identical related HSC donor is not available. The CLIMB-SCD-121 study is a single-arm, open-label, multicentre study, in which 63 patients aged 12 up to and including 35 years with sickle cell disease and documented β^S/β^S, β^S/β^0 or β^S/β^+-SCD genotype and at least two vaso-occlusive crises (VOCs) per year in the two-year period prior to screening were enrolled.

The CLIMB-SCD-121 study is divided into 4 phases. Phase 1 involves screening and pre-mobilisation, phase 2 involves mobilisation and harvesting of autologous CD34+ stem cells as well as production of exagamglogene autotemcel, phase 3 involves myeloablative conditioning and infusion of exagamglogene autotemcel, and phase 4 involves follow-up for 24 months. After successful completion of the study, a transition to the CLIMB-CTX001-131 extension study was possible.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

The mobilisation of CD34-positive stem cells and myeloablation as well as the temporary discontinuation of standard medication are necessary steps prior to exagamglogene autotemcel infusion. Patients with sickle cell disease are at increased risk of inadequate mobilisation and apheresis.

Study participants received red blood cell concentrate transfusions for at least 8 weeks prior to the planned start of mobilisation to maintain HbS levels at < 30% and total Hb level at ≤ 11 g/dl for at least 8 weeks, and received these until the start of their conditioning; disease-modifying therapies (e.g. hydroxyurea/ hydroxycarbamide) had to be discontinued 8 weeks prior to the planned start of mobilisation and conditioning.

The benefit assessment was based on the 2nd data cut-off from 16 April 2023, as subsequently requested by the EMA. Within the framework of the written statement procedure, the pharmaceutical company subsequently submitted the 5th data cut-off from 2 January 2025. The following results relate to the current data cut-off from 2 January 2025.
Of the 63 patients enrolled, 17 (27.0%) discontinued treatment, 5 (7.9%) thereof prior to mobilisation and 12 (19.0%) prior to conditioning. The patients completed a median of 2 mobilisation cycles (min. 1; max. 6). Of the 12 subjects who discontinued the study during mobilisation, 7 discontinued the study because the required minimum quantity of cells was not reached. One subject discontinued the study because they no longer met the inclusion criteria for renal function, and another subject discontinued the study due to lack of compliance. Furthermore, 2 subjects withdrew their consent and one subject discontinued the study due to psychological and physical burden.[2]

The time from therapy initiation (start of mobilisation) to exagamglogene autotemcel infusion is considered an essential part of treatment. The ITT population is therefore used for the benefit assessment.

The primary efficacy endpoint was freedom from severe VOCs for 12 months (VF12).

The median duration of observation following the administration of exagamglogene autotemcel at the 5th data cut-off from 2 January 2025 is 38.2 months (min. 17.8; max. 67.1), with 40 (63.5%) study participants having reached 24 months of follow-up and 28 (44.4%) study participants 36 months.

Indirect comparisons

The pharmaceutical company also presented several adjusted indirect comparisons relating to the endpoint "Severe vaso-occlusive crises". For this, they use aggregated data from different comparator arms from randomised controlled trials (RCT) and carry out "Matching-Adjusted Indirect Comparisons" (MAIC). They also present an indirect comparison with patient-individual data. As part of the written statement procedure, the pharmaceutical company presented further indirect comparisons based on aggregated data on the endpoint "Severe vaso-occlusive crises". These include MAICs and naïve comparisons against control arms of phase III studies. MAICs and naïve evaluations against aggregated study arms are generally considered inappropriate in the context of a benefit assessment. In addition, there are different inclusion and exclusion criteria between the studies (e.g. age limits), which means that the study populations are different. The PES is used as the analysis population for the annualised rate, which is assessed as inappropriate. Based on the available documents,

[2] Module 4 of the dossier informs about the reasons for study discontinuation.

there are also deviating operationalisations of the endpoints (endpoint survey, survey duration) between the RCTs and the single-arm SCD-121 study for VOC survey, so that a comparison is not possible.

The non-randomised, adjusted indirect comparison with patient-individual data is assessed as inappropriate, even taking into account the data subsequently submitted in the written statement procedure. No naïve comparison based on patient-individual data was submitted. The subsequent evaluation refers to five instead of one matching partner and does not refer to the identified base population. The sample size in the submitted evaluation and the sample size in the submitted database differ. The reasons for the deviations could not be explained. Based on the data basis presented (reported baseline characteristics, analysis populations, confounder selection, time-zero, reporting of the model, deviations in the sample sizes), it cannot be assumed that there is sufficient statistical positivity of the two populations for an adjusted analysis.

Overall, the indirect comparisons presented are unsuitable for the research question of the benefit assessment.

On the results of the CLIMB-SCD-121 and CLIMB-CTX001-13 studies:

Mortality

Deaths were collected over the entire period of the CLIMB-SCD-121 and CLIMB-CTX001-131 studies.

Deaths - occurring during the study - related to exagamglogene autotemcel infusion or busulfan administration at the discretion of the investigators were collected as part of the safety assessment until the end of month 12 (or up to 100 days post infusion).

At the 5th data cut-off from 2 January 2025, one death which was assessed on a transplant-related basis occurred.

Morbidity

Severe vaso-occlusive crises

Sickle cell disease-associated vaso-occlusive pain crises and other vaso-occlusive complications felt by patients are considered patient-relevant events.

In the CLIMB-SCD-121 study, the event of a vaso-occlusive crisis was defined as:

- Acute pain requiring hospitalisation in a medical facility and the administration of painkillers (opioids or intravenous non-steroidal anti-inflammatory drugs (NSAIDs)) or blood transfusions,
- occurrence of an acute chest syndrome, which is characterised by the appearance of a new pulmonary infiltrate in conjunction with pneumonia-like symptoms, pain or fever,
- occurrence of priapism that lasts longer than 2 hours and requires hospitalisation in a medical facility, or
- occurrence of splenic sequestration, defined by an enlarged spleen, pain in the upper left quadrant and an acute drop in haemoglobin (Hb) concentration ≥ 2 g/dl.

The evaluations "Freedom from severe VOC for 12 months (VF12)", collected 60 days after the date of the last supportive RBC transfusion as well as the annualised rates compared between the baseline phase and the follow-up phase were presented. The latter are only available for the FAS population. VOCs occurring in the period between the treatment decision and transfusion are not taken into account in the submitted evaluations of the annualised rate.

Taking into consideration the observation period in the CTX001-131 study, 43 of 63 subjects in the ITT population reached VF12, collected 60 days after the date of the last supportive RBC transfusion.

The median freedom from severe VOC for those subjects who have achieved freedom from severe VOC is 33.4 months (min: 12.7; max: 64.5). If a subject has achieved several qualifying periods for VF12, the longest VF12 time is used for the evaluation. In an evaluation collected from the time of infusion without further restriction of the analysis population (FAS, N = 46), severe VOC occurred in 11 subjects post exagamglogene autotemcel infusion.
No statements on the extent of the additional benefit of exagamglogene autotemcel could be derived from these results due to the absence of comparator data.

No suitable data for the benefit assessment are available for the annualised rates of severe VOC. In particular, no data is available for the ITT population. The intra-individual comparison between the baseline phase and the follow-up phase also appears to be not indicated due to the non-deterministic course of the disease. There is also an imbalance in the analysis due to the different observation periods.

General information on patient-reported outcomes

The Patient-Reported Outcomes (PROs) are presented separately for adults and adolescents in the resolution. Of the 50 adults enrolled in the study, 34 (68.0%) received exagamglogene autotemcel. Of the 13 adolescents enrolled, 12 (92.3%) were treated with exagamglogene autotemcel. According to the study protocol, the PROs after baseline were collected for the first time 90 days post exagamglogene autotemcel infusion. Subjects who were not treated with exagamglogene autotemcel and for whom no PROs were collected in the further course of the study are included in the evaluation as non-responders. PROs were not collected during mobilisation and conditioning or immediately post exagamglogene autotemcel infusion.

Pain NRS-11

The "Pain Numeric Rating Scale" (Pain NRS-11) is an 11-point numeric rating scale for self-assessment of the intensity of the pain experienced. Adolescents and adults in the study were surveyed using the generic questionnaire. This is a one-dimensional assessment of pain intensity. The scale ranges from 0 to 10, with 0 representing "no pain" and 10 "the worst possible pain". The exact research question for assessing pain could not be identified in the study documents. It was therefore also not possible to identify the survey period of the research question regarding pain in the documents. The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant responder threshold of 15% are available.

In 13 patients in the age group from ≥ 18 to ≤ 35 years and in one subject in the age group from ≥ 12 to < 18 years, an improvement by 15% was achieved at month 24.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the Pain NRS-11.

EQ-5D-VAS

The visual analogue scale of the European Quality of Life 5-Dimension (EQ-5D-VAS) collects the self-assessment of the general health status. The study participants rated their health status on a vertical scale with scores ranging from 100 ("best perceivable health status") to 0 ("worst perceivable health status"). The youth version of the VAS is identical to the adult VAS.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation. Responder analyses on the improvement or deterioration of the relevant threshold of 15% are available.

In 13 patients in the age group from ≥ 18 to ≤ 35 years and in 4 patients in the age group from ≥ 12 to < 18 years, an improvement of 15% was achieved at month 24.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the EQ-5D-VAS.

Health status using ASCQ-Me

The "Adult Sickle Cell Quality of Life Measurement Information System" (ASCQ-Me) is a disease-specific multidimensional questionnaire for self-assessment of quality of life of adults with SCD. Furthermore, the "Sickle Cell Disease Medical History Checklist" (SCD-MHC) is collected by means of 9 questions, which are intended to describe the severity of the disease of a subject with SCD. The questions relate to symptoms, organ damage, bone damage and treatments which are characteristic of SCD and are answered with "yes" or "no" in each case. The scoring includes all questions that have been answered with "yes". A lower score indicates a better health status.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant responder threshold of 15% are available.

In 7 patients in the age group from ≥ 18 to ≤ 35 years, an improvement by 15% was achieved at month 24.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the ASCQ-Me SCD-MHC.

<u>Quality of life</u>

Quality of life using ASCQ-Me

The ASCQ-Me is a disease-specific multidimensional questionnaire for self-assessment of the quality of life of adults with sickle cell disease. The domains emotional burden, impairment due to pain, impairment due to pain crises (frequency), impairment due to pain crises (severity grade), sleep impairment, impairment of social life and impairment due to stiffness are assessed on a Likert scale.

In the domains "Impairment due to pain crises", a lower score indicates an improvement in quality of life; in the other domains, a higher score indicates an improvement.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant responder threshold of 15% are available. Responder analyses of the "raw scores" and the standardised T-score were presented.

In 10 to 28 patients in the age group from ≥ 18 to ≤ 35 years, an improvement by 15 % was achieved at month 24 in the respective individual domains: Emotional burden 11, impairment due to pain 11, impairment due to pain crises (frequency) 28, impairment due to pain crises (severity grade) 7, sleep impairment 10, impairment of social life and impairment due to stiffness 11.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the ASCQ-Me.

PedsQL

The PedsQL assesses the general health-related quality of life in children and adolescents and was used in the CLIMB-SCD-121 study in study participants who were at least 12 years old. The questionnaire consists of four multi-dimensional scales (physical, emotional, social and school functioning) and 3 summative scores (total score, physical health summative score, psychosocial health summative score). The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]); the values are then transformed into a scale from 1 to 100. Higher scores indicate a higher quality of life.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant 15% threshold are available.

In 6 patients in the age group from ≥ 12 to < 18 years, an improvement in the total score by 15% was achieved at month 24, in 7 patients in the individual health domain and in 6 patients in the psychosocial health domain.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the PedsQL.

PedsQL-SCD

The specific "PedsQL Sickle Cell Disease Module" (PedsQL-SCD) contains 9 scales: Pain and injury, pain effect, pain management and control, care I, care II, emotions, treatment. Communication I and communication II.

The module scales consist of parallel self-report and parent proxy report for children and adolescents aged 5 to 18 years and a parent proxy report for children aged 2 to 4 years.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant responder threshold of 15% are available.

In 6 patients in the age group from ≥ 12 to < 18 years, an improvement in the total score by 15% was achieved at month 24.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the PedsQL-SCD.

FACT-BMT

The "Functional Assessment of Cancer Therapy – Bone Marrow Transplantation" (FACT-BMT) is a questionnaire for self-assessment of health-related quality of life for subjects who have received a bone marrow transplant. The FACT-BMT consists of the "Functional Assessment of Cancer Therapy – General" (FACT-G) and the "Bone Marrow Transplantation Subscale" (BMTS), which assesses treatment-specific aspects of bone marrow transplantation. The FACT-BMT consists of 5 categories with a total of 50 questions, the following domains were assessed: Physical well-being (PWB), social/ family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), bone marrow transplantation subscale (BMTS).

Using a 5-point Likert scale from 0 to 4, a component with a reference period of 7 days is surveyed. In scoring, a high value means a higher quality of life. According to the information provided by the pharmaceutical company, the global scale was transformed from 0 to 200. The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation.

There are uncertainties regarding the transferability of the validity of the questionnaire to therapeutic indication of sickle cell disease. In addition, the scoring was not described in a sufficiently comprehensible manner. Due to the existing uncertainties, the endpoint is presented additionally in the benefit assessment.

The FACT-BMT total score showed an improvement by 15% at month 24 in 8 patients, the FACT-G total score in 12 patients and the BMTS in 8 patients.

<u>Side effects</u>

No study discontinuations due to adverse events were observed in the studies presented.

Adverse events (AEs) occurred in almost all patients in the studies. Severe AEs of grade ≥ 3 occurred in 91.4% of patients. In particular, these were AEs in the system organ classes "Blood and lymphatic system disorders", "Gastrointestinal disorders", "Investigations", "Metabolism and nutrition disorders", "General disorders and administration site conditions" and "Infections and infestations". Haematological and gastrointestinal side effects are characteristic of myeloablative therapy carried out prior to the administration of exagamglogene autotemcel. Serious AEs (SAEs) occurred in 65.5% of patients.

A conclusive assessment of the side effect profile of exagamglogene autotemcel is not possible due to the limited data on long-term safety and the lack of comparator data. Statements on the long-term side effect profile cannot be made without long-term data on the safety profile.

In summary, no conclusive statements on the extent of additional benefit can be derived from the data on side effects.

Overall assessment

The benefit assessment is based on the results of the single-arm, open-label CLIMB-SCD-121 study and the CLIMB-CTX001-131 extension study, from which results on mortality, morbidity, health-related quality of life and side effects are available. As these are single-arm studies, a comparative assessment and thus a quantification of the extent of the additional benefit is not possible on the basis of these data.

Overall, the adjusted and naïve indirect comparisons presented by the pharmaceutical company are unsuitable for the benefit assessment for the reasons mentioned above.

Overall, a non-quantifiable additional benefit is derived for exagamglogene autotemcel since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on the results of the single-arm, open-label CLIMB-SCD-121 study and the CLIMB-CTX001-131 extension study. As these are single-arm studies, a comparative assessment is not possible on the basis of these data. The significance of the evidence is therefore very limited and is therefore categorised as a "hint".

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Casgevy with the active ingredient exagamglogene autotemcel. Casgevy was approved under "exceptional circumstances" as an orphan drug.

The therapeutic indication assessed here is as follows: Treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

For the benefit assessment, the pharmaceutical company presented the results of the pivotal, single-arm, open-label, multicentre phase I/II/III CLIMB-SCD-121 study and the CLIMB-CTX001-131 extension study as well as indirect comparisons for the endpoint "Severe vaso-occlusive crises".

The data presented provides results on mortality, morbidity, quality of life and side effects. No statements on the extent of the additional benefit could be derived due to the absence of comparator data.

Overall, the adjusted and naïve indirect comparisons presented by the pharmaceutical company are unsuitable for the benefit assessment.

As a result, a hint for a non-quantifiable additional benefit of exagamglogene autotemcel is identified since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

In the information provided by the pharmaceutical company in the dossier for the benefit assessment on the derivation of the number of patients in step 3, the percentage value of 39% for recurrent VOC could not be reproduced on the basis of the cited publications. The pharmaceutical company did not submit any further information on this in the written statement procedure either. In addition, the steps in the pharmaceutical company's derivation are only occasionally provided with information on a lower or upper limit, which means that existing uncertainties are only reflected to a limited extent. An indicative estimate of the number of patients from IQWiG's RPDC concept for exagamglogene autotemcel (sickle cell disease) provides further information and sources that are considered to be a better estimate overall for the present resolution.[3] The resolution is therefore based on a separate derivation of the number of patients, which is orientated towards the patient numbers from the RPDC concept.

The prevalence of sickle cell disease in Germany was calculated based on data from the GPOH registry[4] (lower limit: 2,000) and an AOK routine data analysis[5], which was extrapolated to 2025 using an annualised growth rate of 7.25%[6] (upper limit 4,890).

The following calculation steps are used to narrow down this patient group to the target population:

1. The percentage of patients aged ≥ 12 years is 74.1% – 75.8% (1,482 - 3,645 patients).[7, 8]
2. The percentage of patients with ≥ 2 VOC per year is 22.9% – 81.5% (339 – 2,971) per year. The lower limit is based on a US healthcare data analysis of 20,909 patients with sickle cell disease in the period from 2009 to 2013.[9] In the routine data analysis, only VOCs that were subject to outpatient or inpatient treatment are collected. Medical treatment due to ≥ 2 VOC within one year was documented in 22.9% of patients. However, treatment by self-medication cannot be ruled out, which is why an underestimation can be assumed. The study by Rizio et al from 2020, which is based on a survey of 303 US patients with sickle cell disease, is therefore used to estimate the upper limit. Of these, 81.5% stated that they had experienced 2 or more VOCs

[3] Institute for Quality and Efficiency in Health Care. Exagamglogene autotemcel (sickle cell disease). URL: https://www.iqwig.de/download/a23-49_exagamglogen-autotemcel_abd-konzept_v1-0.pdf.
[4] Kunz JB, Lobitz S, Grosse R et al. Sickle cell disease in Germany: Results from a national registry. Pediatric Blood & Cancer 2020; 67(4): e28130. https://dx.doi.org/10.1002/pbc.28130.
[5] Kunz JB, Schlotmann A, Daubenbuchel A et al. Benefits of a Disease Management Program for Sickle Cell Disease in Germany 2011-2019: The Increased Use of Hydroxyurea Correlates with a Reduced Frequency of Acute Chest Syndrome. J Clin Med 2021; 10(19). https://dx.doi.org/10.3390/jcm10194543.
[6] Eleftheriou, A. & Angastiniotis M. (2021). Global Thalassaemia Review 2021, Thalassaemia International Federation.
[7] Kunz JB, Schlotmann A, Daubenbüchel A, Lobitz S, Jarisch A, Grosse R, et al. Age strata (SCD patients age >12; Disease Management Program for Sickle Cell Disease in Germany 2011-2019) as provided by the author upon request.
[8] Federal Statistical Office. Health; detailed diagnostic data of hospital patients [online]. 2018 [accessed: 14 August 2023]. URL: https://www.statistischebibliothek.de/mir/receive/DEHeft_mods_00131400
[9] Shah N, Bhor M, Xie L et al. Evaluation of Vaso-occlusive Crises in United States Sickle Cell Disease Patients: A Retrospective Claims-based Study. J Health Econ Outcomes Res 2019; 6(3): 106-117. https://doi.org/10.36469/9667

within a year. The majority of respondents (76.6%) also stated that they treated their VOC at home as they knew how to manage their pain.[10]
Both sources refer to the US healthcare context, which is why there are uncertainties regarding transferability.

3. The percentage of patients who are eligible for the treatment procedure (in particular myeloablative conditioning) is 54%. In the absence of further data, the percentage value stated by the pharmaceutical company in the dossier was used as a basis.
4. The percentage of patients for whom no HLA-matched, related HSC donor is available is 80 - 86% (147 – 1,380).[11,12]
5. Taking into account a percentage of SHI-insured patients of 88.99%, there are 130 – 1,228 patients in the therapeutic indication of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOC) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

The range of 130 to 1,228 patients represents a minimum and maximum estimate. The range takes into account the existing uncertainties to a greater extent than the estimate submitted by the pharmaceutical company.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Casgevy (active ingredient: exagamglogene autotemcel) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 25 March 2025):

https://www.ema.europa.eu/en/documents/product-information/casgevy-epar-product-information_en.pdf

Treatment with exagamglogene autotemcel should only be initiated and monitored by specialists who are experienced in the treatment of patients with sickle cell disease. Exagamglogene autotemcel must be used in a qualified treatment facility.

The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the use of ATMP exagamglogene autotemcel in the therapeutic indication of sickle cell disease. Further details are regulated in Annex VI "Exagamglogene autotemcel in β-thalassemia and sickle cell disease" of the ATMP Quality Assurance Guideline.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including patient identification card).

[10] Rizio AA, Bhor M, Lin X et al. The relationship between frequency and severity of vaso-occlusive crises and health-related quality of life and work productivity in adults with sickle cell disease. Qual Life Res 2020; 29(6): 1533-1547. https://dx.doi.org/10.1007/s11136-019-02412-5

[11] Hoferer A, Cario H, Corbacioglu S et al. Sickle cell diseases [online]. 2021 [accessed: 14 July 2023]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/sichelzellkrankheiten/@@guideline/html/index.html

[12] Walters MC, Patience M, Leisenring W et al. Barriers to bone marrow transplantation for sickle cell anemia. Biol Blood Marrow Transplant 1996; 2(2): 100-104

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for health professionals who prescribe, use or supervise the use of exagamglogene autotemcel includes information on the important identified risk of delayed platelet engraftment and the important potential risks of neutrophil engraftment failure and oncogenesis associated with genome editing and how to minimise these risks. It also contains instructions on how to provide the patient identification card and the guideline for patients.

The guideline for patients is intended to explain the risks and benefits of exagamglogene autotemcel treatment, the limited data on long-term effects, the signs of low platelet or leucocyte counts and blood cancers, as well as the need to report symptoms immediately to the treating doctor and to always carry the patient identification card with them.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the data of the product information and the data of the pharmaceutical company on the dispensing price from module 3 of the dossier.

Exagamglogene autotemcel is only dispensed to appropriately qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the sales price of the pharmaceutical company, in deviation from the usually taken into account data of the LAUER-TAXE®.

Exagamglogene autotemcel is administered as a single intravenous infusion according to the specifications in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Exagamglogene autotemcel	Single dose	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Exagamglogene autotemcel	3 x 10^6 CD34+ cells/kg BW	3 x 10^6 CD34+ cells/kg BW	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)[13]	Value-added tax[14]	Costs
Medicinal product to be assessed				
Exagamglogene autotemcel	1 single infusion bag	€ 2,200,000	-	€ 2,200,000

LAUER-TAXE® last revised: 15 June 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Exagamglogene autotemcel is a cell product produced from autologous CD34+ stem cells. Therefore, HSC mobilisation and leukapheresis are usually necessary to obtain the cell material. Since HSC mobilisation and leukapheresis are part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 of the Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

Prior to treatment with Casgevy, complete myeloablative conditioning must be carried out according to the product information. The conditioning regimen used in the clinical study and listed in the product information was carried out with busulfan.

The planned intravenously administered busulfan dose was 3.2 mg/kg/day once daily or 0.8

[13] Information from the pharmaceutical company on the sales price from module 3 of the dossier.
[14] According to the information provided by the pharmaceutical company, the medicinal product is exempt from value added tax.

mg/kg every 6 hours for 4 consecutive days. When administered once daily, the recommended AUC target range (0 - 24 h) was 4,500 – 5,500 µM*min and when administered every 6 hours, the AUC target range (0 – 6 h) was 900 – 1,350 µM*min.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: Adults = 77.7 kg[15]; 12-year-olds = 47.1 kg[16]).

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with exagamglogene autotemcel.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps[17]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.

Diagnostics to rule out hepatitis C requires sensibly coordinated steps[18]. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-RNA detection to confirm the diagnosis of an HCV infection.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Appropriate comparator therapy:							
Myeloablative conditioning with busulfan							
- Adults (3.2 mg/kg = 248.6 mg)	8 x 60 mg CIS	€ 1274.37	€ 1.77	€ 59.94	€ 1212.66	4	€ 3,637.98
- 12-year-olds (3.2 mg/kg = 150.7 mg)	8 x 60 mg CIS	€ 1274.37	€ 1.77	€ 59.94	€ 1212.66	4	€ 2,425.32
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43
HCV screening							
Hepatitis C	-	-	-	-	€ 9.02	1.0	€ 9.02

[15] Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de/
[16] Federal Statistical Office, Wiesbaden 2017: http://www.gbe-bund.de/
[17] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection; AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf
[18] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
HCV antibody status (GOP 32618)							
HIV screening							
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.09	1.0	€ 4.09
Abbreviations: CIS = concentrate for the preparation of an infusion solution							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients 12 years of age and older with severe sickle cell disease and recurrent vaso-occlusive crises for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-identical related stem cell donor is not available

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for exagamglogene autotemcel (Casgevy); Casgevy 4 – 13 × 10^6 cells/ml infusion dispersion; last revised: February 2025

2.6 Percentage of study participants at study centres within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Casgevy is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

According to Section 35a, paragraph 1, sentence 3, no. 7 SGB V, the calculation is based on all studies conducted or commissioned by the pharmaceutical company, which they must submit to the G-BA as part of the benefit assessment dossier in the therapeutic indication to be assessed. The approval studies include all studies that were submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed (see Section 4, paragraph 6, sentences 1 and 2 AM-NutzenV in conjunction with Chapter 5 Section 9, paragraph 4, sentences 1 and 2 VerfO).

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is ≥ 5% of the total number of study participants.

Section 2.7.4 of the Common Technical Document (CTD) does not clearly demarcate the studies submitted for the respective therapeutic indication. The percentage of study participants in the CLIMB-SCD-121 study was 0% and in the CLIMB-TDT-111 study it was 30.4%. Taking both studies into account, the total percentage of study participants is above 5%.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore conducted to a relevant extent within the scope of SGB V.

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

On 14 January 2025, the pharmaceutical company submitted a dossier for the benefit assessment of exagamglogene autotemcel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 April 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 6 May 2025.

The oral hearing was held on 26 May 2025.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 13 June 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 24 June 2025, and the draft resolution was approved.

At their session on 3 July 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 April 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	14 May 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	26 May 2025	Conduct of the oral hearing
Working group Section 35a	3 June 2025 17 June 2025	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	24 June 2025	Concluding discussion of the draft resolution
Plenum	3 July 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 July 2025

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

Prof. Hecken