Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Betibeglogene Autotemcel (β-Thalassaemia)

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 reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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, Nos. 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 € 50 million during the last twelve 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 medicinal 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of 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 provided is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by 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 in such a way 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 legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph, 1 sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient betibeglogene autotemcel in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 November 2019. 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, number 1 VerfO on 12 November 2019.

Betibeglogene autotemcel for the treatment of β-thalassaemia 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.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half 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 by the G-BA on the basis of the approval studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate 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 17 February 2020 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 has adopted its 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 G19-19) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for 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 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of betibeglogene autotemcel.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of betibeglogene autotemcel (Zynteglo®) in accordance with the product information

Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available (see sections 4.4 and 5.1).

2.1.2 Extent of the additional benefit and the significance of the proof

In summary, the additional benefit of betibeglogene autotemcel is assessed as follows.

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

Hint for a non-quantifiable additional benefit owing to the fact that the scientific data does not permit quantification

Justification:

For the benefit assessment, the pharmaceutical company presents findings from the studies HGB-204, HGB-205, HGB-207 and HGB-212, as well as supplementary findings from study LTF-303.

The studies presented are divided into four study stages: In stage 1 screening is performed, in stage 2 mobilisation and collection of autologous CD34+ stem cells and production of betibeglogene autotemcel, in stage 3 myeloablative conditioning and infusion of betibeglogene autotemcel, and in stage 4 follow-up for 24 months.

Before the actual treatment with betibeglogene autotemcel, the study therapy includes haematopoietic stem cell (HSC) mobilisation with filgrastim and plerixafor followed by apheresis and complete myeloablative conditioning with busulfan. Subsequently, in study HGB-207 patients received a single infusion of betibeglogene autotemcel containing a dose of ≥ 5.0×10^6 $CD34^+$ cells/kg. In studies HGB-205 and HGB-204 the cell dose was ≥ 3.0×10^6 $CD34^+$ cells/kg. The administered intravenous single dose was $8.79–13.6 \times 10^6$ $CD34^+$ cells/kg in study HGB-205 and $5.2–13.0 \times 10^6$ $CD34^+$ cells/kg in HGB-204. The study intervention is in accordance with the requirements in the product information, which state that the product should be administered as a single intravenous infusion at a minimum dose of 5.0×10^6 $CD34^+$ cells/kg. The intervention (including mobilisation, apheresis and conditioning) in study HGB-212 corresponds to the intervention in study HGB-207.

Only patients with transfusion-dependent β-thalassaemia with a history of transfusions with erythrocyte concentrates of at least 100 ml/kg/year within the last two years before inclusion into the study or receiving ≥ 8 transfusions with erythrocyte concentrates per year during the last two years before inclusion in the study were included in the studies.

Study HGB-204

HGB-204 is a completed open-label, single-arm, phase I/II dose-finding study in which patients with transfusion-dependent β-thalassaemia (regardless of genotype) aged 12 to 35 years were investigated. The study was conducted in Thailand, Australia and the USA between September 2013 and February 2018. In accordance with the marketing authorisation, only the eleven patients without a β^0/β^0 genotype are considered in the benefit assessment. Of these, one patient was excluded from the study due to insufficient mobilisation and collection of autologous CD34+ stem cells, and, therefore, ten patients were infused with betibeglogene autotemcel in phase III.

Study HGB-205

study HGB-205 is a completed open-label, single-arm, phase I/II dose-finding study in which 7 patients with β-haemoglobinopathies (severe sickle cell anaemia and transfusion-dependent β-thalassaemia, regardless of genotype) aged 5 to 35 years were investigated. The study was conducted in France between June 2013 and October 2017. In accordance with the marketing authorisation, only the four patients with transfusion-dependent β-thalassaemia without a β 0/β 0 genotype are considered in the benefit assessment.

Study HGB-207

HGB-207 is an ongoing open-label, single-arm, phase III study to evaluate the efficacy and safety of betibeglogene autotemcel in patients of ≤ 50 years of age with transfusion-dependent β-thalassaemia who do not have a β^0 or IVS-I-110 mutation on both HBB alleles. The study has been conducted in six countries (Germany, United Kingdom, Italy, France, Thailand and the USA) since August 2016. The primary endpoint is transfusion independence. In accordance with the marketing authorisation, only the 16 patients aged ≥ 12 years at the start of the study are considered in the benefit assessment. Of these, one patient withdrew from the study after mobilisation and before conditioning due to pregnancy, and, therefore, 15 patients were infused with betibeglogene autotemcel in phase III.

Study HGB-212

HGB-212 is an ongoing open-label, single-arm study (phase III) in which patients up to and including 50 years of age with transfusion-dependent β-thalassaemia were included. At the time of preparation of the dossier, the study was ongoing and no study findings were yet available. Patients with a mutation other than β0 on one allele were excluded, with the exception of IVS-I-110 mutations. Patients with a β^0/β^0 genotype do not correspond to the approved therapeutic indication. As four patients infused with betibeglogene autotemcel had an IVS-I-110 mutation on an HBB allele and were covered by the marketing authorisation for betibeglogene autotemcel, the data on the transfusion independence endpoint for these patients submitted by the pharmaceutical company in the written statement procedure will be considered in the benefit assessment.

Study LTF-303

LTF-303 is a long-term safety and efficacy follow-up study for patients with haemoglobinopathies who have completed the follow-up phase of the original studies. The study includes both patients with transfusion-dependent β-thalassaemia (TDT) and sickle cell disease (SCD). After administration of the study medication, patients in the study will be followed up every 6 months for the first 5 years and then annually for the 5 to 15 years thereafter.

As all the studies on betibeglogene autotemcel are open-label and non-randomised, in principle, a risk of bias for the study as a whole and for endpoints must be assumed. No indirect comparisons were submitted by the pharmaceutical company.

The analysis of efficacy endpoints was based on the transplant population, which included all patients receiving treatment with betibeglogene autotemcel. The transplant population differs from the ITT population, which included all patients receiving treatment in the study, commencing with mobilisation (study stage 2). The difference between the two underlying study populations comprises 2 patients, one patient each in studies HGB-204 and HGB-207 (see study description).

For HGB-207, the pharmaceutical company presented in its initial dossier analyses of the *a priori* planned interim data cut-off of 12 June 2019. When the dossier was being prepared, HGB-212 was ongoing, so findings from the study were not yet available, i.e. the included patients had not yet completed the necessary observation period of 12 months for the transfusion independence endpoint. To incorporate the findings of the study into the benefit assessment, the pharmaceutical company has submitted in its written statement the findings of a more recent data cut-off from 2 December 2019, which was evaluated at the request of the US regulatory authority (FDA) and the Italian HTA authority (AIFA). The data cut-off for

both studies is considered in the benefit assessment. No data on quality of life and safety are available for this data cut-off.

Mortality

Mortalities were recorded as safety events. No deaths occurred during the studies.

Morbidity

Transfusion independence

The transfusion independence (TI) endpoint is defined as a continuous period of at least 12 months without receiving transfusions of erythrocyte concentrates and a weighted mean Hb concentration of ≥ 9 g/dl at any time after infusion with betibeglogene autotemcel.

Long-term avoidance of transfusions (transfusion independence) while maintaining a defined minimum haemoglobin level is a patient-relevant endpoint in the present therapeutic indication, as this enables the primary therapeutic goal of avoiding anaemia to be achieved.

Transfusion-dependent β-thalassaemia is the result of anaemia caused by significantly reduced production of functional β-globin. This anaemia requires frequent and lifelong transfusions with erythrocyte concentrates. In addition, the required transfusions can, despite iron chelation therapy, lead to increasing iron overload of the organs and subsequent long-term complications.

Other endpoints related to transfusion independence (TI) (e.g. the time from infusion to achieving TI) are not presented in the resolution, as the data contain no information beyond that on transfusion independence. One exception is the current figure for mean TI duration in the studies, which is included in the resolution as a supplement as the endpoint “observed TI duration”.

The transfusion independence endpoint was collected in all the studies. In HGB-204 betibeglogene autotemcel treatment resulted in transfusion independence in 8 of 10 (80%) patients, and in HGB-205, in 3 of 4 (75%) patients. In HGB-207 at the time of the most recent data cut-off, 13 patients out of 15 (of these 14 patients had completed the required follow-up period) (86.7 %) were found to be transfusion-independent. In HGB-212 the figure was 1 patient out of 4 (25.0 %), of which 2 had already completed the required follow-up period. The majority (a mean of approx. 80 %) of patients in HGB-204, HGB-205 and HGB-207 were therefore found to be transfusion-independent after treatment with betibeglogene autotemcel. The median observation period is 19 to 56 months.

For the transfusion independence endpoint, neither direct nor indirect comparisons have been presented. However, due to the established natural course of the disorder, it cannot be assumed that patients suffering from transfusion-dependent β-thalassaemia will spontaneously achieve clinically-relevant higher haemoglobin levels in the natural course of their disorder and/or become independent of regular transfusions with erythrocyte concentrates.

Therefore, the data on transfusion independence very clearly demonstrate that, in comparison with the established natural course of the disorder, there is a significant benefit associated with betibeglogene autotemcel treatment with regard to the primary therapeutic objective in this therapeutic indication, namely prevention of anaemia.

VAS from EQ-5D(-Y)

General state of health was surveyed in HGB-207 by means of the VAS from the EuroQol 5-dimension questionnaire (EQ-5D-3L). The EQ-5D visual analogue scale (VAS) ranges from 0 to 100 and is employed by adult study participants to assess their health status. A value of 0 corresponds to the worst conceivable health status and a value of 100 to the best conceivable health status. In study participants aged 12–17 years, the VAS from the instrument EQ-5D-Y (the "youth version") was used.

The only EQ-5D(-Y) VAS data presented were those from from HGB-207. The findings are considered in the benefit assessment if data are available from at least 70% of the study participants. The return rates for EQ-5D VAS data (for persons ≥ 18 years of age) were over 70% at months 6 and 12, while for EQ-5D-Y VAS data (for persons ≥ 12 and ≤ 17 years of age) the return rate was over 70% at month 6 only. In each case, the resolution presents the most recently collected value with a return rate of over 70%.

On average, the EQ-5D VAS score has increased by 7.29 (SD: 10.44) to a mean score of 91.29 after 12 months compared to baseline, while the score from EQ-5D(-Y) has increased by 24.5 (SD: 20.8) to a mean score of 93.3 after 6 months.

In the absence of comparative data, the findings of the EQ-5D(-Y) endpoint cannot be used to derive any conclusions on the extent of the additional benefit.

Quality of life

Data on quality of life are collected in HGB-207 using PedsQL (Pediatric Quality of Life Inventory), SF-36 (36-Item Short Form Health Survey) and FACT-BMT (Functional Assessment of Cancer Therapy – Bone Marrow Transplant).

PedsQL

PedsQL captures general health-related quality of life in children and adolescents and was used in HGB-207 in study participants who were at least 12 years old. The questionnaire comprises four multi-dimensional scales (Physical Functioning, Emotional Functioning, Social Functioning and School Functioning) and three Summary Scores (Total Scale Score, Physical Health Summary Score and Psychosocial Health Summary Score). The items in the questionnaire employ a 5-point Likert scale from 0 (best function/never) to 4 (worst function/always); the scores are then transformed into a scale from 1 to 100. Higher values indicate a better quality of life.

In HGB-207, PedsQL is recorded at baseline and after 6, 12, 18 and 24 months. At the time of preparation of the benefit assessment, the study had not yet been completed. Its findings were considered if data were available from at least 70% of the study participants. The return rate for PedsQL was over 70% for month 6 only. In each case, the resolution presents the most recently collected value with a return rate of over 70%.

On average, the overall PedsQL score after 6 months has increased by 9.96 (SD: 24.30) points compared to baseline to a mean score of 80.98 points.

SF-36

The SF-36 questionnaire comprises eight dimensions aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores. PCS is scored

on the basis of physical functioning, role-physical, bodily pain and general health and vitality sub-scores. MCS is scored on the basis of vitality, social functioning, role-emotional and emotional well-being sub-scores. Scores range from 0 to 100, with a higher value reflecting a better health status.

In HGB-207, SF-36 is recorded at baseline and after 6, 12, 18 and 24 months. At the time of preparation of the benefit assessment, the study had not yet been completed. Its findings were considered if data were available from at least 70% of the study participants. The return rate for SF-36 was over 70% for months 6 and 12. In each case, the resolution presents the most recently collected value with a return rate of over 70%.

On average, the overall SF-36 – PCS score after 12 months has increased by 2.72 (SD: 2.81) compared to baseline to a mean score of 55.75. On average, the overall SF-36 – MCS score after 12 months has increased by 1.61 (SD: 9.41) compared to baseline to a mean score of 50.20.

FACT-BMT

FACT-BMT is a 47-item instrument that assesses five dimensions of quality of life in people who have undergone bone marrow transplantation; it is composed of the generic FACT-G instrument and the 23-item BMT sub-scale.

The BMT sub-scale comprises 23 items and a maximum score of 40; the FACT-BMT total score is 148. The BMT sub-scale employed cannot be considered as validated and is therefore not drawn on for the benefit assessment. The presentation of the findings are limited to the recorded FACT-G scores, which do not include the BMT sub-scale. FACT-G questions are answered by patients on a scale from 0 (Not at all) to 4 (Very much) and transformed to produce a total score from 0 to 108, a higher score indicating a better state of health.

In HGB-207, FACT-BMT is recorded at baseline and after 3, 6, 12, 18 and 24 months. At the time of preparation of the benefit assessment, the study had not yet been completed. Its findings were considered if data were available from at least 70% of the study participants. The return rate for FACT-BMT was over 70% only for months 6 and 12. In each case, the resolution presents the most recently collected value with a return rate of over 70%.

On average, the overall FACT-G score after 12 months has increased by 4.62 (SD: 14.22) compared to baseline to a mean score of 97.95.

The changes in the quality of life endpoint category were reported descriptively, and no assessment of clinical relevance was performed. Without comparative data, no conclusions can be drawn about changes in quality of life as assessed by PedsQL, SF-36 and FACT-BMT.

In summary, no conclusions can be drawn from the quality of life endpoints on the extent of the additional benefit.

<u>Side effects</u>

In the studies presented, no study withdrawals due to adverse events were recorded.

Adverse events (AE) occurred in almost all patients in the studies. Severe AEs of grade ≥ 3 occurred in 93.8% of the participants in HGB-207 and in 100% and 91% of the participants, respectively, in HGB-205 and HGB-204. These were primarily AEs of the system organ classes “blood and lymphatic system disorders” and “gastrointestinal disorders”. Haematological and gastrointestinal side effects are characteristic for the myeloablative therapy performed before

administration of betibeglogene autotemcel. Serious AEs (SAEs) occurred in 56.3 % of the participants in HGB-207 and in 75% and 54.5% of patients in HGB-205 and HGB-204.

A conclusive assessment of the adverse effect profile of betibeglogene autotemcel cannot be made due to the limited data on long-term safety and the lack of comparative data. In the absence of long-term data on the safety profile, which will be gathered, among other things, in the follow-up study LTF-303, no conclusions on the drug's long-term adverse reaction profile can be made, in particular regarding a potential risk of insertional mutagenesis, which might lead to the development of malignancy.

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

Overall assessment

For the benefit assessment of betibeglogene autotemcel in the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype, data were employed from the open, uncontrolled, ongoing phase III study HGB-207 and the open, uncontrolled, completed phase I/II dose-finding studies HGB-205 and HGB-204, as well as data on the transfusion independence endpoint of the open, uncontrolled, ongoing phase III study HGB-212 and supplementary data from the ongoing follow-up study LTF-303. These studies provide findings on mortality, morbidity, quality of life and side effects.

With the exception of the transfusion independence endpoint, the lack of comparative data prevents any conclusions from being drawn regarding the extent of the additional benefit for any of the patient-relevant endpoints collected in the studies.

The data on transfusion independence very clearly demonstrate that, in comparison with the established natural course of the disorder, there is a significant benefit at endpoint level associated with betibeglogene autotemcel treatment with regard to the primary therapeutic objective in this therapeutic indication, namely, prevention of anaemia.

However, no estimate can be made as to the extent to which transfusion independence exhibited by the majority of patients leads to avoidance of potential complications arising due to the routine transfusions with erythrocyte concentrates already performed. In particular, it remains unclear to what extent iron chelation therapy is still necessary in patients who have achieved transfusion independence. The information provided by the pharmaceutical company in the dossier indicates that only 13 of 32 patients (40.6%) in HGB-204, HGB-205, HGB-207 and HGB-212 were able to discontinue chelation therapy at the time of the data cut-off on 12 June 2019 (operationalised as discontinuation of chelation therapy for at least six months).

Overall, the additional benefit identified for betibeglogene autotemcel is considered to be non-quantifiable, due to the fact that quantification is not possible on the basis of the available scientific data.

Significance of the evidence

The benefit assessment draws on the findings from the open, uncontrolled studies HGB-204, HGB-205 and HGB-207, as well as the findings on the TI endpoint from study HGB-212.

As none of the presented studies have a control arm, it is assumed that there is a fundamentally high risk of bias at study and endpoint levels.

Owing to the small number and limited selection of patients in the studies due to their comprehensive inclusion and exclusion criteria, there are still uncertainties regarding the proportion of patients in the therapeutic indication who achieve transfusion independence after treatment with betibeglogene autotemcel and regarding the durability of transfusion independence. Further uncertainties exist due to the lack of data on the long-term safety of treatment with betibeglogene autotemcel.

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of betibeglogene autotemcel finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Treatment with betibeglogene autotemcel represents a novel therapeutic approach, the long-term effects of which cannot be fully assessed at present, particularly with regard to the drug's safety profile and the durability of transfusion independence in patients. The present limitation is intended to enable further findings on the long-term effects of autotemcel on patient-relevant outcomes to be included in a renewed benefit assessment.

Conditions of the limitation:

A renewed benefit assessment is to be based on the final findings of the studies HGB-207 and HGB-212, as well as on the 5-year follow-up data of the study LTF-303.

In line with the conditions imposed by the EMA, a renewed benefit assessment should also include data from a registry study on the long-term safety and efficacy of betibeglogene autotemcel in patients aged 12 years and older with TDT who do not have a β 0 /β 0 genotype. The registry study should compare data from the product registry REG-501 with data from patients treated with transfusions from an established European registry.

For this purpose, the G-BA considers a limitation of the resolution until 15 May 2025 to be appropriate.

In principle, an extension may be granted if it is justified and clearly demonstrated that the period of the limitation is not sufficient.

In accordance with Section 3, paragraph 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of betibeglogene autotemcel shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of betibeglogene autotemcel (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO).

The possibility that a benefit assessment for betibeglogene autotemcel can be carried out at an earlier point in time for other reasons (cf. Chapter 5, Section 1 paragraph 2, nos 2–6 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Zynteglo® with the active ingredient betibeglogene autotemcel. Betibeglogene autotemcel has been approved as an orphan drug subject to “special conditions” and is indicated for patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

For the benefit assessment of betibeglogene autotemcel data were employed from the open, uncontrolled, ongoing phase III study HGB-207 and the open, uncontrolled, completed phase I/II dose-finding studies HGB-205 and HGB-204, as well as data on the transfusion independence endpoint of the open, uncontrolled, ongoing phase III study HGB-212 and supplementary data from the ongoing follow-up study LTF-303. These studies provide findings on mortality, morbidity, quality of life and side effects.

With the exception of the transfusion independence endpoint, the lack of comparative data prevents any conclusions from being drawn regarding the extent of the additional benefit for any of the patient-relevant endpoints collected in the studies.

The data on transfusion independence very clearly demonstrate that, in comparison with the established natural course of the disorder, there is a significant benefit at endpoint level associated with betibeglogene autotemcel treatment with regard to the primary therapeutic objective in this therapeutic indication, namely, prevention of anaemia.
It remains unclear, however, to what extent the transfusion independence exhibited in the majority of patients prevents the complications that may arise following previous routine transfusions with red cell concentrates and to what extent iron chelation therapy is still necessary in patients who have achieved transfusion independence.

As none of the presented studies have a control arm, it is assumed that there is a fundamentally high risk of bias at study and endpoint levels. In addition, based on the available data, there are still uncertainties regarding the percentage of patients in the therapeutic indication who achieve transfusion independence after treatment with betibeglogene autotemcel, regarding the durability of such transfusion independence and regarding the drug’s long-term safety.

In the overall view, there is a hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

The resolution is limited until 15 May 2025.

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). The G-BA bases the resolution on the estimate of the number of patients derived by the pharmaceutical company in the dossier. However, the number of patients indicated is subject to uncertainties.

As β-thalassaemia has hitherto not been systematically recorded in Germany, the first step in the manufacturer’s calculation is a routine data analysis based on the research database of the Institute for Applied Health Research Berlin (InGef). The manufacturer’s next step is to

calculate on the basis of published papers the percentage of patients with β-thalassaemia who do not have an β 0 /β 0 genotype and for whom no HLA-compatible, related HSC donor is available. The manufacturer's calculations, however, do not take into account whether patients may be eligible for a haematopoietic stem cell transplantation. In addition, it is not clear from the specified papers how the manufacturer arrives at a figure of 47% of β thalassaemia patients who do not have the β 0/ 0 genotype. It should therefore be assumed that the number of patients in the SHI target population specified by the entrepreneur is an overestimate.

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 Zynteglo® (active ingredient: betibeglogene autotemcel) at the following publicly accessible link (last access: 30 April 2020):

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

Under the terms of marketing authorisation, treatment with Zynteglo may only be carried out in qualified treatment facilities and must be initiated and monitored by doctors who are experienced in transplantation of haematopoietic stem cells and treatment of patients with transfusion-dependent β-thalassaemia.

According to the German product information, the marketing authorisation holder must guarantee that, above and beyond routine risk minimisation measures, a system to control distribution of Zynteglo has been established. To ensure the traceability of the patient's cells and the manufactured medicinal product between the treating hospital and the manufacturing facility, Zynteglo may only be supplied by treatment facilities that have been certified by the marketing authorisation holder. The choice of treatment facilities is to be made, where appropriate, in cooperation with national health authorities.

Regarding additional measures for risk minimisation, the pharmaceutical company must provide officially approved training material for medical personnel and an information package including a patient identification card for patients.

As per the German FI, patients are expected to enrol in a registry and participate in long-term follow-up within the registry to improve understanding of the long-term safety and efficacy of Zynteglo.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

The regulations under Section 35a paragraph 3b and Section 136a paragraph 5 SGB V remain unaffected by this.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2020).

In accordance with the product information, betibeglogene autotemcel is to be administered as a single intravenous infusion.

Treatment duration:

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

Usage and 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					
Betibeglogene autotemcel	5–20 × 10^6 CD34+ cells/kg	5–20 × 10^6 CD34+ cells/kg	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal product:

Betibeglogene autotemcel is listed in the LAUER-TAXE® but is only sold as a hospital pack. The active ingredient is therefore currently not subject to the Pharmaceutical Price Ordinance, and there are no rebates according to Section 130 or Section 130a SGB V. The calculation is based on the purchase price of the clinic package plus 19% value added tax. This differs from the information usually taken into account in LAUER-TAXE®.

Designation of the therapy	Package size	Costs (purchase price of clinic pack plus value added tax)
Betibeglogene autotemcel	1 single infusion bag	€ 1,874,250

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2020

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 medical treatment or the prescription of other services when using the medicinal product to be assessed 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 standard expenditure in the course of the treatment are not shown.

Betibeglogene autotemcel is a cell product produced from autologous CD34+ stem cells. Leukapheresis and HSC mobilisation is, therefore, always necessary to obtain the cell material. Because HSC mobilisation and leukapheresis are part of the manufacture of the medicinal product under Section 4 paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

In compliance with the product information, a complete myeloablative conditioning with busulfan must be performed before treatment with Zynteglo. For patients aged ≥ 18 years the proposed busulfan dose was 3.2 mg/kg/day, administered as a daily 3 hour IV infusion for 4 days with a recommended target AUC for 0–24 h of 3800–4500 µM*min. For patients aged 12–17 years the proposed busulfan dose was 0.8 mg/kg/day, administered as a 2-hour IV infusion every 6 hours with a total of 16 doses and a recommended target AUC for 0–6 h of 950–4500 µM*min.

The average body weight from the official representative statistics “Microcensus 2017 – body measurements of the population” were used to calculate the dosages as a function of the body weight (the average body weight of adults is 77.0 kg; the average body weight of 12-year-olds is 47.1 kg).[2]

German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Applications	Costs/patient/year
Medicinal product to be assessed							
Complete myeloablative conditioning with busulfan							
Busulfan 12-year-olds (0.8 mg/kg = 37.7 mg)	8 x 60 mg CIS	€ 2,989.26	€ 1.77	€ 143.52	€ 2,843.97	16 –	€ 5,687.94
Busulfan Adults (3.2 mg/kg = 246.4 mg)	8 x 60 mg CIS	€ 2,989.26	€ 1.77	€ 143.52	€ 2,843.97	4	€ 8,531.91
Abbreviations: CIS = Concentrate for the preparation of an infusion solution							

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2020

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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 12 November 2019, the pharmaceutical company submitted a dossier for the benefit assessment of betibeglogene autotemcel to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 17 February 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 3 March 2020.

The oral hearing was held on 24 March 2020.

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 were discussed at the session of the subcommittee on 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	24 February 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	17 March 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 March 2020	Conduct of the oral hearing
Working group Section 35a	31 March 2020 7 April 2020 21 April 2020	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution
Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

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

Prof. Hecken