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
Somapacitan (growth failure due to growth hormone deficiency, ≥ 3 to < 18 years; growth hormone deficiency in adults)

of 2 May 2024

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 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 German Social Code, Book Five (SGB V). 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 its 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 its 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 somapacitan on 1 November 2023 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 26 October 2023.

Somapacitan for the treatment of growth failure due to growth hormone deficiency is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

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 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 2 February 2024 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) 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 has evaluated the studies relevant for the approval 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 somapacitan.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Somapacitan (Sogroya) in accordance with the product information

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).

Therapeutic indication of the resolution (resolution of 2 May 2024)

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

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

a) Children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency

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

b) Adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated

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

Justification for patient population a)

For the assessment of the additional benefit of somapacitan for children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency, the pharmaceutical company submitted the label-enabling REAL 4 study and the supportive REAL 3 study. The REAL 4 (phase III study) and REAL 3 (phase II study) studies are randomised, open-label, actively controlled studies comparing somapacitan administered once a week with somatropin administered daily.

The REAL 4 study is divided into a 52-week comparator treatment phase and a 156-week, single-arm, open-label safety extension phase. The patients were randomised in a 2:1 ratio to the two treatment groups with somapacitan (N=132) and somatropin (N=68). Randomisation was stratified by region, age group, sex and highest measured GH concentration in the stimulation test.

Therapy-naive, prepubertal children (boys aged ≥ 2.5 years and ≤ 11 years; girls aged ≥ 2.5 years and ≤ 10 years) in Tanner stage 1 were enrolled. GHD diagnosis was carried out by 2 different GH stimulation tests with the highest measured GH concentration of ≤ 10 ng/ml and performed within 12 months prior to randomisation. For children with ≥ 3 pituitary hormone deficiencies, only one GH stimulation test was necessary.

The REAL 3 study comprises a 52-week controlled treatment phase and a 104-week controlled safety extension phase. The patients were randomised in a 1:1:1:1 ratio to the 3 different

doses of treatment with somapacitan once a week (0.04 or 0.08 or 0.16 mg/kg/week) or treatment with somatropin once a day (0.034 mg/kg/day). Stratification was carried out according to region, age group and sex. For the benefit assessment, the dosage of 0.16 mg/kg/week somapacitan (N=14) compared to somatropin (N=14) was taken into account according to the product information.

The study enrolled prepubertal children (boys aged ≥ 2.5 years and ≤ 10 years; girls aged ≥ 2.5 years and ≤ 9 years) in Tanner stage 1 who had not previously received treatment with growth hormone or insulin-like growth factor 1 (IGF-1). GHD diagnosis was carried out by 2 different GH stimulation tests with the highest measured GH concentration of ≤ 7 ng/ml and performed within 12 months prior to screening. For children with ≥ 3 pituitary hormone deficiencies, only one GH stimulation test was necessary.

The patients enrolled in the REAL 3 and REAL 4 studies showed reduced body height and growth rate (determined by the annualized growth rate below the 25th percentile for chronological age and sex according to Prader's standards) as well as a lower bone age than the chronological age.

The primary endpoint of the REAL 3 and REAL 4 studies was the annualized growth rate in cm/year after 52 weeks of treatment. Apart from the primary endpoint, endpoints of the categories mortality, morbidity, quality of life and side effects were collected in both studies.

Mortality

There were no deaths in the REAL 3 and REAL 4 studies.

Morbidity

Body height (z score)

The anthropometric parameter of height is assessed as a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disturbances. Data adjusted for age and sex (z-scores) are preferred over absolute values.

Body height was recorded as standing height (not length) as well as age and sex-adjusted z scores were calculated. The z scores reflect the number of standard deviations (SD) of a value from the normal mean scores, standardised by age and sex. The data were presented as SD values above or below the age-specific reference (≙ 0). A sample of the US general population in the survey periods from 1963 to 1994 was used as comparator data for the z scores. Country-specific z scores were not taken into account.

In the REAL 4 study, there was no statistically significant difference between somapacitan (N=132) and somatropin (N=68) at week 52 for the endpoint "body height (z score)".

In the REAL 3 study, there was a statistically significant difference in favour of somapacitan (N=14) compared to somatropin (N=14) at week 52 for the endpoint "body height (z score)". The statistically significant difference in favour of somapacitan over somatropin is also evident in the long-term data at week 156. However, the clinical relevance of the difference cannot be conclusively assessed.

Due to the high heterogeneity, there was no meta-analytic summary of the results of the REAL 4 and REAL 3 studies at week 52.

Growth rate

The primary endpoint growth rate describes the annual increase in standing height [cm/year] and is only presented additionally, as it does not provide any information on growth other than standing height for the benefit assessment.

For the growth rate endpoint, a statistically significant difference between the treatment groups was seen at week 52 in the REAL 3 study, but not in the REAL 4 study. At week 156, there was no statistically significant difference between the two treatment groups in the REAL 3 study either.

Quality of life

Growth Hormone Deficiency – Child Impact Measure (GHD-CIM) ObsRO

The GHD-CIM ObsRO is a disease-specific instrument for assessing the GHD burden of children and adolescents aged 4 to under 13 years of age. The ObsRO version of the questionnaire used in the REAL 4 and REAL 3 studies is completed by the child's parents or guardians, based on their observations of the child's daily life and health.

In the REAL 4 and REAL 3 studies and on the basis of the meta-analysis, there was no statistically significant difference between somapacitan and somatropin - neither in the overall score nor in the three individual domains of the GHD-CIM ObsRO. There was also no statistically significant difference in the GHD-CIM ObsRO at week 156 in the REAL 3 study.

Growth Hormone Deficiency – Child Treatment Burden Measure (GHD-CTB ObsRO)

The GHD-CTB is a disease-specific instrument to assess the extent of the burden of therapy by injection in children with GHD aged 4 to < 13 years. The ObsRO version of the questionnaire used in the REAL 3 and REAL 4 studies is completed by the child's parents or guardians.

With the statement, the pharmaceutical company provides additional information on the validity of the GHD-CTB ObsRO. Despite its multidimensionality, the GHD-CTB ObsRO only covers a sub-aspect of the quality of life with the injection-related burden of therapy.

Therefore, the results of the GHD-CTB of the two studies are only presented in addition to the quality of life based on the GHD-CIM.

For the GHD-CTB endpoint, there was no statistically significant difference in the total value between the treatment groups in the REAL 3 and REAL 4 studies at week 52. The meta-analysis showed a statistically significant advantage in favour of somapacitan. However, the clinical relevance of the observed effect cannot be deduced from Hedge's g.

In the REAL 3 study, the evaluations of the long-term data at week 156 show a statistically significant difference in favour of somapacitan over somatropin in the total value and in the physical domain of the GHD-CTB ObsRO. Based on the Hedge's g, however, a clinically relevant effect can only be derived for the "physical domain".

When interpreting the results, it must be taken into account that the patients in both studies are in the lower range of possible GHD-CTB values (0-100) and therefore have a low burden of therapy.

In the overall assessment, no advantage can be derived for the quality of life category.

Side effects

At week 52, there were no statistically significant differences between somapacitan and somatropin for the endpoints of severe AEs, SAEs and AEs that led to discontinuation of study medication, neither in the REAL 4 study nor in the REAL 3 study. The long-term data at week 156 of the REAL 3 study also showed no statistically significant differences between the treatment arms for these endpoints.

Overall assessment

For the assessment of the additional benefit of somapacitan for children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency, the pharmaceutical company submitted the label-enabling REAL 4 study and the supportive REAL 3 study. The REAL 4 (phase III study) and REAL 3 (phase II study) studies are randomised, open-label, actively controlled studies comparing somapacitan administered once a week with somatropin administered daily.

There were no deaths in both studies.

For the endpoint category of morbidity, there was no statistically significant difference between the treatment groups for the endpoint "body height (z score)" in the REAL 4 study. In the REAL 3 study, there was a statistically significant advantage of somapacitan over somatropin for this endpoint at week 52 and week 156. Overall, however, the statistically significant difference in the endpoint "body height (z score)" cannot be conclusively assessed with regard to its clinical relevance, so that no conclusions can be drawn on the extent of the additional benefit.

For the endpoint category of quality of life, neither the REAL 4 nor the REAL 3 study showed a statistically significant difference between somapacitan and somatropin based on the GHD-CIM ObsRO. For the GHD-CTB ObsRO endpoint, only the long-term data from week 156 of the REAL 3 study showed a statistically significant and clinically relevant effect in favour of somapacitan over somatropin in the physical domain. Overall, no advantages can be derived in the quality of life category.

In the category of side effects, the overall assessment showed neither advantages nor disadvantages of somapacitan over somatropin.

The overall assessment showed a non-quantifiable additional benefit of somapacitan for children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency because the scientific data basis does not allow quantification.

Significance of the evidence

The risk of bias of the open-label, randomised, actively controlled REAL 4 and REAL 3 studies is classified as high due to the lack of blinding.

The risk of bias for the GHD-CIM ObsRO endpoint of the quality of life category is classified as high in both studies due to the lack of blinding and in the REAL 4 study additionally due to the high percentage of missing values at baseline in both treatment arms. Furthermore, the risk of bias for the GHD-CTB ObsRO endpoint of the quality of life category is classified as high in both studies due to the lack of blinding and in the REAL 3 study additionally due to the very high differences in the return rates between the treatment arms. Due to the further uncertainties in the validation of the instrument, the overall reliability of data is considerably limited.

For the endpoint "body height (z score)", the risk of bias is classified as low up to week 52 in both studies, despite the open-label study design.

Furthermore, a cut-off of ≤ 10 ng/ml and ≤ 7 ng/ml in the highest measured GH concentration in two different GH stimulation tests were defined as inclusion criterion in the REAL 4 and REAL 3 studies. According to the current S2e guideline, a cut-off of < 8 ng/ml at the highest GH concentration measured in two GH stimulation tests is recommended for the diagnosis of GHD in childhood and adolescence. There is therefore uncertainty as to whether less severely affected patients were enrolled in the REAL 4 study.

Overall, the results on patient-relevant endpoints from the REAL 3 and REAL 4 studies do not allow a quantification of the extent of additional benefit in the overall assessment.

The overall significance of the results is low here, which is why the significance of the evidence is classified in the "hint" category.

Justification for patient population b)

For the assessment of the additional benefit of somapacitan for adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated, the pharmaceutical company presented the REAL 1, REAL 2 and REAL JP studies. The studies are each randomised, open-label, actively controlled phase III studies comparing somapacitan administered once a week with somatropin administered daily. The transferability of the results of the Japanese REAL JP study to the German healthcare context cannot be conclusively assessed, but is used for the benefit assessment due to a lack of evidence of a lack of transferability.

In the REAL 1 study, the study participants were randomised in a 2:2:1 ratio (somapacitan: somatropin: placebo) into the treatment groups; stratified by region, sex and diabetes status. The study is divided into a screening phase, a 35-week direct comparator phase and a subsequent extension phase. For the benefit assessment, the actively controlled comparison of somapacitan (N=121) versus somatropin (N=119) during the 35-week direct comparator study phase is taken into account. Adults aged between 23 and 79 years with diagnosed GHD were enrolled.

In the REAL 2 study, study participants were randomised in a 2:1 ratio to the somapacitan (N=61) and somatropin (N=31) treatment groups, stratified by region, sex and diabetes status. The study is divided into a screening phase and a 27-week direct comparator study phase. The study enrolled adults aged 18 to 79 years with diagnosed GHD who had already been treated with human growth hormone.

In the REAL JP study, the study participants were randomised in a 3:1 ratio to the somapacitan (N=46) and somatropin (N=16) treatment groups; stratified by sex. The study is divided into a screening phase and a 53-week direct comparator study phase. The study enrolled adults aged 18 to 79 years with diagnosed GHD who had already been treated with human growth hormone.

The primary endpoint of the REAL 1 study was the change in truncal fat percentage at week 34. The primary endpoint of the REAL 2 and REA JP studies was the incidence of adverse events (including reactions at the injection site). In addition, endpoints of the categories mortality, quality of life and side effects were collected.

When interpreting the study results, it should be taken into account that in the REAL 1, REAL 2 and REAL JP studies, it can be assumed that patients in the somapacitan intervention arms were under-treated due to shortened dose titration phases.

Mortality

There were no deaths in the REAL 1, REAL 2 and REAL JP studies.

Morbidity

Change in truncal fat percentage

In the REAL 1 study, various body composition parameters (including changes in the truncal fat percentage) were measured using whole-body dual-energy X-ray absorptiometry at screening and at week 34.

The primary endpoint "change in truncal fat percentage at week 34" of the REAL 1 study was not included in the benefit assessment due to lack of patient relevance. Furthermore, there are no morbidity endpoints relevant for the benefit assessment.

Quality of life

Health Survey Short Form 36 (SF-36), Version 2

SF-36 is a generic instrument for measuring health-related quality of life, consisting of eight domains and a total of 36 questions. In addition, the 8 domains are summarised into a physical sum scale and a mental sum scale. For the domain and sum scores, higher values mean a better health-related quality of life.

In the REAL 1 study, there was no statistically significant difference between the treatment arms, neither in the physical nor in the psychological sum scale.

Treatment Related Impact Measure – Adult Growth Hormone Deficiency (TRIM-AGHD)

The TRIM-AGHD is a disease-specific, patient-reported questionnaire with 27 items, 26 of which are summarised into 4 domains (energy, psychological/emotional, cognitive and physical). A single item without a domain affects the general energy level. The questions refer to the point in time at which the questionnaire is answered. The items are answered on a 5-point Likert scale for either frequency or severity. Lower values correspond to a better health status.

In the REAL 1 study, the TRIM-AGHD at week 34 showed a statistically significant difference to the disadvantage of somapacitan compared to somatropin. When interpreting this

disadvantage, however, a probable under-treatment of patients in the somapacitan arm must be taken into account. Against this background, the effect cannot be conclusively assessed.

In the REAL 2 and REAL JP studies, no quality of life endpoints were collected.

Overall, the data show neither advantages nor disadvantages for the quality of life category.

Side effects

In the REAL 1 and REAL 2 studies, there was no statistically significant difference between the treatment arms for the endpoints of severe AEs and SAEs.

In the REAL 1 study, there was a statistically significant advantage in favour of somapacitan in the endpoint of AEs that led to discontinuation of the study medication. When interpreting this advantage, however, the probable under-treatment of patients in the somapacitan arm must also be taken into account. The extent to which a longer dose adjustment period, as provided for in the product information, leads to higher doses of somapacitan and these cause further AEs cannot be assessed. Overall, therefore, neither advantages nor disadvantages can be derived in the side effects category.

In the REAL JP study, no severe AEs occurred in either treatment arm. There was no statically significant difference between the two treatment arms for the endpoints of SAEs and AEs that led to discontinuation of the study medication.

Overall assessment

For the assessment of the additional benefit of somapacitan for adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated, the pharmaceutical company presented the REAL 1, REAL 2 and REAL JP studies. The studies are each randomised, open-label, actively controlled phase III studies comparing somapacitan administered once a week with somatropin administered daily.

There were no deaths in the REAL 1, REAL 2 and REAL JP studies.

The primary endpoint "change in truncal fat percentage at week 34" of the REAL 1 study was not included in the benefit assessment due to lack of patient relevance. Furthermore, there are no relevant endpoints for the benefit assessment for the morbidity endpoint category.

In the REAL 1 study, there was no statistically significant difference between the treatment groups in the quality of life endpoint category based on the SF-36 at week 34. Based on the TRIM-AGHD, the REAL 1 study showed a statistically significant disadvantage of somapacitan compared to somatropin at week 34, which cannot be conclusively assessed due to the under-treatment in the verum arm.

In the endpoint category of side effects, the REAL 1 study showed a statistically significant advantage in favour of somapacitan for the endpoint of AEs that led to discontinuation of the study medication. When interpreting the results, however, a probable under-treatment of patients in the somapacitan arm must be taken into account.

Overall, therefore, no advantages or disadvantages can be derived in the categories of quality of life and side effects.

Therefore, the overall assessment showed a non-quantifiable additional benefit for adults with growth hormone deficiency for whom replacement of endogenous growth hormone is indicated, because the scientific data basis does not allow quantification.

Significance of the evidence

The risk of bias of the open-label, randomised, actively controlled REAL 1, REAL 2 and REAL JP studies is classified as high due to the lack of blinding.

The overall significance of the results is low, which is why the significance of the evidence is classified in the "hint" category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Sogroya" with the active ingredient somapacitan. Somapacitan is approved as an orphan drug for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency

b) Adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated

For patient population a), the pharmaceutical company submitted the label-enabling REAL 4 study and the supportive REAL 3 study.

There were no deaths in both studies.

For the morbidity endpoint "body height (z score)", there was no statistically significant difference between the treatment groups in the REAL 4 study. In the REAL 3 study, there was a statistically significant advantage of somapacitan over somatropin for this endpoint at week 52 and week 156. However, the clinical relevance of the difference cannot be conclusively assessed.

No statistically significant differences between somapacitan and somatropin were found in the quality of life endpoint category in either study based on the GHD-CIM ObsRO. For the GHD-CTB endpoint, only in the REAL 3 study did the long-term data at week 156 show a statistically significant advantage of somapacitan over somatropin in the physical domain, for which a clinically relevant effect can be derived from Hedge's g.

Overall, there were neither advantages nor disadvantages in the side effects category.

The overall assessment showed a non-quantifiable additional benefit of somapacitan for children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency because the scientific data basis does not allow quantification.

For patient population b), the REAL 1, REAL 2 and REAL JP studies were submitted by the pharmaceutical company.

When interpreting the results, however, a probable under-treatment of patients in the somapacitan arm must be taken into account.

There were no deaths in all three studies.

For the endpoint category of morbidity, no relevant data for the benefit assessment were available.

In the REAL 1 study, there was no statistically significant difference between the treatment groups in the quality of life endpoint category based on the SF-36 at week 34. Based on the TRIM-AGHD, the REAL 1 study showed a statistically significant disadvantage of somapacitan compared to somatropin at week 34, which cannot be conclusively assessed due to the under-treatment in the verum arm.

In the side effects category, the REAL 1 study showed a statistically significant advantage in favour of somapacitan for the endpoint of AEs that led to discontinuation of the study medication, which cannot be conclusively assessed due to the under-treatment in the verum arm.

Overall, no advantages or disadvantages for somapacitan can therefore be derived for the endpoint category of quality of life and side effects.

Therefore, the overall assessment showed a non-quantifiable additional benefit for adults with growth hormone deficiency for whom replacement of endogenous growth hormone is indicated, because the scientific data basis 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).

The data is based on the patient numbers from the dossier of the pharmaceutical company.

The range given by the pharmaceutical company is subject to uncertainty.

The procedure used by the pharmaceutical company to identify the underlying disease by means of routine data analysis is fraught with uncertainty since it is unclear whether it is possible to reliably identify patients with growth hormone deficiency using ICD-10 codes. It remains questionable whether the ICD-10 codes considered by the pharmaceutical company address patients with growth hormone deficiency in a sufficiently specific and comprehensive manner.

Furthermore, when determining the target population, the pharmaceutical company includes patients aged between ≥ 2.5 and < 18 years, thus taking into account a wider age range than can be inferred from the therapeutic indication. This potentially leads to an overestimation.

Overall, the SHI target population for children aged 3 years of age and over and adolescents determined in the current procedure is higher than in the previous procedures, but is more suitable as an estimate due to the methodological approach chosen. The range of adult patients stated by the pharmaceutical company is subject to uncertainty.

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 Sogroya (active ingredient: somapacitan) at the following publicly accessible link (last access: 23 April 2024):

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

Treatment with somapacitan should only be initiated and monitored by doctors experienced in treating children and adolescents with growth hormone deficiency (paediatric GHD) and adults with growth hormone deficiency (adult GHD).

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Somapacitan	1 x every 7 days	52.1	1	52.1

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs. In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration. The average body measurements were applied for dosages depending on body weight (bw) or body surface area (BSA) (average height of a 3-year-old child: 16.2 kg, average body weight of a 17-year-old adolescent: 67.2 kg)[2].

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					
Somapacitan	Patients ≥ 3 to under 4 years				
	0.16 mg/kg	2.6 mg	2.6 mg	52.1	52.1 x 2.6 mg
	Patients ≥ 17 to under 18 years				
	0.16 mg/kg	10.8 mg	10.8 mg	52.1	52.1 x 10.8 mg
	Adult patients				
	8 mg	8 mg	8 mg	52.1	52.1 x 8 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

2 Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de/.

Costs of the medicinal products:

a) Children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency

and

b) Adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated

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
Medicinal product to be assessed					
Somapacitan 5 mg	5 PEN	€ 2,812.89	€ 2.00	€ 157.35	€ 2,653.54
Somapacitan 10 mg	5 PEN	€ 5,568.13	€ 2.00	€ 314.70	€ 5,251.43
Somapacitan 15 mg	5 PEN	€ 8,323.37	€ 2.00	€ 472.06	€ 7,849.31
Abbreviations: PEN = pre-filled pen					

LAUER-TAXE® last revised: 15 April 2024

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.

No additionally required SHI services are taken into account for the cost representation.

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 designates 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 has 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 has 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 information 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 has 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:

a) Children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency

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 somapacitan (Sogroya); Sogroya® 5 mg/1.5 ml/-10 mg/1.5 ml/-15 mg/1.5 ml solution for injection in a pre-filled pen; last revised: 07/2023

b) Adults with growth hormone deficiency (AGHD) for whom replacement of endogenous growth hormone (GH) is indicated

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

References:
Product information for somapacitan (Sogroya); Sogroya® 5 mg/1.5 ml/-10 mg/1.5 ml/-15 mg/1.5 ml solution for injection in a pre-filled pen; last revised: 07/2023

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 26 October 2023, the pharmaceutical company submitted a dossier for the benefit assessment of somapacitan 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 1 February 2024 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 22 February 2024.

The oral hearing was held on 11 March 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 9 April 2024.

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 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 January 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	14 February 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 March 2024	Conduct of the oral hearing
Working group Section 35a	19 March 2024 16 April 2024	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 Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

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

Prof. Hecken