Gemeinsamer Bundesausschuss

Justification

for 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
Olezarsen (chylomicronemia syndrome)

From 21 May 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 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 of 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, numbers 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seqq. 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. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company shall provide evidence - within three months of being requested to do so by the G-BA - in accordance with Chapter 5 Section 5, paragraphs 1 to 6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy specified by the G-BA in accordance with Chapter 5 Section 6 VerfO, and in this evidence, demonstrate the additional benefit over the appropriate comparator therapy.

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

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover limit 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 decide 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 olezarsen on 1 December 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to 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 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 28 November 2025.

Olezarsen for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS) in adults is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

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 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 2 March 2026 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted their 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 G25-38) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have assessed the studies relevant to the marketing authorisation on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 to 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of olezarsen.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Olezarsen (Tryngolza) in accordance with the product information

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution of 21 May 2026):

See the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults with genetically confirmed familial chylomicronemia syndrome (FCS)

Indication of a minor additional benefit.

Justification:

The pharmaceutical company presented the pivotal phase III Balance study for the benefit assessment of olezarsen.

Balance study

The multicentre, double-blind, randomised, controlled phase III Balance study investigated the efficacy and safety of olezarsen as an adjunct to a low-fat diet in adults with genetically confirmed familial chylomicronemia syndrome (FCS), compared with placebo. Adults with a confirmed homozygous, compound-heterozygous or double-heterozygous mutation and loss of function in type 1-causing genes (such as LPL, GPIHBP1, ApoA5, ApoC2, GPD1 or LMF1) and a fasting triglyceride level ≥ 880 mg/dl at the time of screening were enrolled. Patients with and without a history of confirmed pancreatitis were enrolled.

The subjects enrolled were randomised in a 1:1 ratio to cohorts A (50 mg olezarsen or 0.5 ml placebo) and B (80 mg olezarsen or 0.8 ml placebo), followed by a 2:1 randomisation within each cohort between olezarsen and placebo. The only relevant factor for the benefit assessment is the on-label olezarsen dosage of 80 mg, with the pooled placebo arms serving as a comparison.

The screening phase was followed by a 53-week treatment phase. This was followed by a 13-week follow-up phase, or the study participants had the option of transferring to the open-label, single-arm extension study (ISIS-678354-CS13).

During the treatment phase, subcutaneous administration of the study medication was once monthly. In addition, a diet (≤ 20 g fat per day) had to be followed. Furthermore, any prior lipid-lowering therapy received, consisting of statins, omega-3 fatty acids, fibrates or other lipid-lowering medicines, could be continued at the same dosage during the study.

The study was conducted at 29 study sites across the United States, Canada, Europe and the United Kingdom between December 2020 and November 2023.

Mortality

Fatalities were recorded in the Balance study as part of the safety assessment. There were no deaths in the study.

Morbidity

Confirmed acute pancreatitis

In the Balance study, acute pancreatitis was confirmed by a blinded, independent expert committee ("Acute Pancreatitis Adjudication Committee", PAC) on the basis of pre-specified criteria. "Documented pancreatitis" was classified as independently confirmed acute pancreatitis on the basis of the modified Atlanta diagnostic criteria for acute pancreatitis, whilst "probable pancreatitis" and "possible pancreatitis" were classified on the basis of different criteria.

In the Balance study, there were statistically significantly fewer confirmed cases of acute pancreatitis treated with olezarsen after 12 months compared with placebo.

Hospitalisation

Hospital admissions were recorded during the Balance study using the following pre-specified endpoints: Hospitalisations for any reason (total hospitalisation), visits to the accident and emergency department and the number of inpatient days. In addition, AP-related hospitalisations were analysed.

Only the endpoint of total hospitalisation was used for the benefit assessment.

For the endpoint of total hospitalisation, the calculations provided by the pharmaceutical company in the dossier indicate a positive effect, which is however not statistically significant based on the confidence interval. An own calculation was then carried out using an exact test. For the endpoint of total hospitalisation, there were no statistically significant differences between the treatment arms.

All hospitalisations due to confirmed acute pancreatitis were classified as AP-related hospitalisations. Given the overlap in the operationalisation of the endpoint "confirmed acute pancreatitis" the certification of which by the PAC also required hospitalisation, it is assumed that cases of acute pancreatitis occurring in the Balance study have been collected twice. Consequently, the endpoint of hospitalisations due to AP is only presented additionally here and is not used for the benefit assessment.

Symptomatology assessed using the FCS symptom, PGIS and PGIC

In the Balance study, symptomatology was assessed using several survey tools (FCS-SIS, PGIS and PGIC). Due to some overlap in the content of the questionnaires, it is likely that some responses have been collected multiple times.

Responder analyses of deterioration and improvement in symptomatology are available for each questionnaire. As around a quarter of subjects in the olezarsen arm and a third of subjects in the placebo arm showed no symptoms at baseline according to the PGIS, and therefore an improvement in symptomatology was not possible for these subjects, the responder analyses of deterioration after 12 months of treatment are used here.

The *FCS symptom* scale is a domain of the *Familial Chylomicronemia Syndrome – Symptom and Impact Scale (FCS-SIS)* questionnaire and assesses the severity of patient-reported FCS symptomatology. It includes the following items: abdominal pain, physical fatigue, trouble

thinking and diarrhoea. The severity of each symptom was collected daily on an 11-point scale ranging from 0 ("no symptom") to 10 ("worst possible symptom"). The total score was calculated using the mean value of the 4 symptom items.

In the dossier, responder analyses of improvement or deterioration of the total symptom score at months 6 or 12, respectively, using a response criterion of 15% of the scale range, were presented.

For the endpoint of deterioration in symptomatology as assessed using the FCS-SIS, there was no statistically significant difference between the treatment groups after 12 months of treatment.

The *Patient Global Impression of Severity (PGIS)* assesses the severity of the patient-reported FCS symptomatology experienced over the past week. Severity grading was done using a 5-point Likert scale from 0 ("no symptoms") to 4 ("very severe symptoms").

For the PGIS, responder analyses of the percentage of subjects who showed an improvement (defined as a change from baseline < 0) or a deterioration (defined as a change from baseline ≥ 0) at months 6 and 12, respectively, compared with baseline, are available.

For the endpoint of deterioration in symptom severity as assessed using the PGIS, there was no statistically significant difference between the treatment groups after 12 months of treatment.

In this context, the *Patient Global Impression of Change (PGIC)* assesses the patient-reported change in FCS symptomatology since the start of treatment. The self-assessment was carried out using a 5-point Likert scale ranging from 0 ("much better") to 4 ("much worse").

For the PGIC, responder analyses of the percentage of subjects who showed an improvement (defined as a score < 2.5) and a deterioration (defined as a score ≥ 2.5) at months 6 and 12, respectively, compared with baseline, are available. However, the returns to the PGIC at month 12 varied considerably between the treatment arms, meaning that this cannot be used for the benefit assessment.

Change in fasting triglyceride levels

In the present therapeutic indication, the blood triglyceride level is a clinically relevant parameter used for diagnosis and therapy management. The therapeutic goal in the treatment of FCS is to lower blood triglyceride levels in order to reduce the risk of acute pancreatitis, amongst other things. However, the symptomatology is different from patient to patient in those with FCS, and there is only limited evidence for the symptom-relevant threshold blood triglyceride levels.

For the primary endpoint of the Balance study "change in the percentage of fasting triglyceride levels", there was a statistically significant advantage in favour of olezarsen compared with placebo after a treatment duration of 12 months.

Health-related quality of life

Health-related quality of life was assessed in the Balance study using several questionnaires (FCS-Impact, PROMIS-29 + 2, PROMIS Short Form – Pain Interference 8a and PROMIS Short Form – Cognitive Function 4a). No data for the PROMIS Short Form – Cognitive Function 4a were provided in the dossier. The questionnaire is not considered for the benefit assessment as the return rates at baseline were also below 70%.

The *Impact Scale* (Impact domain of the FCS-SIS questionnaire) assesses disease-specific quality of life of those with FCS. It comprises 13 items that assess current quality of life on a 5-point

scale ranging from 0 ("never") to 4 ("always"). The mean value for the 13 items was examined at 6 and 12 months, respectively, in comparison with baseline. 15% of the scale range is used as the response criterion for the responder analyses of improvement or deterioration.

For the endpoint of deterioration in health-related quality of life, assessed using the FCS-Impact and used for the benefit assessment, there was no statistically significant difference between the treatment groups after 12 months of treatment.

The *Patient-Reported Outcome Measurement Information System 29 (PROMIS-29)* is a self-reported questionnaire for generic assessment of the health-related quality of life of adults. It consists of 7 domains (depression, anxiety, physical functioning, pain interference, fatigue, sleep disorder and ability to participate in social roles/ activities) and a single item on pain intensity.

In the dossier, the pharmaceutical company presented the PROMIS 29+2, to which a domain relating to cognitive functioning has been added. However, no suitable studies on validity are available for this addition; consequently, the results of the PROMIS-29 domain scores are used here for the benefit assessment. No data on the physical or mental component summary score are available.

In each of the individual domains of PROMIS 29, there were no statistically significant differences between the treatment groups after 12 months of treatment.

The *PROMIS Short Form (SF) – Pain Interference 8a* assesses self-reported impairment due to pain over the past 7 days. 8 items are queried here on a 5-point scale; higher scores indicate a greater degree of impairment due to pain.

Half of the questionnaire items are identical to those in the pain impairment domain of the PROMIS-29. Furthermore, it is unclear whether the questionnaire adequately captures the multidimensional construct of quality of life. Against this background, the results of the PROMIS SF – Pain interference 8a are only presented additionally.

Side effects

Severe adverse events (AEs) and serious AEs (SAEs)

In terms of the overall rates of severe AEs (CTCAE grade 3 or 4), there was a statistically significant advantage in favour of olezarsen compared with placebo after a treatment duration of 12 months. In terms of the overall rates of SAEs, there was no statistically significant difference between the treatment arms after a treatment duration of 12 months.

For severe AEs and SAEs, respectively, there was a statistically significant advantage in favour of olezarsen over placebo in the SOC "gastrointestinal disorders" at the SOC level. Some of the underlying events at the PT level (pancreatitis, necrotising pancreatitis, acute pancreatitis, chronic pancreatitis) are attributable to the underlying disease.

In the written statement procedure, the pharmaceutical company subsequently submitted the results on severe AEs, SAEs and the SOC "gastrointestinal disorders", from which pancreatitis events had been excluded. Based on these data, a statistically significant advantage of olezarsen over placebo is further observed in terms of the overall rates of severe AEs; however, no statistically significant difference between the treatment groups is observed in terms of the overall rates of SAEs as well as the SOC "gastrointestinal disorders" (severe AEs/SAEs).

Overall, it does not seem plausible that more severe AEs would occur with the administration of a sham intervention than with the administration of the study medication. In this case, it

cannot be ruled out that the safety analyses may include other potential events related to the underlying disease in addition to the pancreatitis events. The effects shown can therefore only be interpreted to a limited extent.

Therapy discontinuation due to AEs

In terms of therapy discontinuation due to AEs, there was no statistically significant difference between the treatment groups.

Major adverse cardiovascular events (MACE)

Events classified as MACE were assessed by a blinded, independent committee in accordance with the MACE adjudication charter. There is no rationale for classifying the MACE endpoint under the "safety" endpoint category. Furthermore, it cannot be ruled out in this case that events related to the underlying disease have been collected.

For the MACE endpoint, there was no statistically significant difference between the treatment groups.

Overall assessment

The present assessment is based on the results of the randomised, double-blind, placebo-controlled phase 3 Balance study, which investigated the subcutaneous administration of olezarsen compared with placebo in adults with FCS over a 12-month period. Data on different endpoints from the endpoint categories of mortality, morbidity, health-related quality of life and side effects are available.

There were no deaths in the study.

For the endpoint "confirmed acute pancreatitis" in the endpoint category of morbidity, there was a statistically significant advantage of olezarsen over placebo. For the endpoint of total hospitalisation and for symptomatology, as assessed using the FCS-SIS and PGIS questionnaires, there were no statistically significant differences between the treatment groups at month 12 in each case. The primary endpoint "change in the percentage of fasting triglyceride levels" is a clinically relevant parameter used for diagnosis and therapy management in this therapeutic indication. There was a statistically significant difference in favour of olezarsen compared with placebo after a treatment duration of 12 months.
In the overall assessment of morbidity endpoints, an advantage of olezarsen over placebo is observed based on the positive effect in the "confirmed acute pancreatitis" endpoint; this advantage is considered to be minor.

For the endpoint category of health-related quality of life, assessed using the FCS-Impact and PROMIS-29 questionnaires, there were no statistically significant differences between the treatment groups.

For the severe AEs and the SOC "gastrointestinal disorders" in the endpoint category of side effects, there was a statistically significant advantage of olezarsen over placebo. Based on the subsequently submitted data, which do not include pancreatitis events, there continued to be a statistically significant advantage of olezarsen over placebo in terms of severe AEs. In terms of the endpoints of serious AEs and therapy discontinuation due to AEs, there were no statistically significant differences between the treatment groups. In summary, it cannot be ruled out in this case that the safety analyses may include other potential events related to the underlying disease in addition to the pancreatitis events. Overall, taking all endpoints in the category of side effects into account, there were no relevant differences for the benefit assessment.

The overall analysis of the available results on patient-relevant endpoints showed an advantage in the endpoint category of morbidity with regard to the key endpoint of "confirmed acute pancreatitis" for this disease. Based on the results of the Balance study, the G-BA classified the extent of the additional benefit of olezarsen for the treatment of adults with FCS as minor overall.

Significance of the evidence

The risk of bias in the Balance study is considered to be unclear, particularly due to the stratified randomisation procedure combined with a small study population. Despite the imbalances in some baseline characteristics, no systematic one-sided skewness in the distribution of relevant prognostic factors is apparent, and the differences observed are not considered large given the sample size. Furthermore, uncertainty regarding the implementation of the low-fat diet in the Balance study remains.

Despite the uncertainty, the significance of the evidence is classified in the "indication" category overall.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Tryngolza with the active ingredient olezarsen. Tryngolza was approved as an orphan drug and is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

In this assessment, the pharmaceutical company presented the randomised, double-blind, placebo-controlled phase 3 Balance study, which investigated the subcutaneous administration of olezarsen compared with placebo in adults with FCS over a period of 12 months.

There were no deaths in the study.

For the endpoint "confirmed acute pancreatitis" in the endpoint category of morbidity, there was a statistically significant advantage of olezarsen over placebo. For the endpoint of total hospitalisation and for symptomatology, there were no statistically significant differences between the treatment groups at month 12. The primary endpoint "change in the percentage of fasting triglyceride levels" is a clinically relevant parameter used for diagnosis and therapy management in this therapeutic indication. There was a statistically significant difference in favour of olezarsen compared with placebo after a treatment duration of 12 months.

For the endpoint category of health-related quality of life, there were no statistically significant differences between the treatment groups.

With regard to the endpoint category of side effects, it cannot be ruled out in this case that the analyses may include other potential events related to the underlying disease in addition to the pancreatitis events. For the severe AEs (without pancreatitis events), there was a statistically significant lower harm with olezarsen compared with placebo. In terms of the endpoints of serious AEs and therapy discontinuation due to AEs, there were no statistically significant differences between the treatment groups. Overall, taking all endpoints in the category of side effects into account, there were no relevant differences for the benefit assessment.

The risk of bias in the Balance study is considered to be unclear, particularly due to the stratified randomisation procedure combined with a small study population. Furthermore, uncertainty regarding the implementation of the low-fat diet in the Balance study remains.

In the overall assessment, an indication of a minor additional benefit of olezarsen for the treatment of adults with genetically confirmed familial chylomicronemia syndrome (FCS) is found on the basis of the advantage shown in the endpoint "confirmed acute pancreatitis".

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 range given is plausible, but is subject to uncertainty due to the rarity of the disease and the lack of reliable data.

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 Tryngolza (active ingredient: olezarsen) at the following publicly accessible link (last access: 15 April 2026):

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

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 March 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

According to the product information, the recommended dose of olezarsen is 80 mg, administered as a subcutaneous injection once monthly.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Olezarsen	1 x monthly	12.0	1	12.0

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					
Olezarsen	80 mg	80 mg	1 x 80 mg	12.0	12 x 80 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with genetically confirmed familial chylomicronemia syndrome (FCS)

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					
Olezarsen 80 mg	1 PEN	€ 29,799.06	€ 1.77	€ 1,698.54	€ 28,098.75
Abbreviations: PEN = solution for injection in a pre-filled pen					

LAUER-TAXE® last revised: 15 March 2026

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 additional SHI services required 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 designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

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

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

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between statutory 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:

Adults with genetically confirmed familial chylomicronemia syndrome (FCS)

- No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for olezarsen (Tryngolza); Tryngolza 80 mg solution for injection in a pre-filled pen; last revised: November 2025

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

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

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is 0% of the total number of study participants according to the information provided by the pharmaceutical company.

In the dossier, the pharmaceutical company provided information on a total of 3 studies (Balance study (ISIS 678354-CS3), ISIS 678354-CS7 as well as ISIS 678354-CS13) in the present therapeutic indication, with a total percentage of 0% study participants at German study sites.

However, the open-label extension study ISIS 678354-CS13 should not be included in the calculation, as it includes only patients who took part in the Balance clinical study already referred to. Furthermore, a comparison with the Common Technical Document (CTD) identified the likewise relevant studies ISIS 678354-CS8, ISIS 678354-CS2, AKCEA-CS1 and ISIS 678354-CS20, for which no data are available in the dossier. Taking into account the additional relevant studies, the percentage of study participants at study sites within the scope of SGB V remains at 0%, as none of the relevant studies included participants at German study sites.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant percentage within the scope of SGB V.

3. Bureaucratic costs calculation

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

4. Process sequence

On 28 November 2025, the pharmaceutical company submitted a dossier for the benefit assessment of olezarsen 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 2 March 2026 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 statements was 23 March 2026.

The oral hearing was held on 7 April 2026.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 24 April 2026.

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 Subcommittee's session on 12 May 2026, and the draft resolution was approved.

At their session on 21 May 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	24 February 2026	Information of the benefit assessment of the G-BA
Working group Section 35a	31 March 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2026	Conduct of the oral hearing,
Working group Section 35a	14 April 2026 5 May 2026	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 May 2026	Concluding discussion of the draft resolution
Plenum	21 May 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 May 2026

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

Prof. Hecken