Vutrisiran (transthyretin amyloidosis with cardiomyopathy)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis with cardiomyopathy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hATTR-CM	hereditary transthyretin amyloidosis with cardiomyopathy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
TTR	transthyretin
wtATTR-CM	wild-type transthyretin amyloidosis with cardiomyopathy

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug vutrisiran. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 7 July 2025.

Research question

The aim of this report is to assess the added benefit of vutrisiran in comparison with tafamidis as the appropriate comparator therapy (ACT) in patients with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of vutrisiran

Therapeutic indication	**ACT**[a]
Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)	tafamidis[b, c]

a. Presented is the ACT specified by the G-BA.
b. It is assumed that in both study arms individualized appropriate treatment of the respective organ manifestation (such as heart failure and/or polyneuropathy) corresponding to the generally accepted current state of medical knowledge is provided, taking into account the special characteristics of the disease ATTR amyloidosis, and that this is documented as concomitant treatment.
c. It is assumed that liver transplantation or heart transplantation is not an option at the time of therapy with vutrisiran.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloidosis with cardiomyopathy; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

The RCT HELIOS-B was identified in the review of the completeness of the study pool. The HELIOS-B study is a double-blind, ongoing RCT comparing vutrisiran with placebo. The study included adult patients with ATTR-CM. In compliance with the summary of product characteristics (SmPC) treatment with vutrisiran was given for a planned period of up to

36 months. The primary outcome of the study was a composite outcome of all-cause mortality and recurrent cardiovascular events.

The company identified the HELIOS-B study as part of the information retrieval. However, it did not consider the study to be suitable for the assessment of the added benefit and justified its exclusion with a lack of conformity with the defined ACT in the control arm of the study.

The HELIOS-B study was unsuitable for the benefit assessment of vutrisiran as monotherapy compared with tafamidis as monotherapy. However, a relevant proportion of the patients included were already receiving treatment with tafamidis at the time of randomization, which was to be continued in the further course of the study. The Helios-B study thus contained potentially suitable data for the benefit assessment of treatment with vutrisiran + tafamidis compared with tafamidis. However, the company did not present these data in the dossier.

Results on added benefit

Since no suitable data were available for the given research question, there is no hint of an added benefit of vutrisiran in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of vutrisiran.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Vutrisiran – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)	tafamidis[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that in both study arms individualized appropriate treatment of the respective organ manifestation (such as heart failure and/or polyneuropathy) corresponding to the generally accepted current state of medical knowledge is provided, taking into account the special characteristics of the disease ATTR amyloidosis, and that this is documented as concomitant treatment.
c. It is assumed that liver transplantation or heart transplantation is not an option at the time of therapy with vutrisiran.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloidosis with cardiomyopathy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of vutrisiran in comparison with tafamidis as the appropriate comparator therapy (ACT) in patients with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of vutrisiran

Therapeutic indication	**ACT[a]**
Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)	tafamidis[b, c]
a. Presented is the ACT specified by the G-BA. b. It is assumed that in both study arms individualized appropriate treatment of the respective organ manifestation (such as heart failure and/or polyneuropathy) corresponding to the generally accepted current state of medical knowledge is provided, taking into account the special characteristics of the disease ATTR amyloidosis, and that this is documented as concomitant treatment. c. It is assumed that liver transplantation or heart transplantation is not an option at the time of therapy with vutrisiran. ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloidosis with cardiomyopathy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on vutrisiran (status: 7 May 2025)
- Bibliographical literature search on vutrisiran (last search on 7 May 2025)
- Search of trial registries / trial results databases for studies on vutrisiran (last search on 7 May 2025)
- Search on the G-BA website for vutrisiran (last search on 7 May 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on vutrisiran (last search on 22 July 2025); for search strategies, see I Appendix A of the full dossier assessment

The RCT HELIOS-B [3-7] was identified in the review of the completeness of the study pool. The company also identified the HELIOS-B study as part of the information retrieval. However, it did not consider the study to be suitable for the assessment of the added benefit and justified its exclusion with a lack of conformity with the defined ACT in the control arm of the study. The company presented the HELIOS-B study in Module 4 B of the dossier only as supplementary information and did not use it for the derivation of the added benefit.

The following sections describe the characteristics of the HELIOS-B study and discuss its suitability for the benefit assessment.

Design of HELIOS-B

Table 5 and Table 6 describe the HELIOS-B study.

Table 5: Characteristics of HELIOS-B – RCT, direct comparison: vutrisiran vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HELIOS-B	RCT, double-blind, parallel	Adults (18–85 years) with hereditary[b] or wild-type[c] transthyretin amyloidosis[d] with cardiomyopathy[e] ▪ NYHA class I–III[f] ▪ tafamidis-naive or on tafamidis treatment ▪ Karnofsky performance status ≥ 60%	vutrisiran (N = 326) placebo (N = 329) With tafamidis therapy at baseline: vutrisiran (N = 130) placebo (N = 129)	Screening: 45 days Treatment: 30 to 36 months[g] Follow-up: up to 18 months[h]	87 study centres in Argentina, Australia, Austria, Belgium, Canada, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israel, Japan, Latvia, Lithuania, Netherlands, Norway, Peru, Poland, Portugal, South Korea, Spain, Sweden, United Kingdom, United States 11/2019–ongoing Data cut-off (primary analysis): 8 May 2024	Primary: composite outcome of all-cause mortality or recurrent cardiovascular events[i] Secondary: all-cause mortality, morbidity, health-related quality of life, AEs

Table 5: Characteristics of HELIOS-B – RCT, direct comparison: vutrisiran vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company in Module 4.
b. Defined based on meeting all of the following criteria: documentation of a TTR pathogenic mutation consistent with hereditary amyloidosis; evidence of cardiac involvement by echocardiography with an interventricular septal wall thickness > 12 mm; amyloid deposits in cardiac or noncardiac tissue or technetium (^{99m}Tc) scintigraphy with grade 2 or 3 cardiac uptake if monoclonal gammopathy of undetermined significance (MGUS) has been excluded; documentation of TTR protein in the tissue in patients with evidence of MGUS.
c. Defined based on meeting all of the following criteria: documentation of the absence of pathogenic TTR mutation; evidence of cardiac involvement by echocardiography with an interventricular septal wall thickness > 12 mm; amyloid deposits in cardiac tissue with TTR protein identification or ^{99m}Tc scintigraphy with grade 2 or 3 cardiac uptake if MGUS has been excluded; in patients with evidence of a MGUS: documentation of TTR protein in cardiac tissue or documentation of TTR protein in noncardiac tissue and ^{99m}Tc scintigraphy with grade 2 or 3 cardiac uptake.
d. Patients with known light chain amyloidosis, leptomeningeal amyloidosis or prior or anticipated heart, liver or other organ transplantation were excluded.
e. Medical history of heart failure with ≥ 1 prior hospitalization for heart failure, or clinical evidence of heart failure manifested by signs and symptoms of volume overload or elevated intracardiac pressure that currently requires treatment with a diuretic.
f. Patients with NYHA class IV or NYHA class III heart failure in combination with stage III ATTR amyloidosis (defined as NT-proBNP > 3000 ng/L and eGFR < 45 mL/min) were excluded from study participation.
g. In the double-blind treatment phase, treatment was given for a maximum of 36 months or 30 months after inclusion of the last patient, whichever came first. Patients in both study arms were then able to continue treatment with vutrisiran in an open-label extension phase for up to 2 years.
h. The figure refers to patients who discontinued the treatment phase prematurely. Patients who completed the planned double-blind treatment phase and continued treatment with vutrisiran in the open-label extension phase were followed up for at least 90 days after the last dose of study medication in the extension phase.
i. Defined as cardiovascular hospitalizations, indeterminate hospitalizations for heart failure, and urgent health care visits (non-elective visits including home visits) where heart failure was the primary reason for the visit and where intravenous diuretics had to be administered.

AE: adverse event; ATTR: transthyretin amyloidosis; MGUS: monoclonal gammopathy of undetermined significance; N: number of randomized patients; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; ^{99mTc}: technetium; TTR: transthyretin

Table 6: Characteristics of the interventions in HELIOS-B – RCT, direct comparison: vutrisiran vs. placebo

Study	Intervention	Comparison
HELIOS-B	vutrisiran 25 mg every 3 months, SC	Placebo, every 3 months, SC
	▪ Dose modifications were not allowed ▪ Interruptions for AEs related to the study treatment were allowed	
	Allowed prior treatment ▪ tafamidis **Disallowed prior treatment** ▪ TTR-lowering treatment (including revusiran, patisiran or inotersen) or participation in a gene therapy trial for hATTR ▪ diflunisal: ≥ 30-day washout period before the first dose of study treatment ▪ doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid: 30-day washout period before the first dose of study treatment ▪ Investigational TTR stabilizer drugs: 3-month washout period before the first dose of study treatment ▪ Non-dihydropyridine calcium channel blockers (e.g. verapamil, diltiazem) **Allowed concomitant treatment** ▪ tafamidis: continuation of prior treatment[a]; in patients without[b] prior tafamidis treatment, initiation of treatment with tafamidis during the study was only permitted if tafamidis was approved and commercially available for ATTR-CM in the respective country and if the investigator was not already planning at study start to commence active treatment with tafamidis during screening or the first 12 months after randomization ▪ Required: vitamin A daily ▪ Any concomitant treatment (including required prescription or over-the-counter medications, herbal preparations, minerals or vitamins) for the treatment of diseases and the patient's welfare **Disallowed concomitant treatment** ▪ diflunisal, TTR-lowering agents (e.g. patisiran or inotersen) ▪ ursodeoxycholic acid, tauroursodeoxycholic acid, doxycycline ▪ Non-dihydropyridine calcium channel blockers ▪ Clinical investigational products	

a. Patients who were already receiving tafamidis therapy at baseline were to continue this for the entire duration of the study, provided this was medically appropriate according to the investigator's assessment.
b. Patients who had previously been treated with tafamidis and had not received tafamidis for at least 30 days prior to screening were also considered patients without prior tafamidis treatment.

AE: adverse event; ATTR-CM: transthyretin amyloidosis with cardiomyopathy; hATTR: hereditary ATTR amyloidosis; RCT: randomized controlled trial; SC: subcutaneous; TTR: transthyretin

The HELIOS-B study is a double-blind, ongoing RCT comparing vutrisiran with placebo in patients with ATTR-CM.

The study included adult patients aged 18 to 85 years diagnosed with hereditary (hATTR-CM) or wild-type transthyretin amyloidosis with cardiomyopathy (wtATTR-CM), by documentation or absence of a pathogenic mutation in the transthyretin (TTR) gene. In both cases, the

diagnosis had to include cardiac involvement shown by echocardiography. Another inclusion criterion was amyloid deposits in cardiac or non-cardiac tissue (in hATTR-CM) or in cardiac tissue (in wtATTR-CM). Patients with New York Heart Association (NYHA) class IV heart failure or class III heart failure in combination with ATTR stage III were excluded from participation in the study. Patients had to have a Karnofsky performance status of ≥ 60% and, if polyneuropathic symptoms were present, a polyneuropathy disability score of ≤ II. Patients were not allowed to have known severe renal impairment and the estimated glomerular filtration rate (eGFR) had to be at least 30 mL/min/1.73 m^2.

In the study, a total of 655 patients were assigned in a 1:1 ratio to treatment with 25 mg vutrisiran (N = 326) or placebo (N = 329). Randomization was stratified by baseline tafamidis use (yes versus no), ATTR disease type (hATTR-CM versus wtATTR-CM), and NYHA class (NYHA class I or II and age < 75 years versus all other).

In compliance with the summary of product characteristics (SmPC) [8] treatment with vutrisiran was given for a planned period of up to 36 months. Patients in both study arms were then able to continue treatment with vutrisiran in an open-label extension phase for up to 2 years. In addition to the treatment with the study medication, any concomitant medication was permitted and was documented, excluding the exceptions listed in Table 6. Individualized appropriate treatment of the respective organ manifestation (such as heart failure and/or polyneuropathy), taking into account the special features of the disease ATTR amyloidosis, was thus possible in both study arms.

Patients who were already receiving on-label treatment with commercially available tafamidis at baseline [9] were to continue this treatment for the entire study duration, if possible, in accordance with the investigator's decision. Patients who were not treated with tafamidis at baseline, and for whom tafamidis therapy was not planned either during the screening phase or in the 12 months following randomization, were included in the study as a tafamidis-naive subpopulation in accordance with the study inclusion criteria. In the course of the study, this group of patients could also start tafamidis treatment according to the investigator's decision if tafamidis was approved and commercially available for ATTR-CM in the respective country. Hence, tafamidis was not part of the study medication.

The primary outcome of the study was a composite outcome of all-cause mortality and recurrent cardiovascular events. The latter included all cardiovascular or indeterminate hospitalizations for heart failure, as well as all urgent non-elective doctor visits (including home visits) where heart failure was the primary reason for the visit and where intravenous diuretics had to be administered. With the exception of home visits, all recurrent cardiovascular events were continuously adjudicated by an independent clinical events committee, which was blinded for the assigned treatment with the study drug, to determine whether each event was to be classified as cardiovascular. Other patient-relevant outcomes

were all-cause mortality, outcomes in the categories morbidity and health-related quality of life and adverse event outcomes.

The HELIOS-B study is still ongoing. At the time of the benefit assessment, the prespecified primary analysis of the study was available with the 1st data cut-off from 8 May 2024 (database lock on 14 June 2024), which was to be conducted after the last patient had completed the double-blind treatment phase as planned or prematurely. A further data cut-off is planned at the end of the study after completion of the open-label extension phase.

Approach of the company

The company assessed the study HELIOS-B it identified as not suitable for the benefit assessment. It justified this by stating that in the HELOIS-B study, the ACT tafamidis was not used as a comparator for a direct comparison with vutrisiran. It described that in the study, any tafamidis therapy given at baseline could be continued as background therapy in both treatment arms, but that the design of the study was not intended to investigate a therapeutic effect of vutrisiran in comparison with tafamidis. Among other things, the study was not sufficiently powered within the stratum that received tafamidis as background therapy to demonstrate statistically significant treatment differences. In the company's view, a treatment comparison within the stratum with tafamidis as background therapy did not allow an adequate assessment of the therapeutic effect of vutrisiran in comparison with tafamidis for this benefit assessment. It rightly noted that a comparison of monotherapy with vutrisiran (from the subpopulation without tafamidis background therapy) versus monotherapy with tafamidis (from the subpopulation of the placebo arm with tafamidis background therapy) would be across both strata, which would no longer correspond to a randomized comparison.

In Module 4 B of the dossier, the company additionally presented results of the 1st data cut-off on the outcome categories of mortality, morbidity, health-related quality of life and adverse events both for the overall population and for the subpopulation without tafamidis background therapy. The company did not present the subpopulation with tafamidis background therapy, however. In Module 4 B, it also did not conduct any of the subgroup analyses predefined in the study documents.

Assessment of the company's approach

The HELIOS-B study is an RCT comparing vutrisiran versus placebo for the treatment of wtATTR-CM or hATTR-CM. The G-BA specified tafamidis as the ACT.

The company's justification for excluding the study from the benefit assessment initially appeared understandable, as vutrisiran was compared with placebo in the HELIOS-B study. The HELIOS-B study was therefore unsuitable for the benefit assessment of vutrisiran as monotherapy compared with tafamidis as monotherapy. However, a relevant proportion of 40% of the patients included were already receiving treatment with tafamidis at the time of

randomization, which was to be continued in the further course of the study. For this reason, the international HELIOS-B study included a subpopulation of patients for the comparison of vutrisiran add-on therapy to tafamidis (vutrisiran + tafamidis) versus tafamidis as monotherapy.

The Helios-B study thus contained potentially suitable data for the benefit assessment of treatment with vutrisiran + tafamidis compared with tafamidis. However, the company did not present these data in the dossier. This is not comprehensible, as the subpopulation of patients with existing tafamidis background therapy was already discussed in the consultation with the G-BA and was considered by the company itself to be a correct implementation of the ACT [10]. The SmPC for vutrisiran does not contain any restrictions on the add-on use of vutrisiran with existing tafamidis therapy and also contains results on subgroup analyses of the subpopulation with tafamidis background therapy [8]. The use as an add-on therapy is therefore assessed as on-label. The publications on HELIOS-B [3-5] as well as the European Public Assessment Report [11] also contain results on subgroup analyses of this subpopulation. The European Medicines Agency (EMA) also considers the analysis of the subpopulation with tafamidis background therapy to be relevant.

For this benefit assessment, the data of the HELIOS-B study of the subpopulation with tafamidis therapy at baseline were considered relevant for the assessment of vutrisiran add-on therapy to tafamidis versus tafamidis.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of vutrisiran for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy. There is no hint of an added benefit of vutrisiran in comparison with the ACT tafamidis.

I 5 Probability and extent of added benefit

Table 7 summarizes the result of the assessment of added benefit of vutrisiran in comparison with the ACT.

Table 7: Vutrisiran – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)	tafamidis[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that in both study arms individualized appropriate treatment of the respective organ manifestation (such as heart failure and/or polyneuropathy) corresponding to the generally accepted current state of medical knowledge is provided, taking into account the special characteristics of the disease ATTR amyloidosis, and that this is documented as concomitant treatment.
c. It is assumed that liver transplantation or heart transplantation is not an option at the time of therapy with vutrisiran.

ACT: appropriate comparator therapy; ATTR-CM: transthyretin amyloidosis with cardiomyopathy; G-BA: Federal Joint Committee

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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