Vutrisiran (hereditary transthyretin amyloidosis with neuropathy)

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 of persons concerned was received within 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
AE	adverse event
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
FAP	familial amyloidotic polyneuropathy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hATTR amyloidosis	hereditary transthyretin amyloidosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KPS	Karnofsky performance status
mNIS	modified Neurologic Impairment Score
NCI	National Cancer Institute
NIS	neuropathy impairment score
NYHA	New York Heart Association
PND	polyneuropathy disability
RCT	randomized controlled trial
R-ODS	Rasch-Built Overall Disability Score
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 18 October 2022.

Research question

The aim of the present report is to assess the added benefit of vutrisiran in comparison with the appropriate comparator therapy (ACT) in patients with hereditary transthyretin amyloidosis (hATTR amyloidosis) with stage 1 or 2 polyneuropathy.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2. Research question for the benefit assessment of vutrisiran

Therapeutic indication	**ACT**[a]
Adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy[b]	Tafamidis (only for hATTR amyloidosis with stage 1 polyneuropathy) or patisiran

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that liver transplantation is not an option at the time of therapy with vutrisiran.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hAATR amyloidosis, and is documented as concomitant treatment.

G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin amyloidosis

The assessment is 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 added benefit.

Study pool and study design

The HELIOS-A study was used for the benefit assessment.

The HELIOS-A study is an open-label currently ongoing RCT with several study phases. It included patients aged 18 to 85 years with hATTR amyloidosis. Patients had to have a neuropathy impairment score (NIS) of 5 to 130, a polyneuropathy disability (PND) score ≤ IIIb and a Karnofsky performance status (KPS) ≥ 60% at baseline. A liver transplantation that had

been performed or was pending within the 18-month treatment phase was an exclusion criterion. The New York Heart Association (NYHA) classification had to be ≤ II at baseline.

A total of 164 patients were randomized in a 3:1 ratio and allocated to treatment with vutrisiran or patisiran. The duration of the treatment phase - according to the Summary of Product Characteristics (SPC) either vutrisiran subcutaneously every 3 months or patisiran intravenously every 3 weeks - was 18 months. This study phase represents the comparison of the intervention to be assessed with the ACT and is relevant for the present benefit assessment. All included patients had already completed this study phase or had discontinued the study.

In addition to the treatment with the study medication, any concomitant medication was permitted and documented, except for medication that is a causative therapy option against hATTR amyloidosis. Individual adequate treatment could thus be performed in both study arms.

At the start of the study, all patients had stage 1 or 2 familial amyloidotic polyneuropathy (FAP).

Risk of bias

The risk of bias across outcomes was rated as low for the HELIOS-A study.

The results of all outcomes have a high risk of bias. For the outcomes on morbidity, this results from the open-label study design. For all outcomes on adverse events (AEs), including mortality, there is a high risk of bias in the effects estimated by relative risks (RRs) from the different lengths of observation periods provided in the study design. In addition, the available outcomes on AEs include a relevant proportion of events that can be both side effects and symptoms of the disease.

Results

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Morbidity

Symptoms (Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QoL-DN])

Symptoms were recorded using the Norfolk QoL-DN. Compared with the start of the study, no statistically significant difference between treatment groups was shown at the end of the 18-month treatment phase with vutrisiran or patisiran. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Symptoms (10-metre walk test [10-MWT])

With regard to the walking speed over a 10-metre distance, there is no statistically significant difference between the treatment groups at the end of the 18-month treatment phase with vutrisiran or patisiran compared to the start of the study. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Health status

The health status was recorded using the EQ-5D-5L visual analogue scale (VAS). Compared with the start of the study, no statistically significant difference between treatment groups was shown at the end of the 18-month treatment phase with vutrisiran or patisiran. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Health-related quality of life

In the HELIOS-A study, no outcome suitable to reflect the health-related quality of life was recorded. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Side effects

Serious AEs

For SAEs, there was a statistically significant difference between treatment groups in favour of vutrisiran. There was a hint of lesser harm from vutrisiran in comparison with patisiran.

Severe AEs

For severe AEs, there was a statistically significant difference between treatment groups in favour of vutrisiran. There was a hint of lesser harm from vutrisiran in comparison with patisiran.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for discontinuation due to AEs. There is no hint of greater or lesser harm from vutrisiran in comparison with patisiran; greater or lesser harm is therefore not proven.

Infusion related reaction

The analysis presented by the company is not suitable for the benefit assessment; however, serious infusion reactions are considered in the overall rate of SAEs.

Specific AEs

A statistically significant difference between the treatment groups in favour of vutrisiran was shown for the specific AE "injury, poisoning and procedural complications (severe AEs)". There was a hint of lesser harm from vutrisiran in comparison with patisiran.

A statistically significant difference between treatment groups in favour of vutrisiran was found for the specific AEs "infections and infestations (SAEs)" and "cardiac failure (SAEs)". In each case, there was a hint of lesser harm from vutrisiran in comparison with patisiran.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug vutrisiran compared with the ACT is assessed as follows:

The overall consideration yields positive effects of vutrisiran over patisiran for the outcomes of SAEs and severe AEs.

In summary, there is a hint of minor added benefit of vutrisiran over patisiran for patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

Table 3 presents a summary of the probability and extent of 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**
Adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy[b]	Tafamidis (only for hATTR amyloidosis with stage 1 polyneuropathy) or patisiran	Hint of minor added benefit[d]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that liver transplantation is not an option at the time of therapy with vutrisiran.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hAATR amyloidosis, and is documented as concomitant treatment.
f. The HELIOS-A study included only patients with a KPS ≥ 60% and an NYHA classification ≤ II. It remains unclear whether the observed effects are transferable to patients with a KPS < 60 or an NYHA classification > II.

G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin amyloidosis; KPS: Karnofsky performance status; NYHA: New York Heart Association

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of vutrisiran in comparison with the ACT in patients with hATTR amyloidosis with stage 1 or 2 polyneuropathy.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of vutrisiran

Therapeutic indication	**ACT[a]**
Adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathyb	Tafamidis (only for hATTR amyloidosis with stage 1 polyneuropathy) or patisiran

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that liver transplantation is not an option at the time of therapy with vutrisiran.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hAATR amyloidosis, and is documented as concomitant treatment.

G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin amyloidosis

The company cited patisiran as ACT.

The assessment is 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. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on vutrisiran (status: 19 August 2022)
- bibliographical literature search on vutrisiran (last search on 19 August 2022)
- search in trial registries / trial results databases for studies on vutrisiran (last search on 19 August 2022)
- search on the G-BA website for vutrisiran (last search on 19 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on vutrisiran (last search on 02 November 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: vutrisiran versus patisiran

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
HELIOS-A	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: vutrisiran versus patisiran

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HELIOS-A	RCT, open-label, parallel	Adults with hATTR amyloidosis and a polyneuropathy disability (PND) score ≤ IIIb	Vutrisiran (N = 122) patisiran (N = 42)	Screening: 42 days treatment: 18-month randomized treatment phase (vutrisiran 25 mg every 3 months vs. patisiran 0.3 mg/kg every 3 weeks) 42-month randomized extension phase[b] (vutrisiran 25 mg every 3 months vs. vutrisiran 50 mg every 6 months) observation period: until 1 year after the last administration of vutrisiran	57 study centres in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Cyprus, France, Germany, Greece, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Portugal, Sweden, Spain, Taiwan, United Kingdom, USA start of study: 14 February 2019-ongoing	Primary: change in mNIS+7 compared to the placebo group in the APOLLO study[c] secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The randomized extension phase is not relevant for this benefit assessment and is no longer shown in the following tables.
c. APOLLO is an RCT comparing patisiran with placebo over a period of 18 months. It included adults with hATTR amyloidosis and a PND score ≤ IIIb.

hATTR amyloidosis: hereditary transthyretin amyloidosis; mNIS+7: modified Neurologic Impairment Score +7; N: number of randomized patients; PND: polyneuropathy disability; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: vutrisiran versus patisiran

Study	Intervention	Comparison
HELIOS-A	Vutrisiran 25 mg every 3 months, SC	Patisiran 0.3 mg/kg[a] every 3 weeks, IV
	Premedication before patisiran at least 60 minutes before start of the infusion[b]: ▪ intravenous corticosteroids (dexamethasone 10 mg or equivalent)[c] ▪ oral paracetamol (500 mg) ▪ intravenous H1 blockers (diphenhydramine 50 mg or equivalent) ▪ intravenous H2 blockers (ranitidine 50 mg or equivalent)	
	Non-permitted pretreatment ▪ transthyretin-lowering treatment or participation in a trial with a gene therapy for hATTR amyloidosis **permitted concomitant treatment** ▪ topical drugs and vitamins including vitamin A ▪ NSAIDs **non-permitted concomitant treatment** ▪ inotersen ▪ tafamidis, doxycycline and tauroursodeoxycholic acid had to be discontinued at least 14 days before the start of the study medication. ▪ diflunisal had to be discontinued at least 3 days before the start of the study medication.	

a. The recommended maximum dose for patients with a body weight ≥ 100 kg is 30 mg.
b. Additional or higher doses of the premedication were allowed as required.
c. After at least 3 infusions of patisiran not entailing any infusion-related reactions occurred, a reduction of the corticosteroid dose was recommended. Reduction was also possible in cases of poor tolerance.

H1/2: type 1/2 histamine receptor; hATTR-Amyloidose: hereditary transthyretin amyloidosis; IV.: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous

The HELIOS-A study is an open-label currently ongoing RCT with several study phases. It included patients aged 18 to 85 years with hATTR amyloidosis. Patients had to have an NIS of 5 to 130, a PND score ≤ IIIb and a KPS ≥ 60% at baseline. A liver transplantation that had been performed or was pending within the 18-month treatment phase was an exclusion criterion. The NYHA classification had to be ≤ II at baseline.

A total of 164 patients were randomized in a 3:1 ratio and allocated to treatment with vutrisiran or patisiran. The duration of the treatment - according to the respective SPC either vutrisiran subcutaneously every 3 months or patisiran intravenously every 3 weeks - was 18 months [8,9]. This study phase represents the comparison of the intervention to be assessed with the ACT and is relevant for the present benefit assessment. All included patients had already completed this study phase or had discontinued the study.

118 patients of the vutrisiran arm and 38 patients of the patisiran arm were included in the extension phase of the study. With the protocol amendment of 14 February 2022, the

extension phase was extended from 18 months to 42 months. The first administration of vutrisiran in the extension phase took place after about 3 months for patients who had already received vutrisiran before. For patients who had previously received patisiran, the first dose of vutrisiran was given as part of the extension phase approximately 4 weeks after the end of the 18-month treatment phase with patisiran. The extension phase and the subsequent 1-year observation phase of the study are not relevant for the present benefit assessment, as they do not enable a comparison with the ACT. In addition, the treatment with vutrisiran carried out in the extension phase (in particular the dosage regimen of 50 mg vutrisiran every 6 months, which deviates from the SPC) does not represent a subsequent therapy for patients after the 18-month treatment phase that results from therapy standards [8-10].

In addition to the treatment with the study medication, any concomitant medication was permitted and documented, excluding the exceptions listed in Table 7. Individual adequate treatment could thus be performed in both study arms. All patients received at least 1 concomitant medication, including most frequently vitamin A (61% in the vutrisiran arm and 48% in the patisiran arm), viral vaccines (mainly against COVID-19) and antiepileptic drugs.

Data cut-offs were planned to take place at month 9 and at the end of the 18-month treatment phase, at month 9 of the extension phase and at the end of the study.

The company presented analyses at month 9 and at the end of the 18-month treatment phase.

Primary outcome of the study was the change in the modified Neurologic Impairment Score +7 (mNIS+7) of the vutrisiran arm of the HELIOS-A study compared to the placebo arm of the APOLLO study [11]. The APOLLO study is an RCT in which adults with hATTR amyloidosis and a PND score ≤ IIIb were treated with patisiran or placebo over a period of 18 months. Further outcomes of the HELIOS-A study were morbidity and side effects.

In Module 4 A, the company presents analyses comparing the vutrisiran arm with the patisiran arm of the HELIOS-A study and uses these results to derive an added benefit. It presents the results of the comparison of vutrisiran versus placebo as supplementary information. In the present benefit assessment, the comparison of the study arms vutrisiran and patisiran of the HELIOS-A study is used for the assessment. The comparison of vutrisiran with placebo, however, is irrelevant as administration of placebo does not correspond to the ACT.

Table 8 shows the characteristics of the patients in the included study.

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: vutrisiran versus patisiran (multipage table)

Study characteristic category	**Vutrisiran N[a] = 122**	**Patisiran N[a] = 42**
HELIOS-A		
Age [years], mean (SD)	58 (13)	58 (11)
Sex [F/M], %	35/65	36/64
Family origin, n (%)		
White	86 (71)	29 (69)
Asian	21 (17)	8 (19)
Black or African American	4 (3)	4 (10)
2 or more specifications	1 (1)	0 (0)
Other	10 (8)	1 (2)
Region, n (%)		
North America	27 (22)	8 (19)
Western Europe	42 (34)	20 (48)
Rest of the world	53 (43)	14 (33)
NIS[b], n (%)		
< 50	78 (64)	27 (64)
≥ 50–< 100	39 (32)	13 (31)
≥ 100	5 (4)	2 (5)
Stage of FAP, n (%)		
1	84 (69)	31 (74)
2	38 (31)	11 (26)
PND score, n (%)		
I	44 (36)	15 (36)
II	50 (41)	17 (41)
IIIA	16 (13)	7 (17)
IIIB	12 (10)	3 (7)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	1.9 (0.0; 15.3)	2.4 (0.1; 12.5)
Genotype, n (%)		
V30M	54 (44)	20 (48)
Other mutations	68 (56)	22 (52)
KPS, n (%)		
60	17 (14)	5 (12)
70–80	73 (60)	27 (64)
90–100	32 (26)	10 (24)

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: vutrisiran versus patisiran (multipage table)

Study characteristic category	**Vutrisiran N[a] = 122**	**Patisiran N[a] = 42**
NYHA class		
No cardiac failure	68 (56)	21 (50)
I	11 (9)	5 (12)
II	43 (35)	16 (38)
Treatment discontinuation, n (%)[c]	5 (4)	4 (10)
Study discontinuation, n (%)[c]	4 (3)	4 (10)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Mean value of non-missing surveys for screening visits 2 and 3 with imputation of missing components. Missing values of one of the individual domains (NIS-weakness, NIS-reflexes, NIS-sensation) were replaced with the second value recorded in the double survey at the respective time point of recording. If both values of the individual domain were missing, the respective value was replaced with the mean value of the patients without missing values of the respective individual domain (within the study group). Here, NIS-weakness was an exception: if both double surveys were missing at a survey time, the NIS was counted as missing.
c. Data refer to the 18-month randomized treatment phase of vutrisiran vs. patisiran. The data include 2 deaths in the vutrisiran arm and 3 deaths in the patisiran arm.

FAP: familial amyloidotic polyneuropathy; F: female; KPS: Karnofsky performance status; M: male; n: number of patients in the category, N: number of randomized patients; NIS: neuropathy impairment score; NYHA: New York Heart Association; PND: polyneuropathy disability; RCT: randomized controlled trial; SD: standard deviation; V30M: Valin30Methionine

At baseline, patient characteristics were balanced between the two HELIOS-A treatment groups. The patients' mean age was 58 years, and the majority were white (approx. 70%) and male (65%). About half of the patients had NYHA class I or II cardiac failure. All patients had stage 1 (approx. 70%) or 2 FAP and the majority had a NIS < 50 (64%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: vutrisiran versus patisiran

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
HELIOS-A	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low.

Limitations resulting from the open-label study design are described in Section I 4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company states that the study was conducted in 22 countries in Europe, North America, South America, Central America, Asia and Australia and that the subgroup analysis for the characteristic “region (North America vs. Western Europe vs. rest of the world)” showed no indication of effect modification. The patient characteristics of mutation type and age are consistent with a distribution that would be expected in patients in Germany.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Symptoms, recorded using the Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QoL-DN] questionnaire
  - Symptoms, recorded using the 10-MWT
  - Health status, recorded using the EQ-5D VAS
- health-related quality of life
- Side effects
  - Serious AEs (without consideration of the Preferred Terms (PTs) that contain “amyloid” and “progression”)
  - Severe AEs (without consideration of the PTs that contain “amyloid” and “progression”; for a definition of the severities see text below)
  - Discontinuation due to AEs
  - Infusion related reaction
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: vutrisiran versus patisiran

Study	Outcomes											
	All-cause mortality	Symptoms (Norfolk QoL-DN)	Symptoms (10-MWT)	Health status (EQ-5D-5L VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion related reaction	Injury, poisoning and procedural complications (SOC, severe AE[a])	Infections and infestations (SOC, SAE)	Heart failure (SMQ narrow scope, SAE)
HELIOS-A	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	No[c]	Yes	Yes	Yes

a. Severe AEs are operationalized as severe or medically significant but not immediately life-threatening; hospitalization or prolonged stays in hospital indicated; impairing; limiting self-care in daily life (e. g. bathing, dressing and undressing, feeding, toileting, taking medication, and not confined to bed); or life-threatening consequences; urgent intervention indicated; or death due to adverse events. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
b. Outcome not recorded; the company allocated the Norfolk QoL-DN instrument to health-related quality of life (see text below).
c. The analysis presented by the company is not suitable for the benefit assessment; however, serious infusion reactions are considered in the overall rate of SAEs (see text below).

10-MWT: 10-metre walk test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Norfolk QoL-DN

The Norfolk QoL-DN questionnaire used in the HELIOS-A study consists of 35 questions distributed across the domains of physical functioning/large nerve fibres (15 questions), activities of daily living (5 questions), symptoms (8 questions), small nerve fibres (4 questions) and autonomic functioning (3 questions). The patients' answers to individual questions are converted into points and an overall score is formed from this, whereby a lower number of points means less or milder symptoms. The total score of the Norfolk QoL-DN can reach values from -4 to 136. The questionnaire used has been validated in the present indication and is a suitable instrument for recording symptoms and activities of daily life [12-14]. The company assigned the Norfolk QoL-DN questionnaire to health-related quality of life. However, the Norfolk QOL-DN does not reflect the psychological and social dimensions of

health-related quality of life [15]. In the present benefit assessment, it is therefore assigned to morbidity.

The company presented analyses of binary data in which a patient was already included as a responder with any improvement in the total score, i.e. decrease in the total score (< 0 points), as well as analyses of continuous data. The analysis of continuous data (total score of the Norfolk QoL-DN) was used as the company did not provide analyses of a response criterion with 15% of the scale range. Moreover, the sole consideration of improvement in a progressive disease such as hATTR amyloidosis would not be appropriate.

10-MWT

The 10-MWT records the walking speed over a 10-metre distance. In addition to the analysis of continuous data, the company presented an analysis of binary data in which patients with any improvement, i.e. increase in walking speed (> 0 m/s), were rated as responders. This criterion is not suitable for depicting an improvement on a patient-relevant scale. Moreover, since hATTR amyloidosis is a progressive disease, considering improvement alone would not be appropriate. In the present benefit assessment, the analysis is therefore based on continuous data.

Only 3 time points of documentation were planned and took place during the 18-month treatment phase (study start, month 9 and month 18). Each point of documentation included the measurement of walking speed over a 10-metre distance on 2 days at intervals of 24 hours to 7 days. If the distance could not be managed, the score was 0. The mean value was calculated from the two scores. If only one measurement was available at the time point of documentation, it was included in the analysis.

EQ-5D-5L VAS

In addition to the analysis of continuous data, the company presented an analysis of binary data in which patients with any improvement by ≥ 15 points were rated as responders. Although a suitable response criterion of 15% of the scale range was available here, the analysis of continuous data was used in the present benefit assessment. hATTR amyloidosis is a progressive disease. Therefore, the sole consideration of responder analyses on improvement would not have been appropriate in the present therapeutic indication.

Approach of the company for analyses on continuous data

Only 3 time points of documentation were planned and took place during the 18-month treatment phase (study start, month 9 and month 18). The company chose a mixed-effects model with repeated measures (MMRM) as analyses on continuous data.

It is assumed that all recorded data were used for parameter estimate. The company stated a difference from the start of the study to month 18.

Further outcomes on morbidity presented by the company

Hospitalization

The company presented analyses of hospitalization due to any cause and hospitalization due to cardiovascular events. Hospitalization due to cardiovascular events can in principle be a suitable operationalization for severe cardiovascular symptoms. However, as no further information was available on the operationalization and the underlying events, the analyses on hospitalization due to cardiovascular events were not used in the present benefit assessment. The outcome of hospitalization due to any cause is presented as supplementary information (see I Appendix B of the full dossier assessment).

mNIS+7 and NIS

The company presented analyses on the change in the mNIS+7 and NIS score. Both instruments are based on the physician's assessment and are used to record sensorimotor abilities and loss of sensation. Parameters are recorded that are not considered to be directly relevant to the patient (e.g. stimulus conduction tests). Outcomes from the survey using mNIS+7 and NIS were therefore not included in the present benefit assessment.

FAP and PND score

The company presented analyses on the change of FAP stage and PND score. FAP stage (stage 0: asymptomatic; stage 1: ambulatory without assistive devices, symptoms of polyneuropathy limited to lower limbs; stage 2: mobile but dependent on walking aids for ambulation, worsening and extension of polyneuropathic symptoms; stage 3: wheelchair dependence or bedriddenness, generalized weakness and severe polyneuropathic symptoms in all limbs) and PND score (I: sensory disorders, but unrestricted mobility; II: restricted mobility without the need for walking aids; IIIa: locomotion only possible with a unilateral walking aid; IIIb: locomotion only possible with bilateral walking aids; IV: dependence on a wheelchair or bedriddenness) are assessed by the physician and are intended to reflect the patient's mobility.

FAP stage and PND score were recorded by the physician at the day of the visit at baseline, month 9 and month 18. Change to a lower FAP stage or a lower PND score was assessed as an improvement, change to a higher FAP stage or a higher PND score was considered a deterioration and a constant FAP stage or a constant PND score meant stabilisation. For the analyses on the PND score, no information is available on whether the scores IIIa and IIIb were assessed separately. Changes in the FAP stage and the PND score were not used in the present benefit assessment. The significance of a change can vary depending on the individual patient and the baseline score. There is also uncertainty, particularly in the case of low FAP stages and PND scores, as to whether the physician's assessment of mobility during the visit reflects the patient's mobility in everyday life with sufficient certainty. The Norfolk QoL-DN provides

analyses of a questionnaire that depicts morbidity in the present field of application in a more comprehensive and patient-reported manner.

Rasch-Built Overall Disability Score (R-ODS)

The company presented no data showing that the R-ODS is validated in the therapeutic indication of hATTR amyloidosis with polyneuropathy. The C-ODS was disregarded in the present benefit assessment.

Side effects

The analyses presented for the continuously recorded outcomes (AEs, all-cause mortality and hospitalizations) included events up to the end of the 18-month treatment phase plus the time up to the first administration of vutrisiran in the extension phase. Due to the different dosing regimen of vutrisiran and patisiran, the maximum observation period for these outcomes is 18 months plus 84 days for the vutrisiran arm and 18 months plus 28 days for the patisiran arm. Information on the actual observation period for the continuously recorded outcomes is not available. Due to the overall long observation period in both arms, if events up to the first administration of vutrisiran in the extension phase were taken into account, the observation period in the patisiran arm would be about 90% of the observation period in the vutrisiran arm. For the consideration of the relative risks (RRs), the observation durations in the study arms are considered sufficiently similar. However, the difference in the observation periods is taken into account when assessing the outcome-specific risk of bias (see Section I 4.2).

The company presented analyses for the outcomes of severe AEs and SAEs in which PTs containing the term "amyloid" or "progression" were excluded. This analysis was used for the present benefit assessment. However, the exclusion of these terms only led to the exclusion of events in isolated cases and had no effect on the proportions of patients with events compared to the analysis without exclusion of these PTs. Due to the heterogeneity of the symptoms of the underlying disease hATTR amyloidosis [10], it remains unclear to what extent the events that occurred represent side effects or the progression or symptoms of the underlying disease. This is taken into account when assessing the outcome-specific risk of bias (see Section I 4.2).

Severe AEs

According to the study protocol, the severity of AEs was assessed using the following criteria:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated

- Moderate: minimal, local or non-invasive intervention indicated; impairment of age-appropriate important activities of daily life (e. g. preparing meals, buying food or clothes, using a telephone, managing money)
- Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolonged stays in hospital indicated; impairing; limiting self-care in daily life (e. g. bathing, dressing and undressing, feeding, toileting, taking medication, and not confined to bed); or life-threatening consequences; urgent intervention indicated; or death due to AEs.

This definition corresponds verbatim to the comprehensive definition of the Common Terminology Criteria for Adverse Events (CTCAE) grades specified by the National Cancer Institute (NCI) [16]. The definition of a severe AE in the study protocol covers NCI CTCAE grades 3, 4 and 5. However, in the Case Report Form (CRF) of the study, the definition of severity was not listed again. In addition, if the severity was not specified, the event was imputed as severe. There is no information of how many events this affected. Moreover, although the results for severe AEs are consistent with the results for SAEs in terms of statistical significance, they differ to a clear extent (see Section I 4.3). In the present benefit assessment, the results on severe AEs were used, but the extent is estimated to be non-quantifiable.

Infusion related reaction

In the HELIOS-A study, infusion-related reactions were documented as AEs (PT “infusion related reaction”). In principle, due to the open-label study design (without placebo infusion) and regular intravenous administration, events in the PT "infusion related reaction" could only be recorded in the comparator arm. Thus, there are no usable (comparative) data for the benefit assessment, but serious infusion reactions were considered in the overall rate of SAEs (see below). In order to obtain the comparative data required for the benefit assessment, it is necessary to consider all symptomatic AEs (e. g. “back pain”, regardless of whether they are infusion-related or not) within the framework of the AE analysis. For this purpose, the respective symptoms had to be included in the AE analyses via the corresponding PT (e.g. PT “back pain”) (as, for instance, in the MAIA study, see [17]). This allows taking these events into account in the benefit assessment even if they occurred in unblinded studies comparing orally or subcutaneously and intravenously administered drugs. However, this approach was not chosen in the present HELIOS-A study. In the HELIOS-A study, events underlying the AE of infusion-related reactions were documented, but were not included in the analyses on AEs. An assessment of the severity of these events was not planned. These events (e.g. back pain) are thus missing in the analyses on AEs. For the superordinate AE outcomes (e.g. SAEs), this has no relevant impact, as it makes no difference whether a patient is included in the analyses with the event “infusion-related reaction” or with an underlying event. The most common events were back pain (3 patients with event), headache, pruritus, flush and hypotension (2 patients with event each). The total of 21 different PTs are distributed over 9 different system

organ classes (SOCs). In the present data constellation, the impact of the unconsidered events on the analyses at SOC and PT level are considered to be negligible.

In order to obtain a complete picture of infusion-related reactions, an aggregate analysis of these specific AEs (e.g. by means of a prespecified PT list) would in principle be desirable, in which corresponding PTs for both treatment groups are included independently of a documented connection with an infusion.

The company did not assign the PT "infusion-related reaction" to the primary SOC "injury, poisoning and procedural complications", but to the SOC "immune system disorders", without justifying this.
It was not checked whether other PTs were not assigned to the primary SOC.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: vutrisiran vs. patisiran

Study	Study level	Outcomes											
		All-cause mortality	Symptoms (Norfolk QoL-DN)	Symptoms (10-MWT)	Health status (EQ-5D-5L VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion related reaction	Injury, poisoning and procedural complications (SOC, severe AE[a])	Infections and infestations (SOC, SAE)	Heart failure (SMQ narrow scope, SAE)
HELIOS-A	L	H[b]	H[c]	H[c]	H[c]	–[d]	H[b, e]	H[b,c,e,f]	H[b,c,e]	–[g]	H[b,c,e,f]	H[b, e]	H[b, e]

a. Severe AEs are operationalized as severe or medically significant but not immediately life-threatening; hospitalization or prolonged stays in hospital indicated; impairing; limiting self-care in daily life (e. g. bathing, dressing and undressing, feeding, toileting, taking medication, and not confined to bed); or life-threatening consequences; urgent intervention indicated; or death due to adverse events. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
b. Observation +84 days and +24 days after last dose in the intervention and the control arm, thus systematically differing observation period between the arms for potentially informative reasons.
c. Lack of blinding in subjective outcomes or subjective outcome recording.
d. Outcome not recorded; the company allocated the Norfolk QoL-DN instrument to health-related quality of life (see Section I 4.1).
e. Including a relevant proportion of events that can be both side effects and symptoms.
f. If the severity was not specified, the event was imputed as severe.
g. The analysis presented by the company is unsuitable for the benefit assessment (see Section I 4.1).

10-MWT: 10-metre walk test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

There are no data on health-related quality of life and infusion-related reactions whose risk of bias should have been assessed. The results of all other outcomes have a high risk of bias.

For the patient-reported outcomes, the 10-MWT and discontinuation due to AEs, this results from the open-label study design. This also applies to the superordinate and specific outcomes on severe AEs, which were not defined according to detailed AE-specific criteria but only according to the superordinate CTCAE criteria in this study.

Deaths were recorded within the framework of the AEs. For all outcomes on AEs, including mortality, there is a high risk of bias in the effects estimated by RRs from the different lengths of observation periods provided in the study design. In addition, the available outcomes on AEs include a relevant proportion of events that can be both side effects and symptoms of the disease.

I 4.3 Results

Table 12 and Table 13 summarize the results on the comparison of vutrisiran with patisiran in patients with hATTR amyloidosis with stage 1 or 2 polyneuropathy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 12: Results (mortality, side effects) – RCT, direct comparison: vutrisiran versus patisiran (multipage table)

Study outcome category outcome	Vutrisiran		Patisiran		Vutrisiran vs. patisiran
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
HELIOS-A					
Mortality[b]					
All-cause mortality	122	2 (1.6)	42	3 (7.1)	0.23 [0.04; 1.33][c]; 0.078
Side effects[b, d]					
AEs[e] (supplementary information)	122	119 (97.5)	42	41 (97.6)	Not applicable
SAEs[e]	122	32 (26.2)	42	18 (42.9)	0.61 [0.39; 0.97] 0.045
Severe AEs[e, f]	122	19 (15.6)	42	16 (38.1)	0.41 [0.23; 0.72] 0.002
Discontinuation due to AEs	122	3 (2.5)	42	3 (7.1)	0.34 [0.07; 1.64] 0.174
Infusion related reaction	Analysis unsuitable[g]				
Injury, poisoning and procedural complications (SOC, severe AE[f])[h]	122	1 (0.8)	42	3 (7.1)	0.12 [0.01; 1.07]; 0.031[i]
Infections and infestations (SOC, SAE)	122	9 (7.4)	42	8 (19.0)	0.39 [0.16; 0.94] 0.034
Heart failure (SMQ narrow scope, SAE)	122	4 (3.3)	42	5 (11.9)	0.28 [0.08; 0.98] 0.036

Table 12: Results (mortality, side effects) – RCT, direct comparison: vutrisiran versus patisiran (multipage table)

Study outcome category outcome	Vutrisiran N	Vutrisiran patients with event n (%)	Patisiran N	Patisiran patients with event n (%)	Vutrisiran vs. patisiran RR [95% CI]; p-value[a]

a. p-value: IQWiG calculation (unconditional exact test, CSZ method according to [18]).
b. During the 18-month randomized treatment phase of vutrisiran vs patisiran; including events that occurred after the 18-month randomized treatment phase of vutrisiran vs. patisiran but before the first dose of vutrisiran in the extension phase, i.e. + 84 days in the vutrisiran arm and + 28 days in the patisiran arm.
c. Effect and CI: Institute's calculation.
d. Including a relevant proportion of events that can be both side effects and symptoms.
e. Events whose PT included the terms “amyloid” or “progression” were not taken into account.
f. Severe AEs are operationalized as severe or medically significant but not immediately life-threatening; hospitalization or prolonged stays in hospital indicated; impairing; limiting self-care in daily life (e. g. bathing, dressing and undressing, feeding, toileting, taking medication, and not confined to bed); or life-threatening consequences; urgent intervention indicated; or death due to adverse events. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
g. The analysis presented by the company is not suitable for the benefit assessment; however, serious infusion reactions are considered in the overall rate of SAEs (see Section I 4.1).
h. Included PTs are „fall“, „ankle fracture“ und „foot fracture“. The company did not assign the PT "infusion-related reactions" to the primary SOC "injury, poisoning and procedural complications", but to the SOC "immune system disorders”.
i. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NCI: National Cancer Institute; PT: Preferred Term; SMQ: randomized controlled trial; SOC: System Organ Class; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: vutrisiran versus patisiran

Study outcome category outcome	Vutrisiran			Patisiran			Vutrisiran vs. patisiran
	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 18 LS mean[b] (SE)	LS MD [95% CI]; p-value[c]
HELIOS-A							
Morbidity							
Symptoms							
Norfolk QoL-DN total score[d]	113	47.1 (26.3)	0.9 (1.7)	38	47.3 (29.9)	3.6 (2.9)	-2.7 [-9.2; 3.7]; 0.401
Physical functioning/large nerve fibres	113	23.1 (13.8)	-0.3 (0.9)	38	23.0 (14.9)	2.1 (1.6)	-2.4 [-5.9; 1.1]
Every day activities	113	5.7 (5.7)	1.2 (0.4)	38	5.0 (5.6)	0.5 (0.6)	0.7 [-0.7; 2.0]
Symptoms	112	11.0 (6.1)	-0.4 (0.5)	38	11.2 (7.3)	0.4 (0.8)	-0.7 [-2.5; 1.0]
Small nerve fibres	113	4.6 (4.2)	0.9 (0.3)	38	5.1 (4.5)	0.8 (0.5)	0.0 [-1.1; 1.1]
Autonomous functioning	113	2.7 (2.9)	-0.5 (0.2)	38	3.0 (2.8)	-0.2 (0.3)	-0.3 [-0.9; 0.4]
10-MWT [m/s]	113	1.01 (0.39)	-0.03 (0.03)	38	1.01 (0.40)	-0.07 (0.04)	0.04 [-0.06; 0.14]; 0.441
Health status							
EQ-5D-5L VAS[e]	112	64.5 (18.5)	-0.5 (1.3)	37	63.0 (16.1)	-5.3 (2.3)	4.8 [-0.3; 9.9]; 0.067
Health-related quality of life							
Outcome not recorded[f]							

a. Number of patients considered in the analysis to calculate the effect estimation; the values at baseline are based on 120 to 122 patients in the intervention arm and 41 to 42 patients in the control arm.
b. From the MMRM analysis.
c. Effect, CI and p-values: MMRM with unstructured variance matrix, baseline value as continuous covariable, treatment, visit, genotype, age at onset of disease and NIS at baseline (< 50 vs. ≥ 50) as categorical factors, interaction term treatment × visit. Effect refers to the change from baseline at the time point 18 months.
d. Lower values indicate minor symptoms (scale range -4 to 136). Negative effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
e. Higher values mean a better health status (scale range 0 to 100). Positive effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
f. The company assigned the Norfolk QoL-DN instrument to health-related quality of life (see Section I 4.1).

10-MWT: 10-metre walk test; CI: confidence interval; LS: least squares; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; NIS: neuropathy impairment score; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Morbidity

Symptoms (Norfolk QoL-DN)

Symptoms were recorded using the QoL-DN. Compared with the start of the study, no statistically significant difference between treatment groups was shown at the end of the 18-month treatment phase with vutrisiran or patisiran. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Symptoms (10-MWT)

With regard to the walking speed over a 10-metre distance, there is no statistically significant difference between the treatment groups at the end of the 18-month treatment phase with vutrisiran or patisiran compared to the start of the study. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Health status

Health status was surveyed by EQ-5D-5L VAS. Compared with the start of the study, no statistically significant difference between treatment groups was shown at the end of the 18-month treatment phase with vutrisiran or patisiran. There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Health-related quality of life

In the HELIOS-A study, no outcome suitable to reflect the health-related quality of life was recorded (for justification, see Section I 4.1). There was no hint of an added benefit of vutrisiran compared to patisiran; an added benefit is therefore not proven.

Side effects

SAEs

For SAEs, there was a statistically significant difference between treatment groups in favour of vutrisiran. There was a hint of lesser harm from vutrisiran in comparison with patisiran.

Severe AEs

For severe AEs, there was a statistically significant difference between treatment groups in favour of vutrisiran. There was a hint of lesser harm from vutrisiran in comparison with patisiran.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for discontinuation due to AEs. There is no hint of greater or lesser harm from vutrisiran in comparison with patisiran; greater or lesser harm is therefore not proven.

Specific AEs

A statistically significant difference between the treatment groups in favour of vutrisiran was shown for the specific AE "injury, poisoning and procedural complications (severe AEs)". There was a hint of lesser harm from vutrisiran in comparison with patisiran.

A statistically significant difference between treatment groups in favour of vutrisiran was found for the specific AEs "infections and infestations (SAEs)" and "cardiac failure (SAEs)". In each case, there was a hint of lesser harm from vutrisiran in comparison with patisiran.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- FAP (1 vs. 2)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

For the binary data, the interaction test of the company was performed by logistic regression with Firth correction, i.e. related to the odds ratio (OR), not to the RR. Therefore, own interaction tests were calculated using the uncorrected RRs for situations in which the interaction p-values from the logistic regression of the company were below 0.3. This concerned the superordinate outcomes on SAEs and on severe AEs, each with the characteristic "sex".

Using the methods described above, the available subgroup results do not reveal any effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [19].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 14).

Table 14: Extent of added benefit at outcome level: vutrisiran versus patisiran (multipage table)

Outcome category **outcome**	**Vutrisiran vs. patisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	1.6% vs. 7.1% RR 0.23 [0.04; 1.33] p = 0.078	Lesser/added benefit not proven
Morbidity		
Symptoms (Norfolk QoL-DN[c])	0.9 vs. 3.6 LS MD: -2.7 [-9.2; 3.7] p = 0.401	Lesser/added benefit not proven
Symptoms (10-MWT [m/s])	-0.03 vs. -0.07 LS MD: 0.04 [-0.06; 0.14] p = 0.441	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS[d])	-0.5 vs. -5.3 LS MD: 4.8 [-0.3; 9.9] p = 0.067	Lesser/added benefit not proven
Health-related quality of life		
Outcome not recorded[e]		
Side effects[f]		
SAEs	26.2% vs. 42.9% RR: 0.61 [0.39; 0.97] p = 0.045 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"
Severe AEs	15.6% vs. 38.1% RR: 0.41 [0.23; 0.72] p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Discontinuation due to AEs	2.5% vs. 7.1% RR: 0.34 [0.07; 1.64] p = 0.174	Greater/lesser harm not proven
Infusion related reaction	Analysis unsuitable[g]	Greater/lesser harm not proven
Injury, poisoning and procedural complications (severe AEs)	0.8% vs. 7.1% RR: 0.12 [0.01; 1.07] p = 0.031 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"

Table 14: Extent of added benefit at outcome level: vutrisiran versus patisiran (multipage table)

Outcome category **outcome**	**Vutrisiran vs. patisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infections and infestations (SAEs)	7.4% vs. 19.0% RR: 0.39 [0.16; 0.94] p = 0.034 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"
Cardiac failure (SAE)	3.3% vs. 11.9% RR: 0.28 [0.08; 0.98] p = 0.036 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. Lower values indicate fewer symptoms (scale range -4 to 136). Negative effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
d. Higher values mean a better health status (scale range 0 to 100). Positive effects (vutrisiran versus patisiran) indicate an advantage for the intervention.
e. Outcome not recorded; the company allocated the Norfolk QoL-DN instrument to health-related quality of life (see Section I 4.1).
f. Includes events which can be both side effects and symptoms of the disease.
g. The analysis presented by the company is not suitable for the benefit assessment; however, serious infusion reactions are considered in the overall rate of SAEs (see Section I 4.1).

10-MWT: 10-metre walk test; AE: adverse event: CI: confidence interval; CI_u: upper limit of the confidence interval; CI_L: lower limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; LS: least squares; MD: mean difference; NCI: National Cancer Institute; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of vutrisiran in comparison with patisiran

Positive effects	**Negative effects**
Serious/severe side effects[a] ▪ SAEs: hint of lesser harm – extent: “minor” ▫ infections and infestations (SAEs): hint of lesser harm – extent: minor ▫ cardiac failure (SAEs): hint of lesser harm – extent: “minor” ▪ severe AEs: hint of lesser harm - extent: “non-quantifiable” ▫ injury, poisoning and procedural complications (severe AEs): hint of lesser harm - extent: "non-quantifiable"	–
There are no data on the outcome of health-related quality of life	
a. Includes events which can be both side effects and symptoms of the disease. AE: adverse event; SAE: serious adverse event	

The overall consideration yields positive effects of vutrisiran over patisiran for the outcomes of SAEs and severe AEs. Events may be included that can be assigned to both side effects and symptoms of the disease.

In summary, there is a hint of minor added benefit of vutrisiran over patisiran for patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

Table 16 summarizes the result of the assessment of added benefit of vutrisiran in comparison with the ACT.

Table 16 Vutrisiran – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with hATTR amyloidosis with stage 1 or stage 2 polyneuropathyb	Tafamidis (only for hATTR amyloidosis with stage 1 polyneuropathy) or patisiran	Hint of minor added benefit[d]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that liver transplantation is not an option at the time of therapy with vutrisiran.
c. It is assumed that a patient-specific adequate treatment of the respective organ manifestation (such as cardiac failure and/or polyneuropathy) corresponding to the state of medical knowledge is carried out in both study arms, taking into account the special features of the disease hAATR amyloidosis, and is documented as concomitant treatment.
f. The HELIOS-A study included only patients with a KPS ≥ 60% and an NYHA classification ≤ II. It remains unclear whether the observed effects are transferable to patients with a KPS < 60 or an NYHA classification > II.

G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin amyloidosis; KPS: Karnofsky performance status; NYHA: New York Heart Association

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit from the results of the HELIOS-A study.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. 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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