Patisiran (hereditary transthyretin-mediated amyloidosis with polyneuropathy)

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

EXTRACT

Project: A23-118 Version: 1.0 Status: 27 Feb 2023 DOI: 10.60584/A23-118_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Patisiran (hereditäre Transthyretin-Amyloidose mit Polyneuropathie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Patisiran (hereditary transthyretin-mediated amyloidosis with polyneuropathy) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 November 2023

Internal Project No.

A23-118

DOI-URL

https://doi.org/10.60584/A23-118_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Thomas Henze, Regensburg, Germany

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.

IQWiG employees involved in the dossier assessment

- Anne-Kathrin Petri
- Lars Beckmann
- Tobias Effertz
- Christopher Kunigkeit
- Katrin Nink
- Veronika Schneck
- Claudia Selbach
- Dorothea Sow

Keywords

Patisiran, Amyloid Neuropathies, Benefit Assessment, NCT03759379

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
10-MWT	10-metre walking test
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
CSZ	convexity, symmetry, z-score
FAP	familial amyloidotic polyneuropathy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hATTR	hereditary transthyretin-mediated amyloidosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KPS	Karnofsky performance status
LS	least squares
MD	mean difference
MMRM	mixed-effects model with repeated measures
mNIS+7	modified Neurologic Impairment Score +7
NCI	National Cancer Institute
NIS	neuropathy impairment score
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NYHA	New York Heart Association
PND	polyneuropathy disability
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug patisiran. 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 30 November 2023.

Research question

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

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

Table 2: Research question for the benefit assessment of patisiran

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 **vutrisiran**[c]
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 patisiran. 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 hATTR amyloidosis, and is documented as concomitant treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin-mediated amyloidosis	

The company designated only vutrisiran as the ACT, thus deviating from the G-BA's specification. This is irrelevant insofar as vutrisiran is an ACT option.

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 deriving any added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

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

The HELIOS-A study is the pivotal study for vutrisiran, which compares vutrisiran with patisiran. The company has already presented this study in the procedure for vutrisiran. In the course of this procedure, the study has already been assessed by IQWiG in dossier assessment A22-114 and the associated addendum A23-12.

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 1:3 ratio and allocated to treatment with patisiran or vutrisiran. The duration of the treatment phase - according to the respective Summary of Product Characteristics (SPC) either patisiran intravenously every 3 weeks or vutrisiran subcutaneously every 3 months - 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 risk of bias of the result on the outcome of overall survival was rated as low.

There are no data on health-related quality of life and infusion-related reactions.

The results of the patient-reported outcomes assessed using the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) and EQ-5D visual analogue scale (VAS), the 10-metre walking test (10-MWT) and discontinuation due to adverse events (AEs) have a high risk of bias as a result of the open-label study design. This also applies to the results of the superordinate and specific outcomes on severe AEs, which were not defined according to detailed AE-specific criteria but only according to the superordinate Common Terminology Criteria for Adverse Events (CTCAE) criteria in this study.

The available outcomes on AEs include a relevant proportion of events that can be both side effects and symptoms of the disease. Consequently, the risk of bias for the results of all outcomes related to side effects is high.

Results

Based on the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of all-cause mortality, and at most hints for all other outcomes due to the high risk of bias.

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found. There is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Morbidity

Symptoms (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 patisiran or vutrisiran. There is no hint of an added benefit of patisiran in comparison with vutrisiran; 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 patisiran or vutrisiran compared to the start of the study. There is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Health status

Health status was surveyed by EQ-5D 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 patisiran or vutrisiran. There is no hint of an added benefit of patisiran in comparison with vutrisiran; 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 is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

A statistically significant difference between treatment groups to the disadvantage of patisiran was shown for the SAEs. This results in a hint of greater harm from patisiran in comparison with vutrisiran.

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of patisiran was shown for the severe AEs. This results in a hint of greater harm from patisiran in comparison with vutrisiran.

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 patisiran in comparison with vutrisiran; greater or lesser harm is therefore not proven.

Infusion-related reaction

No suitable data are available for the outcome of infusion related reaction. There is no hint of greater or lesser harm from patisiran in comparison with vutrisiran; greater or lesser harm is therefore not proven.

Other specific AEs

For the specific AEs injury, poisoning and procedural complications (severe AEs), infections and infestations (SAEs), cardiac failure (SAEs), gastrointestinal disorders (SAEs) and general disorders and administration site conditions (SAEs), a statistically significant difference was observed between the treatment groups to the disadvantage of patisiran. In each case, this results in a hint of greater harm from patisiran in comparison with vutrisiran.

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

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

The overall consideration yields only negative effects of patisiran over vutrisiran 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 lesser benefit of patisiran over vutrisiran for patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

Table 3 shows a summary of the probability and extent of added benefit of patisiran.

Table 3: Patisiran – 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 **vutrisiran**[c]	Hint of lesser 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 patisiran.
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 hATTR amyloidosis, and is documented as concomitant treatment.
d. 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.

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

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2018. There, the G-BA had identified a considerable added benefit of patisiran based on the approval-justifying placebo-controlled APOLLO study.

I 2 Research question

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

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

Table 4: Research question for the benefit assessment of patisiran

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 **vutrisiran**[c]
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 patisiran. 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 hATTR amyloidosis, and is documented as concomitant treatment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; hATTR amyloidosis: hereditary transthyretin-mediated amyloidosis	

The company designated only vutrisiran as the ACT, thus deviating from the G-BA's specification. This is irrelevant insofar as vutrisiran is an ACT option.

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 deriving any 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 lists on patisiran (status: 14 September 2023)
- bibliographical literature search on patisiran (last search on 12 September 2023)
- search in trial registries/trial results databases for studies on patisiran (last search on 14 September 2023)
- search on the G-BA website for patisiran (last search on 14 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on patisiran (last search on 18 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

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

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)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
ALN-TTRSC02-002 (HELIOS-A[d])	No	Yes	No	Yes [1]	Yes [2-4]	Yes [5-8]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the 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.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The HELIOS-A study is the pivotal study for vutrisiran, which compares vutrisiran with patisiran. The company has already presented this study in the procedure for vutrisiran [8]. In

the course of this procedure, the study has already been assessed by IQWiG in dossier assessment A22-114 and the associated addendum A23-12 [6,7].

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: patisiran versus vutrisiran

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-group	Adults with hATTR amyloidosis and a polyneuropathy disability (PND) score ≤ IIIb	Patisiran (N = 42) vutrisiran (N = 122)	Screening: 42 days treatment: 18-month randomized treatment phase (patisiran 0.3 mg every 3 weeks vs. vutrisiran 25 mg every 3 months) 42-month randomized extension phase[b] (vutrisiran 25 mg every 3 months vs. vutrisiran 50 mg every 6 months)[c] observation period: up to 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, United States start of study: 14 February 2019-ongoing	Primary: change in mNIS+7 for vutrisiran compared to the placebo group in the APOLLO study[d] secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only 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. With Protocol Amendment 6 (March 2023), all patients who had been assigned to treatment with vutrisiran 50 mg every 6 months in the extension phase were switched to vutrisiran 25 mg every 3 months.
d. 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.

AE: adverse event; hATTR amyloidosis: hereditary transthyretin-mediated 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: patisiran versus vutrisiran

Study	Intervention	Comparison
HELIOS-A	Patisiran 0.3 mg/kg[a] every 3 weeks, IV[a]	Vutrisiran 25 mg every 3 months, SC
	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)	▪
	Disallowed pretreatment ▪ TTR-lowering treatment or participation in a trial with a gene therapy for hATTR amyloidosis **allowed concomitant treatment** ▪ Topical drugs and vitamins including vitamin A ▪ NSAIDs **disallowed 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/H2: type 1/2 histamine receptor; hATTR amyloidosis: hereditary transthyretin-mediated amyloidosis; IV.: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; TTR: transthyretin

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 NIS of 5 to 130, a polyneuropathy disability (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 New York Heart Association (NYHA) classification had to be ≤ II at baseline.

A total of 164 patients were randomized in a 1:3 ratio and allocated to treatment with patisiran or vutrisiran. The duration of the treatment phase - according to the respective Summary of Product Characteristics (SPC) either patisiran intravenously every 3 weeks or vutrisiran subcutaneously every 3 months - was 18 months [9,10]. 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.

38 patients of the patisiran arm and 118 patients of the vutrisiran 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. 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 first administration of vutrisiran in the extension phase took place after about 3 months for patients who had already received vutrisiran before. The extension phase and the subsequent 1-year observation phase of the study are not relevant for the present benefit assessment, as only vutrisiran was administered during these phases. 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 [9-11].

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 (48% in the patisiran arm and 61% in the vutrisiran 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 [12]. 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. The APOLLO study is not relevant for the present benefit assessment as administration of placebo does not correspond to the ACT. Further outcomes of the HELIOS-A study were morbidity and side effects.

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

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: patisiran versus Vutrisiran (multipage table)

Study characteristic category	**Patisiran N[a] = 42**	**Vutrisiran N[a] = 122**
HELIOS-A		
Age [years], mean (SD)	58 (11)	58 (13)
Sex [F/M], %	36/64	35/65
Family origin, n (%)		
White	29 (69)	86 (70)
Asian	8 (19)	21 (17)
Black or African American	4 (10)	4 (3)
2 or more specifications	0 (0)	1 (1)
Other	1 (2)	10 (8)
Region, n (%)		
North America	8 (19)	27 (22)
Western Europe	20 (48)	42 (34)
Rest of the world	14 (33)	53 (43)
NIS[b], n (%)		
< 50	27 (64)	78 (64)
≥ 50 − < 100	13 (31)	39 (32)
≥ 100	2 (5)	5 (4)
Stage of FAP, n (%)		
Stage 1	31 (74)	84 (69)
Stage 2	11 (26)	38 (31)
PND score, n (%)		
Stage I	15 (36)	44 (36)
Stage II	17 (40)	50 (41)
Stage IIIa	7 (17)	16 (13)
Stage IIIb	3 (7)	12 (10)
Disease duration: time between first diagnosis and randomization [years], median [min; max]	2.4 (0.1; 12.5)	1.9 (0.0; 15.3)
Genotype, n (%)		
V30M	20 (48)	54 (44)
Other mutations	22 (52)	68 (56)
KPS, n (%)		
60	5 (12)	17 (14)
70-80	27 (64)	73 (60)
90-100	10 (24)	32 (26)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: patisiran versus Vutrisiran (multipage table)

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

a. Number of randomized patients. Values which are based on different 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 patisiran vs. vutrisiran. The data include 3 deaths in the patisiran arm and 2 deaths in the vutrisiran 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: patisiran vs. vutrisiran

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; SCT: stem cell transplantation							

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 under 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 adverse events (SAEs) (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: patisiran versus vutrisiran

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

10-metre walking 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 [13-15]. 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 [16]. In the present benefit assessment, it is therefore assigned to morbidity.

As previously in the procedure for vutrisiran [8], 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 again did not provide analyses of a response criterion with 15% of the scale range. As already described in the dossier assessment for vutrisiran, 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. As previously in the procedure for vutrisiran, 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. As previously described in the dossier assessment for vutrisiran, this criterion is not suitable for depicting an improvement to a patient-relevant extent. 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.

During the 18-month treatment phase, the survey was conducted as planned at only 3 points in time (at baseline, 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 VAS

As previously in the procedure for vutrisiran, in addition to the analysis of continuous data, the company again presented an analysis of binary data In this analysis, patients with any improvement by ≥ 15 points were rated as responders. Although a suitable response criterion of 15% of the scale range is available here, considering improvement alone would not be appropriate in the present therapeutic indication since hATTR amyloidosis is a progressive disease. In the present benefit assessment, the analysis is therefore again based on continuous data.

Approach of the company for analyses on continuous data

During the 18-month treatment phase, the survey was conducted as planned at only 3 points in time (at baseline, 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 in the effect estimation 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. As previously in the procedure for vutrisiran, no further information is available on the operationalization and the underlying events. Therefore, the analyses on hospitalization due to cardiovascular events are again not included 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 considered in the present benefit assessment. However, the results are presented in the appendix as supplementary information (see I Appendix B of the full dossier 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. However,

the company still does not make it clear whether the PND scores IIIa and IIIb were analysed separately in these analyses. Changes in the FAP stage and the PND score were again 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 therapeutic indication in a more comprehensive and patient-reported manner. The information on FAP stages and PND scores provided by the company in the dossier is presented without effect estimates in the appendix as supplementary information (see I Appendix B of the full dossier assessment).

Rasch-Built Overall Disability Score (R-ODS)

As previously in the procedure for vutrisiran, 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. The results of the R-ODS are presented in the appendix as supplementary information (see I Appendix B of the full dossier assessment).

Side effects

The presented analyses of side effects included events that occurred up to the end of the 18-month treatment phase plus up to 28 days after the last dose for patisiran and plus up to 84 days after the last dose for vutrisiran. According to the information provided by the company in Module 4 A, the results presented for these outcomes in both treatment arms represent an observation period of 84 weeks.

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 [11], 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 in the assessment of the outcome-specific risk of bias (see 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 adverse events.

This definition corresponds verbatim to the comprehensive definition of the CTCAE grades specified by the National Cancer Institute (NCI) [17]. 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. Furthermore, the study did not use the complete CTCAE grading system, including the specific definitions for many PTs. If the severity was not specified, the event was imputed as severe. However, as there were no missing values for severity, this did not affect any event. 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). The results on severe AEs are used in the present benefit assessment. However, as in the dossier assessment for vutrisiran, the extent of this is considered to be non-quantifiable.

Infusion-related reaction

In the HELIOS-A study, no specific AEs were predefined that could represent infusion-related reactions and at the same time could be recorded in both study arms. In the HELIOS-A study, infusion-related reactions were documented under the PT “infusion related reaction”. However, due to the open-label study design (without placebo infusion) and regular intravenous administration, events in this PT could only be recorded in the intervention arm. There are no usable (comparative) data for assessing the benefit.

To obtain a complete picture of infusion-related reactions, it would in principle be desirable to conduct an aggregated analysis of specified AEs (e.g. by means of a predefined PT list) including the corresponding PTs for both treatment groups, regardless of any documented relation to an infusion.

As previously described, infusion-related reactions were documented in the HELIOS-A study under the PT “infusion related reaction” that could not be recorded for the comparator arm. Events underlying this PT were not included in the analyses of system organ classes (SOCs) and PTs primarily presented in Module 4 A. An assessment of the severity of these events was

not planned. 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 [18]). 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, the underlying events of the PT "Infusion-related reaction" were documented in the CRF. In the annex to Module 4 A, the company presents a post hoc analysis of the underlying SOCs and PTs. This analysis was already presented by the company in the commenting procedure on vutrisiran and assessed by IQWiG in the context of Addendum A23-12 [7,8]. This analysis was also used for the present benefit assessment.

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 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 in Module 4 A. In the oral hearing on vutrisiran, the company stated that these infusion reactions were triggered by reactions of the immune system [19]. The company thus deviates again from the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification for this PT. This is of no consequence for the present benefit assessment, however.

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 – direct comparison: patisiran vs. vutrisiran

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

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. Lack of blinding in subjective outcomes or subjective recording of outcomes.
c. Outcome not recorded; the company allocated the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) instrument to health-related quality of life.
d. Including a relevant proportion of events that can be both side effects and symptoms.
e. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs.

10-MWTC 10-metre walking 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

The risk of bias of the result on the outcome of overall survival was rated as low.

There are no data on health-related quality of life and infusion-related reactions.

The results of the patient-reported outcomes assessed using Norfolk QoL-DN and EQ-5D VAS, the 10-MWT and discontinuation due to AEs have a high risk of bias as a result of the open-label study design. This also applies to the results of 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.

The available outcomes on AEs include a relevant proportion of events that can be both side effects and symptoms of the disease. Consequently, the risk of bias for the results of all outcomes related to side effects is high.

I 4.3 Results

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

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

Study outcome category outcome	Patisiran		Vutrisiran		Patisiran vs. vutrisiran
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
HELIOS-A					
Mortality					
All-cause mortality[b]	42	3 (7.1)	122	2 (1.6)	4.36 [0.75; 25.19][c]; 0.078
Side effects[b, d]					
AEs[e] (supplementary information)	42	41 (97.6)	122	119 (97.5)	Not applicable
SAEs[e]	42	18 (42.9)	122	32 (26.2)	1.63 [1.03; 2.59]; 0.045
Severe AEs[e, f]	42	16 (38.1)	122	19 (15.6)	2.45 [1.39; 4.30]; 0.002
Discontinuation due to AEs	42	3 (7.1)	122	3 (2.5)	2.91 [0.61; 13.84]; 0.174
Infusion-related reaction	Analysis unsuitable[g]				
Injury, poisoning and procedural complications (SOC, severe AE[f])[h]	42	3 (7.1)	122	1 (0.8)	8.71 [0.93; 81.52]; 0.031[i]
Infections and infestations (SOC, SAE)	42	8 (19.0)	122	9 (7.4)	2.58 [1.07; 6.26]; 0.034
Heart failure (SMQ narrow scope, SAE)	42	5 (11.9)	122	4 (3.3)	3.63 [1.02; 12.89]; 0.036
Gastrointestinal disorders (SOC, SAE)[j]	42	3 (7.1)	122	1 (0.8)	8.71 [0.93; 81.52]; 0.031
General disorders and administration site conditions (SOC, SAE)[k]	42	4 (9.5)	122	1 (0.8)	11.62 [1.34; 101.06]; 0.008

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

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

a. Institute's calculation, unconditional exact test (CSZ method according to [20]).
b. During the 18-month randomized treatment phase patisiran vs. vutrisiran (up to week 84).
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 should not be 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" and „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.
j. Included PTs are "constipation" and "lip oedema".
k. Included PTs are "asthenia", "general physical health deterioration", "phlebitis at the infusion site", "chest pain", "heat sensation" and "swelling face".

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: Standardized MedDRA Query; 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: patisiran versus Vutrisiran (multipage table)

Study outcome category outcome	Patisiran			Vutrisiran			Patisiran vs. vutrisiran
	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]	38	47.3 (29.9)	3.6 (2.9)	113	47.1 (26.3)	0.9 (1.7)	2.7 [−3.7; 9.2]; 0.401
Supplementary information:							
Physical functioning/ large nerve fibres	38	23.0 (14.9)	2.1 (1.6)	113	23.1 (13.8)	-0.3 (0.9)	2.4 [-1.1; 5.9]
Activities of daily living	38	5.0 (5.6)	0.5 (0.6)	113	5.7 (5.7)	1.2 (0.4)	-0.7 [-2.0; 0.7]
Symptoms	38	11.2 (7.3)	0.4 (0.8)	112	11.0 (6.1)	-0.4 (0.5)	0.7 [-1.0; 2.5]
Small nerve fibres	38	5.1 (4.5)	0.8 (0.5)	113	4.6 (4.2)	0.9 (0.3)	0.0 [-1.1; 1.1]
Autonomous functioning	38	3.0 (2.8)	-0.2 (0.3)	113	2.7 (2.9)	-0.5 (0.2)	0.3 [-0.4; 0.9]
10-MWT [m/s]	38	1.01 (0.40)	-0.07 (0.04)	113	1.01 (0.39)	-0.03 (0.03)	-0.04 [−0.14; 0.06]; 0.441
Health status							
EQ-5D VAS[e]	37	63.0 (16.1)	-5.3 (2.3)	112	64.5 (18.5)	-0.5 (1.3)	-4.8 [−9.9; 0.3]; 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 41 to 42 patients in the intervention arm and 120 to 122 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 (patisiran versus vutrisiran) indicate an advantage for the intervention.
e. Higher values mean a better health status (scale range 0 to 100). Positive effects (patisiran versus vutrisiran) 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).

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

Study outcome category outcome	Patisiran			Vutrisiran			Patisiran vs. vutrisiran
	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]
10-MWT: 10-metre walking test; CI: confidence interval; LS: least squares; MD: mean difference; MMRM: mixed-effects model with 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							

Based on the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of all-cause mortality, and at most hints for all other outcomes due to the high risk of bias.

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found. There is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Morbidity

Symptoms (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 patisiran or vutrisiran. There is no hint of an added benefit of patisiran in comparison with vutrisiran; 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 patisiran or vutrisiran compared to the start of the study. There is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Health status

Health status was surveyed by EQ-5D 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 patisiran or vutrisiran. There is no hint of an added benefit of patisiran in comparison with vutrisiran; 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 Sections I 4.1). There is no hint of an added benefit of patisiran in comparison with vutrisiran; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference between treatment groups to the disadvantage of patisiran was shown for the SAEs. This results in a hint of greater harm from patisiran in comparison with vutrisiran.

Severe AEs

A statistically significant difference between treatment groups to the disadvantage of patisiran was shown for the severe AEs. This results in a hint of greater harm from patisiran in comparison with vutrisiran.

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 patisiran in comparison with vutrisiran; greater or lesser harm is therefore not proven.

Infusion-related reaction

No suitable data are available for the outcome of infusion related reaction. There is no hint of greater or lesser harm from patisiran in comparison with vutrisiran; greater or lesser harm is therefore not proven.

Other specific AEs

For the specific AEs injury, poisoning and procedural complications (severe AEs), infections and infestations (SAEs), cardiac failure (SAEs), gastrointestinal disorders (SAEs) and general disorders and administration site conditions (SAEs), a statistically significant difference was observed between the treatment groups to the disadvantage of patisiran. In each case, this results in a hint of greater harm from patisiran in comparison with vutrisiran.

General disorders and administration site conditions (SAEs)

A major effect to the disadvantage of patisiran is shown for the specific AE “general disorders and administration site conditions” (SAE). A total of 5 patients were affected by the heterogeneous events summarized under this specific AE (PTs "asthenia", "general physical health deterioration", "phlebitis at the infusion site", "chest pain", "heat sensation" and "swelling face"). With "phlebitis at the infusion site", a PT is included that could only be recorded in the intervention arm and that affected 1 patient. If this PT is not taken into

account and the affected patient is not additionally included in the analysis with one of the other PTs, this specific AE would affect 3 vs. 1 patients and the size of the effect would be minor. Due to this data situation, the extent of this effect is rated as non-quantifiable.

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 when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one 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.

As previously in the procedure for vutrisiran, the company's interaction testing for the binary data 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, patient groups with therapeutically important added benefit[3]

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 IQWiG *General Methods* [22].

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 added benefit at outcome level

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

[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 [18,21].

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

Outcome category **outcome**	**Patisiran vs. vutrisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	7.1% vs. 1.6% RR: 4.36 [0.75; 25.19] p = 0.078	Lesser/added benefit not proven
Morbidity		
Symptoms (Norfolk QoL-DN[c])	3.6 vs. 0.9 LS MD: 2.7 [-3.7; 9.2] p = 0.401	Lesser/added benefit not proven
Symptoms (10-MWT [m/s])	-0.07 vs. -0.03 LS MD −0,04 −0,14; 0,06] p = 0.441	Lesser/added benefit not proven
Health status (EQ-5D VAS[d])	-5.3 vs. -0.5 LS MD −4,8 [−9,9; 0,3] p = 0.067	Lesser/added benefit not proven
Health-related quality of life		
Outcome not recorded[e]		
Side effects[f]		
SAEs	42.9% 26.2% RR: 1.63 [1.03; 2.59] RR: 0.61 [0.39; 0.97][g] p = 0.045 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_o < 1.00$ greater harm, extent: “minor”
Severe AEs	38.1% vs. 15.6% RR: 2.45 [1.39; 4.30] RR: 0.41 [0.23; 0.72][g] p = 0.002 probability: “hint”	Outcome category: serious/severe side effects greater harm, extent: “non-quantifiable”
Discontinuation due to AEs	7.1% vs. 2.5% RR: 2.91 [0.61; 13.84] p = 0.174	Greater/lesser harm not proven
Infusion-related reaction	Analysis unsuitable[h]	Greater/lesser harm not proven
Injury, poisoning and procedural complications (SOC, severe AEs)	7.1% vs. 0.8% RR: 8.71 [0.93; 81.52] RR: 0.12 [0.01; 1.07][g] p = 0.031 probability: “hint”	Outcome category: serious/severe side effects greater harm, extent: “non-quantifiable”

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

Outcome category **outcome**	**Patisiran vs. vutrisiran** **proportion of events (%) or LS mean** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infections and infestations (SOC, SAE)	19.0% vs. 7.4% RR: 2.58 [1.07; 6.26] RR: 0.39 [0.16; 0.94][g] p = 0.034 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Heart failure (SMQ narrow scope, SAE)	11.9% vs. 3.3% RR: 3.63 [1.02; 12.89] RR: 0.28 [0.08; 0.98][g] p = 0.036 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Gastrointestinal disorders (SOC, SAE)	7.1% vs. 0.8% RR: 8.71 [0.93; 81.52] RR: 0.11 [0.01; 1.07][g] p = 0.031 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"[i]
General disorders and administration site conditions (SOC, SAE)	9.5% vs. 0.8% RR: 11.62 [1.34; 101.06] RR: 0.09 [0.01; 0.749][g] p = 0.008 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"[j]

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 (patisiran versus vutrisiran) indicate an advantage for the intervention.
d. Higher values mean a better health status (scale range 0 to 100). Positive effects (patisiran versus vutrisiran) indicate an advantage for the intervention.
e. Outcome not recorded; the company allocated the Norfolk QoL-DN instrument to health-related quality of life.
f. Includes events that can be both side effects and symptoms of the disease.
g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs.
i. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; the extend is rated as "minor".
j. See Section I 4.3.

10-MWT: 10-metre walking 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 patisiran in comparison with vutrisiran

Positive effects	Negative effects
–	Serious/severe side effects[a] ▪ SAEs: hint of greater harm – extent: “minor” ▫ infections and infestations: hint of greater harm – extent: “minor” ▫ cardiac failure: hint of greater harm – extent: “minor” ▫ gastrointestinal disorders: hint of greater harm – extent: "minor" ▫ general disorders and administration site conditions: hint of greater harm – extent: "non-quantifiable" ▪ Severe AEs: hint of greater harm – extent: “non-quantifiable” ▫ injury, poisoning and procedural complications (severe AEs): hint of greater 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 only negative effects of patisiran over vutrisiran 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 lesser benefit of patisiran over vutrisiran for patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy.

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

Table 16: Patisiran – 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 **vutrisiran[c]**	Hint of lesser 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 patisiran.
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 hATTR amyloidosis, and is documented as concomitant treatment.
d. 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.

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

The assessment described above deviates from that of the company, which derived no indication of an added benefit from the results of the HELIOS-A study.

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2018. There, the G-BA had identified a considerable added benefit of patisiran based on the approval-justifying placebo-controlled APOLLO study.

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.

1. Alnylam Pharmaceuticals. HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis); Clinical Study Report 2; Month 18 Analysis for ALN-TTRSC02-002 (Vutrisiran) [unpublished]. 2022.

2. Alnylam Pharmaceuticals. HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) [online]. 2023 [Accessed: 04.01.2024]. URL: https://clinicaltrials.gov/study/NCT03759379.

3. Alnylam Pharmaceuticals. HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) [online]. [Accessed: 04.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002098-23.

4. CMIC. HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients With Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis) [online]. 2022 [Accessed: 04.01.2024]. URL: https://jrct.niph.go.jp/en-latest-detail/jRCT2080224769.

5. Adams D, Tournev IL, Taylor MS et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid 2023; 30(1): 1-9. https://doi.org/10.1080/13506129.2022.2091985.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vutrisiran (hereditäre Transthyretin-Amyloidose mit Polyneuropathie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a22-114_vutrisiran_nutzenbewertung-35a-sgb-v_v1-0.pdf.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vutrisiran (hereditäre Transthyretin-Amyloidose mit Polyneuropathie); Addendum zum Projekt A22-114 (Dossierbewertung) [online]. 2023 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a23-12_vutrisiran_addendum-zum-projekt-a22-114_v1-0.pdf.

8. Gemeinsamer Bundesausschuss. Nutzenbewertung nach § 35a SGB V: Nutzenbewertungsverfahren zum Wirkstoff Vutrisiran (Hereditäre Transthyretin-Amyloidose mit Polyneuropathie (Stadium 1 oder 2)) [online]. 2023 [Accessed: 23.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/892/.

9. Alnylam Germany. Onpattro 2 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 06.12.2023]. URL: https://www.fachinfo.de.

10. Alnylam Germany. Amvuttra 25 mg Injektionslösung in einer Fertigspritze [online]. 2023 [Accessed: 06.12.2023]. URL: https://www.fachinfo.de.

11. Schilling M, Auer-Grumbach M, Baron R et al. Hereditäre Transthyretinamyloidose (ATTRv-Amyloidose). DGNeurologie 2020; 3(5): 369-383.

12. Adams D, Gonzalez-Duarte A, O'Riordan WD et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med 2018; 379(1): 11-21. https://doi.org/10.1056/NEJMoa1716153.

13. Vinik EJ, Hayes RP, Oglesby A et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technol Ther 2005; 7(3): 497-508. https://doi.org/10.1089/dia.2005.7.497.

14. Vinik EJ, Paulson JF, Ford-Molvik SL, Vinik AI. German-translated Norfolk quality of life (QOL-DN) identifies the same factors as the English version of the tool and discriminates different levels of neuropathy severity. J Diabetes Sci Technol 2008; 2(6): 1075-1086. https://doi.org/10.1177/193229680800200616.

15. Vinik EJ, Vinik AI, Paulson JF et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst 2014; 19(2): 104-114. https://doi.org/10.1111/jns5.12059.

16. Smith SC, Lamping DL, Maclaine GD. Measuring health-related quality of life in diabetic peripheral neuropathy: a systematic review. Diabetes Res Clin Pract 2012; 96(3): 261-270. https://doi.org/10.1016/j.diabres.2011.11.013.

17. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE); Version 5.0 [online]. 2017 [Accessed: 23.01.2024]. URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Daratumumab (neu diagnostiziertes multiples Myelom, Stammzelltransplantation nicht geeignet) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse); Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-126_daratumumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

19. Gemeinsamer Bundesausschuss. Vutrisiran: mündliche Anhörung gemäß § 35 a Abs. 2 SGB V - stenografisches Wortprotokoll [online]. 2023 [Accessed: 23.01.2024]. URL: https://www.g-ba.de/downloads/91-1031-892/2023-02-20_Wortprotokoll_Vutrisiran_D-877.pdf.

20. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

21. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

22. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-118.html.