15 May 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Amvuttra (vutrisiran)

Treatment of transthyretin-mediated amyloidosis
EU/3/18/2026

Sponsor: Alnylam Netherlands B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues
Other names	Amvuttra, Vutrisiran
International Non-Proprietary Name	Vutrisiran
Tradename	Amvuttra
Orphan condition	Treatment of transthyretin-mediated amyloidosis
Sponsor's details:	Alnylam Netherlands B.V. Antonio Vivaldistraat 150 1083 HP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alnylam UK Limited
COMP opinion	19 April 2018
EC decision	25 May 2018
EC registration number	EU/3/18/2026
Post-designation procedural history	
Transfer of sponsorship	Transfer from Alnylam UK Limited to Alnylam Netherlands B.V. – EC decision of 21 February 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig / Fátima Ventura
Applicant	Alnylam Netherlands B.V.
Application submission	15 October 2024
Procedure start	02 November 2024
Procedure number	EMA/H/C/005852/II/0015
Invented name	Amvuttra
Therapeutic indication	Amvuttra is indicated for the treatment of hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (hATTR-PN). Amvuttra is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). Further information on Amvuttra can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/amvuttra

CHMP opinion	25 April 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Joao Rocha / Elisabeth Johanne Rook
Sponsor's report submission	21 November 2024
COMP discussion and adoption of list of questions	14-15 April 2025
Oral explanation	13 May 2025
COMP opinion	15 May 2025

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues was considered justified based on non-clinical in vivo data showing a reduction in levels of circulating transthyretin after administration of the proposed product;
- the condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy;
- the condition was estimated to be affecting less than 0.2 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. This is based on a new mechanism of action that may result in the product being effective in a broader patient population than the currently authorised product as supported by non-clinical in vivo data and preliminary clinical data. The Committee considered that this constitutes a clinically relevant advantage.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2022 was based on the following grounds:

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of transthyretin-mediated amyloidosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Amvuttra may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has submitted clinical data demonstrating that vutrisiran is efficacious in a subset of patients with moderate-severe renal impairment for whom inotersen is contraindicated. In addition, the clinical data showed that vutrisiran is of comparable efficacy with patisiran and also demonstrating a major contribution to patient care compared to patisiran.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Amvuttra, synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues, vutrisiran for treatment of transthyretin-mediated amyloidosis (EU/3/18/2026) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Transthyretin amyloidosis (ATTR) is a rare, multisystem, progressive, debilitating, and ultimately fatal disease resulting from the deposition of misfolded Transthyretin (TTR) as amyloid fibrils in various organs, predominantly the nerves and heart (Castaño and Maurer, 2019; Ruberg et al., 2019).

Transthyretin-mediated amyloidosis is a rapidly progressive, multisystem, debilitating, and ultimately fatal disease encompassing wild-type ATTR (wtATTR) and hereditary ATTR (hATTR) (Adams 2021b; Gertz 2017; Grodin 2019; Lane 2019; Y. Parman 2016). In both wtATTR amyloidosis and hATTR amyloidosis, the tetrameric TTR protein becomes destabilised and disassociates into dimers and monomers, which subsequently misfold and aggregate as amyloid fibrils and plaques in the extracellular space of various tissues, [Hou 2007] including the heart, peripheral nervous system, gastrointestinal tract, kidney, central nervous system, and eye, leading to cellular injury and organ dysfunction.

The most clinically important manifestations are the result of involvement of the peripheral nervous system and the heart. Accumulation of amyloid fibrils in the heart causes an infiltrative, restrictive cardiomyopathy (ATTR-CM) resulting in progressive clinical heart failure associated with high mortality and morbidity. Patients with ATTR-CM typically experience frequent hospitalizations for heart failure, irreversible loss of physical function, and worsening health status and quality of life (QoL). Advanced ATTR-CM causes some of the most deleterious adverse clinical outcomes in ATTR (Castaño and Maurer, 2019; Ioannou et al., 2023; Ruberg et al., 2019).

The approved extension of the therapeutic indication "Amvuttra is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)" falls within the scope of the designated orphan condition "Treatment of transthyretin-mediated amyloidosis".

Intention to diagnose, prevent or treat

The medical plausibility was confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the chronically debilitating and life-threatening nature of the condition. In both early and later stages of cardiomyopathy, patients continue to suffer unrelenting disease progression with rapid, steady declines in functional capacity and quality of life, frequent hospitalisations, and death. In a recent, large natural history study, patients who were only mildly affected at diagnosis suffered substantial worsening and morbidity over a median follow-up period of 28 months; mild disease severity was defined as ATTR amyloidosis disease Stage 1a (NT-proBNP ≤500 ng/L or ≤1000 ng/L if in atrial fibrillation, estimated glomerular filtration rate [eGFR] ≥45 mL/min/1.73 m2) and furosemide equivalent diuretic requirement of <0.75 mg/kg. With ongoing cardiac amyloid deposition,

congestive HF steadily worsened, as indicated by rising diuretic usage, NT-proBNP levels, and NYHA Classification and by a falling eGFR. Furthermore, patients demonstrated an increasing prevalence of atrial fibrillation, stroke or transient ischemic attacks, and pacemaker placement for atrioventricular block or bradyarrhythmia (Law 2022).

A recent systematic review and meta-analysis of outcomes in 95 published studies reported a survival rate of 76.0% at 2 years and 48.0% at 5 years after a diagnosis of ATTR amyloidosis in patients (with either cardiomyopathy and/or polyneuropathy) who were not being treated with TTR-targeted therapy, reinforcing the presence of persistently high rates of mortality in the natural disease course of ATTR (Antonopoulos 2022).

The COMP has previously accepted that the clinical course of ATTR can be chronically debilitating due to the development of polyneuropathy and cardiomyopathy. The severe nature of ATTR amyloidosis earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

To support the maintenance of orphan designation for vutrisiran, the sponsor undertook a structured approach to estimate the prevalence of ATTR amyloidosis in the European Union (EU). The estimation strategy stratified the prevalence across three principal subtypes:

- Hereditary ATTR amyloidosis with polyneuropathy (hATTR-PN)
- Hereditary ATTR amyloidosis with cardiomyopathy (hATTR-CM)
- Wild-type ATTR amyloidosis (wtATTR)

Where available, prevalence estimates were derived from published epidemiological studies and national datasets. In the absence of country-specific data, the sponsor extrapolated from representative countries, primarily France, selected on the basis of established diagnostic infrastructure and documented disease awareness.

Hereditary ATTR Amyloidosis with Polyneuropathy

Prevalence data for hATTR-PN were identified for 13 EU Member States. These data, sourced from epidemiological literature, patient registries, and hospital databases, revealed marked geographic variation, consistent with the disease's known endemicity in regions such as Portugal (1.803/10,000) and Sweden (0.491/10,000) (Lobato 2003; Gorram 2021; Hellman 2008). Lower prevalence figures were observed in non-endemic countries (e.g. Germany, Ireland) (Parman et al. 2016; Reilly 1995).

In EU Member States lacking specific data, the prevalence reported in France (0.076/10,000) was used for extrapolation, based on the presence of a national referral network and considered a conservative and methodologically justified proxy [Schmidt 2018].

Based on 2024 Eurostat population data, the estimated number of prevalent hATTR-PN cases in the EU was 4,641, corresponding to a point prevalence of 0.103 per 10,000.

Hereditary ATTR Amyloidosis with Cardiomyopathy

Prevalence data for hATTR-CM were available for Austria, Denmark, France, Hungary, and Italy, with estimates ranging from 0.005 to 0.027 per 10,000 (Auer-Grumbach 2020; Frederiksen 1962; Pozsonyi 2021). As with hATTR-PN, the prevalence estimate from France (0.009/10,000) was used for extrapolation to other EU Member States.

Mixed phenotypes (neurological and cardiac) were accounted for within the hATTR-PN population to avoid duplication. The sponsor also acknowledged that genotypes typically associated with cardiomyopathy, such as V122I, may evolve to include neuropathic features (Buxbaum 2017; Jacobson 1997).

The total estimated number of hATTR-CM cases in the EU in 2024 was 412, corresponding to a prevalence of 0.009 per 10,000.

Combined prevalence of hereditary ATTR Amyloidosis

Combining both hereditary forms of ATTR amyloidosis (hATTR-PN and hATTR-CM), the total number of affected individuals in the EU was estimated at 5,053, corresponding to a combined prevalence of 0.112 per 10,000. Although a proportion of cases may exhibit overlapping phenotypes (estimated at 13–36% depending on genotype [Gentile 2023]), classification was based on the predominant presentation at diagnosis.

Wild-Type ATTR Amyloidosis

The sponsor also evaluated the prevalence of wtATTR amyloidosis using recent population-based studies and national administrative datasets. Key sources included:

- Lauppe et al. (2021, 2022): Analyses of national registers in Sweden and the Nordic countries, reporting ATTR-CM prevalence (including wtATTR and hATTR)
- Damy et al. (2020): A nationwide claims-based analysis in France
- Cappelli et al. (2023): A population-based study in Tuscany, Italy, reporting a wtATTR-specific prevalence of 0.90 per 10,000

The sponsor selected the estimate from Cappelli et al. for extrapolation to the EU population. This study provided the most recent data, focused exclusively on confirmed wtATTR cases, and was conducted in a region with a high median age, representative of the affected demographic (Falk 2012; Ruberg 2012a). Moreover, use of the upper-bound prevalence aligns with the EMA's recommendation to consider a worst-case scenario where appropriate.

Applying this prevalence rate to the EU population (449,206,579 as of 1 January 2024, Eurostat) yielded an estimated 40,429 prevalent wtATTR cases.

Overall Prevalence of ATTR Amyloidosis in the EU

To estimate the total prevalence of ATTR amyloidosis in the European Union, the sponsor aggregated the prevalence figures derived for each of the three principal subtypes: hereditary ATTR with polyneuropathy (hATTR-PN), hereditary ATTR with cardiomyopathy (hATTR-CM), and wild-type ATTR (wtATTR). Based on the methodologies and data sources described the number of prevalent cases in 2024 was estimated as follows: hATTR-PN: 4,641 patients; hATTR-CM: 412 patients and wtATTR: 40,429 patients. This results in a total of 45,482 individuals estimated to be affected by ATTR amyloidosis across the EU. When applied to the total EU population of 449,206,579 (as of January 1, 2024, Eurostat), this corresponds to an overall prevalence of 1.012 per 10,000 population.

The sponsor should justify the inclusion and choice of sources selected for the prevalence estimation and describe the methodology used for these calculations. The sponsor should consider recently published studies, particularly those reflecting increased prevalence rates following advancements in scintigraphy use, as these provide more direct and updated prevalence calculations.

Due to significant uncertainties surrounding many of the underlying assumptions, the sponsor should elaborate on the prevalence estimate for the proposed orphan condition. This recalculation should be grounded in up-to-date and relevant epidemiological studies and registries that accurately reflect the target population. Furthermore, the sponsor is asked to conduct a sensitivity analysis to assess the potential impact of these assumptions on the prevalence estimate. This analysis should consider variability across demographic factors such as age groups, particularly those that may disproportionately contribute to an over- or underestimation. Emphasis should be placed on data sources that align with current diagnostic practices to ensure a more reliable and representative estimate.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The current pharmacological treatments approved in the EU for ATTR are tafamidis, inotersen, patisiran and acoramidis (Table 1).

Table 1. Current pharmacological treatments approved in the EU for ATTR

Proprietary name	**Generic name**	**Therapeutic indication**	**Satisfactory method**
VYNDAQEL	Tafamidis	Treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (VYNDAQEL 20 mg soft capsules)	Yes, since Amvuttra specifically targets the same patient population as Vyndaqel.
		Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (VYNDAQEL 61 mg soft capsules)	
TEGSEDI	Inotersen	Treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)	No, since it is indicated solely for the treatment of polyneuropathy in hATTR therefore, not relevant comparator for the intended patient population of Amvuttra.
ONPATTRO	Patisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients with Stage 1 or Stage 2 polyneuropathy	No, since it is indicated solely for the treatment of polyneuropathy in hATTR therefore, not relevant comparator for the intended patient population of Amvuttra.

BEYONTTRA	Acoramidis	Treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)	Yes, since Amvuttra specifically targets the same patient population as Beyonttra.
WAINZUA	Eplontersen	Treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy	No, since it is indicated solely for the treatment of polyneuropathy in hATTR therefore, not relevant comparator for the intended patient population of Amvuttra.

Based on the above table the authorised medicinal products which are considered as satisfactory methods are Vyndaqel (tafamidis) and Beyonttra (acoramidis).

As this is an extension of indication, only the new indication of ATTR-CM is assessed.

Significant benefit

The sponsor engaged with the European Medicines Agency (EMA) to obtain protocol assistance (EMEA/H/SA/3876/2/2019/PA/II) regarding the evidence required to demonstrate a significant benefit of Amvuttra over existing treatments for patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM), including both wild-type and hereditary forms. Based on the available knowledge and the assumptions at the time, significant benefit of vutrisiran was proposed to be demonstrated over tafamidis by indirect comparisons of efficacy within the HELIOS-B study as well as between the HELIOS-B study and the Phase 3 study of tafamidis, ATTR-ACT. Significant benefit over Orthotopic liver transplantation (OLT) was proposed to be based on major contribution to patient care due to the absence of lifetime burden of immunosuppressive drugs. The COMP agreed that the proposed clinical development of vutrisiran could be sufficient to demonstrate significant benefit when taking into consideration the recommendations made in the written advice letter. At the time of protocol assistance in 2019 significant benefit over acoramidis was not specifically discussed.

The claim of significant benefit is based on the results from HELIOS-B study, a global, randomised, double-blind, placebo-controlled clinical study in adult patients with ATTR-CM. Patients were randomized 1:1 to receive 25 mg of Amvuttra subcutaneously once every 3 months, or matching placebo. At baseline, 40% of patients were receiving treatment with tafamidis. Treatment assignment was stratified by baseline tafamidis use, ATTR disease type (wtATTR or hATTR amyloidosis), and by baseline severity of disease and age (New York Heart Association (NYHA) Class I or II and age < 75 years versus all other).

Of the patients who received Amvuttra, at baseline, the median patient age was 77 years (range 45 to 85 years) and 92% were male. Eighty five percent (85%) of patients were Caucasian, 7% were Black or African American, 6% were Asian. Eighty nine percent (89%) of patients had wtATTR amyloidosis and 11% had hATTR amyloidosis.

The primary efficacy endpoint was the composite outcome of all-cause mortality and recurrent CV events (CV hospitalisations and urgent heart failure [UHF] visits) during the double-blind treatment period of up to 36 months, evaluated in the overall population and in the monotherapy population (defined as patients not receiving tafamidis at study baseline).

Amvuttra led to significant reductions in the risk of all-cause mortality and recurrent CV events compared to placebo in the overall and monotherapy populations of 28.2% and 32.8%, respectively.

Approximately 77% of all deaths in HELIOS-B were CV-related. The rate of both CV deaths and non-CV deaths was lower in Amvuttra-treated patients compared to placebo. Of the total number of CV events, 87.9% were CV hospitalisations, and 12.1% were UHF visits.

- **Significant benefit of Amvuttra (vutrisiran) over Vyndaqel (tafamidis)**

The sponsor claimed significant benefit of Amvuttra (vutrisiran) over Vyndaqel (tafamidis) based on a clinically relevant advantage in terms of improved efficacy in the target patient population.

The first argument was that treatment with tafamids cannot prevent disease progression in the whole group of patients. The mortality rate in the tafamidis arm remains high at 30% at month 30 (Maurer 2018). In addition, while improvements with tafamidis treatment relative to placebo were observed in 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire – Overall Summary (KCCQ-OS), on average, tafamidis-treated patients still showed steady and substantial progression of disease compared to baseline during the course of the study (LS mean worsening from baseline of approximately 55 m in 6-MWT and approximately 8 points in KCCQ-OS in the pooled tafamidis group at month 30) (Hanna 2021; Maurer 2018).

The second argument is the improved efficacy based on HELIOS B in the subgroup of patients with background tafamidis treatment.

The protocol for HELIOS-B study allowed on-label use of tafamidis for the treatment of ATTR-CM, where commercially available. Patients were stratified by baseline tafamidis use. At baseline, the number of patients then on tafamidis (hereafter referred to as background tafamidis subgroup) was 259 (39.6%) of 654 randomised patients. The sponsor claimed that the baseline demographics and disease characteristics of the background tafamidis subgroup were balanced between vutrisiran and placebo arms (Table 2) (Table 3); accordingly, the background tafamidis subgroup baseline characteristics were deemed by the sponsor to be suitable to inform an unbiased comparison between patients randomised to vutrisiran vs. those randomised to placebo.

Table 2. HELIOS-B: Baseline demographic characteristics in the background tafamidis subgroup

Demographic	Background Tafamidis Subgroup		
	Placebo (N=129)	**Vutrisiran (N=130)**	**Total (N=259)**
Age at randomisation (years)			
Mean (SD)	74.9 (6.2)	74.4 (7.5)	74.6 (6.9)
Median (min, max)	75.0 (46, 85)	77.0 (45, 85)	76.0 (45, 85)
Age group (years), n (%)			
< 65	9 (7.0)	17 (13.1)	26 (10.0)
65 to <75	45 (34.9)	33 (25.4)	78 (30.1)
≥ 75	75 (58.1)	80 (61.5)	155 (59.8)
Sex, n (%)			
Male	123 (95.3)	121 (93.1)	244 (94.2)
Female	6 (4.7)	9 (6.9)	15 (5.8)
Race, n (%)			
White	106 (82.2)	108 (83.1)	214 (82.6)
Black or African American	13 (10.1)	13 (10.0)	26 (10.0)
Asian	4 (3.1)	6 (4.6)	10 (3.9)
Not reported	6 (4.7)	3 (2.3)	9 (3.5)
Other	0	0	0
Ethnicity, n (%)			
Not Hispanic or Latino	125 (96.9)	127 (97.7)	252 (97.3)
Hispanic or Latino	0	1 (0.8)	1 (0.4)
Not reported	4 (3.1)	1 (0.8)	5 (1.9)
Unknown	0	1 (0.8)	1 (0.4)
Region[a], n (%)			
Europe	42 (32.6)	46 (35.4)	88 (34.0)
US	82 (63.6)	76 (58.5)	158 (61.0)
Rest of World	5 (3.9)	8 (6.2)	13 (5.0)

Abbreviations: DB=double-blind; max=maximum; min=minimum; SD=standard deviation; US=United States.
Note: Baseline is defined as the last non-missing measurement before the first dose in the DB Period.
[a] Europe includes Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Spain, Sweden, and United Kingdom. Rest of World includes Argentina, Australia, Canada, Israel, Japan, Peru, and South Korea.

Table 3. HELIOS-B: Baseline disease characteristics in the background tafamidis subgroup

Parameter	**Background Tafamidis Subgroup**		
	Placebo (N=129)	**Vutrisiran (N=130)**	**Total (N=259)**
ATTR amyloidosis type, n (%)			
wtATTR amyloidosis	115 (89.1)	116 (89.2)	231 (89.2)
hATTR amyloidosis	14 (10.9)	14 (10.8)	28 (10.8)
Time since ATTR amyloidosis diagnosis (years)			
Median (min, max)	1.53 (0.1, 10.8)	1.26 (0.0, 11.1)	1.36 (0.0, 11.1)
Age (years) at ATTR amyloidosis symptom onset, n (%)			
Median (min, max)	73.0 (44, 84)	74.5 (44, 85)	74.0 (44, 85)
Baseline tafamidis use n (%)			
No	0	0	0
Yes	129 (100.0)	130 (100.0)	259 (100.0)
Time from start of tafamidis therapy to start of study drug (months)			
Median (min, max)	11.30 (1.1, 65.5)	9.18 (1.1, 65.3)	10.84 (1.1, 65.5)
NYHA class, n (%)			
I	23 (17.8)	34 (26.2)	57 (22.0)
II	89 (69.0)	78 (60.0)	167 (64.5)
III	17 (13.2)	18 (13.8)	35 (13.5)
NT-proBNP (ng/L)			
Median (min, max)	1746.00 (317.0, 6530.0)	1759.50 (322.0, 7541.0)	1759.0 (317.0, 7541.0)
NT-proBNP, n (%)			
>2000 ng/L	55 (42.6)	50 (38.5)	105 (40.5)
>3000 ng/L	32 (24.8)	26 (20.0)	58 (22.4)
Troponin I (ng/L)			
Median (min, max)	68.30 (10.0, 631.5)	64.85 (11.2, 8712.0)	67.00 (10.0, 8712.0)
eGFR (mL/min/1.73m2)			
Median (min, max)	64.0 (33, 133)	64.5 (29, 123)	64.0 (29, 133)
ATTR amyloidosis disease stage, n (%)			
Stage 1	91 (70.5)	95 (73.1)	186 (71.8)
Stage 2	32 (24.8)	32 (24.6)	64 (24.7)
Stage 3	6 (4.7)	3 (2.3)	9 (3.5)

Abbreviations: ATTR=transthyretin-mediated (amyloidosis); DB=double-blind; eGFR= estimated glomerular filtration rate; hATTR=hereditary ATTR (amyloidosis); max=maximum; min=minimum; NT-proBNP=*N*-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; wtATTR=wild-type ATTR (amyloidosis).
Note: Baseline is defined as the last non-missing measurement before the first dose in the DB Period.

The sponsor claimed that although not powered to show a statistically significant difference, in pre-specified analyses, vutrisiran treatment showed a consistent trend for improvement across all efficacy endpoints over placebo in the background tafamidis subgroup (Table 4), including reduction in risk of the composite endpoint of all-cause mortality and recurrent CV events of 21.5%; reduction in risk of

the secondary endpoint all-cause mortality of 41.2%; and a nominally statistically significant improvement over placebo in 6-MWT change from baseline to month 30 of 18.44 meters.

Table 4. Summary of efficacy analyses in the background tafamidis subgroup of HELIOS-B

Endpoint	Background Tafamidis Subgroup (N=259)	
	Treatment Effect Estimation	**Treatment Effect (95% CI)**
Outcome endpoints		
Primary endpoint: Composite outcome of all-cause mortality and recurrent CV events during the DB Period	Hazard ratio[a]	0.785 (0.511, 1.207)
Component analysis: All-cause mortality during the DB Period	Hazard ratio[b]	0.626 (0.326,1.202)
Component analysis: Recurrent CV events during the DB Period	Relative risk ratio[c]	0.826 (0.614, 1.111)
Secondary endpoint: All-cause mortality through 42 months	Hazard ratio[d]	0.588 (0.320, 1.081)
Endpoint	**Background Tafamidis Subgroup (N=259)**	
	Treatment Effect Estimation	**Treatment Effect (95% CI)**
Other secondary endpoints		
6-MWT change from baseline at Month 30	LS mean difference[e]	18.44 (0.42, 36.47)
KCCQ-OS change from baseline at Month 30	LS mean difference[e]	1.75 (-2.85, 6.35)
Proportion with stable or improved NYHA Class at Month 30	Adjusted % difference[f]	3.0 (-8.4, 14.4)

Abbreviations: 6-MWT=6-minute walk test; ATTR=transthyretin-mediated (amyloidosis); CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CV=cardiovascular; DB=double-blind; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS=least squares; LVAD=left ventricular assist device; MCMC=Markov Chain Monte Carlo; MMRM=mixed model repeated measures; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PH=proportional hazard.
Notes: Based on events as adjudicated by the Clinical Events Committee and determined by Investigators. Analyses were based on subgroup data only.
[a] Deaths after study withdrawal were not included in analysis. All-cause mortality included heart transplantation and LVAD placement. Based on modified Andersen-Gill model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA Class, and age group as covariates.
[b] Deaths after study withdrawal were included in analysis. Based on Cox PH model with treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA Class, and age group as covariates.
[c] Based on Poisson regression model with treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA Class, and age group as covariates and the logarithm of the follow-up time as an offset variable.
[d] Deaths after end of study were included in the analysis. All-cause mortality included heart transplantation and LVAD placement. Based on Cox PH model including treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class, and age group as covariates.
[e] Missing change values due to amyloidosis disease progression (for 6-MWT only) and death were imputed using 20 random samples with replacement from the worst 10% of observed change from baseline of all patients at the same visit from the same treatment group and baseline tafamidis use group, capped by 0-baseline distance (for 6-MWT)/baseline domain score (for KCCQ-OS, where each domain score was imputed separately). Based on MMRM analysis with baseline 6-MWT/KCCQ-OS as a covariate and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.
[f] Derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA Class values due to death, heart transplantation, and LVAD placement were imputed as Class IV and the other missing NYHA Class values were imputed using an MCMC procedure including selected baseline

variables and postbaseline NYHA Class assessments. For each imputed dataset, common risk difference and standard error were based on CMH method stratified by baseline NT-proBNP.

The sponsor also presented the efficacy results in the subset of patients in the subgroup of background tafamidis who, in the opinion of the Investigator, were experiencing disease progression despite treatment with tafamidis before enrolling in HELIOS-B.

In this subset of the background tafamidis subgroup, treatment with vutrisiran was associated with numerically favourable results compared to placebo including reduction in the composite endpoint of all-cause mortality and recurrent CV events of 41.2% and reduction in all-cause mortality of 56.0% (Table 5). Trends were consistently favouring vutrisiran across endpoints, except for the proportion with stable or improved NYHA class. While being a small subgroup of the study population not powered to show statistically significant difference, the sponsor claimed that these results are relevant from a significant benefit perspective as they might be suggestive of vutrisiran's efficacy in patients for whom the currently approved treatment is unsatisfactory in managing the disease.

Table 5. Summary of efficacy analyses in tafamidis progressors in the background tafamidis subgroup

	Tafamidis Progressors in the Background Tafamidis Subgroup (N=61)	
Endpoint	**Treatment Effect Estimation**	**Treatment Effect (95% CI)**
Outcome endpoints		
Primary endpoint: Composite outcome of all-cause mortality and recurrent CV events during the DB Period	Hazard ratio[a]	0.588 (0.218, 1.584)
Secondary endpoint: All-cause mortality through 42 months	Hazard ratio[b]	0.440 (0.131,1.478)
Other secondary endpoints		
6-MWT change from baseline at Month 30	LS mean difference[c]	8.96 (-34.29, 52.20)
KCCQ-OS change from baseline at Month 30	LS mean difference[c]	5.48 (-4.71, 15.67)
Proportion with stable or improved NYHA Class at Month 30	Adjusted % difference[d]	-3.2 (-29.2, 22.8)

Abbreviations: 6-MWT=6-minute walk test; ATTR=transthyretin-mediated (amyloidosis); CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CV=cardiovascular; DB=double-blind; KCCQOS=Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS=least squares; LVAD=left ventricular assist device; MCMC=Markov Chain Monte Carlo; MMRM=mixed model repeated measures; NTproBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PH=proportional hazard.
Notes: Based on events as adjudicated by the Clinical Events Committee and determined by Investigators. Analyses were based on subgroup data only.
[a] Deaths after study withdrawal were not included in analysis. Allcause mortality included heart transplantation and LVAD placement. Based on modified Andersen-Gill model including treatment group, logtransformed NTproBNP, type of ATTR amyloidosis, NYHA Class, and age group as covariates.
[b] Deaths after end of study were included in the analysis. Allcause mortality included heart transplantation and LVAD placement. Based on Cox PH model including treatment group, logtransformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class, and age group as covariates.
[c] Missing change values due to amyloidosis disease progression (for 6-MWT only) and death were imputed using 20 random samples with replacement from the worst 10% of observed change from baseline of all patients at the same visit from the same treatment group and baseline tafamidis use group, capped by 0-baseline distance (for 6MWT)/baseline domain score (for KCCQ-OS). Based on MMRM analysis with baseline 6MWT/KCCQ-OS as a covariate and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.
[d] Derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA Class values due to death, heart transplantation, and LVAD placement were imputed as Class IV and the other missing NYHA Class values were imputed using an MCMC procedure including

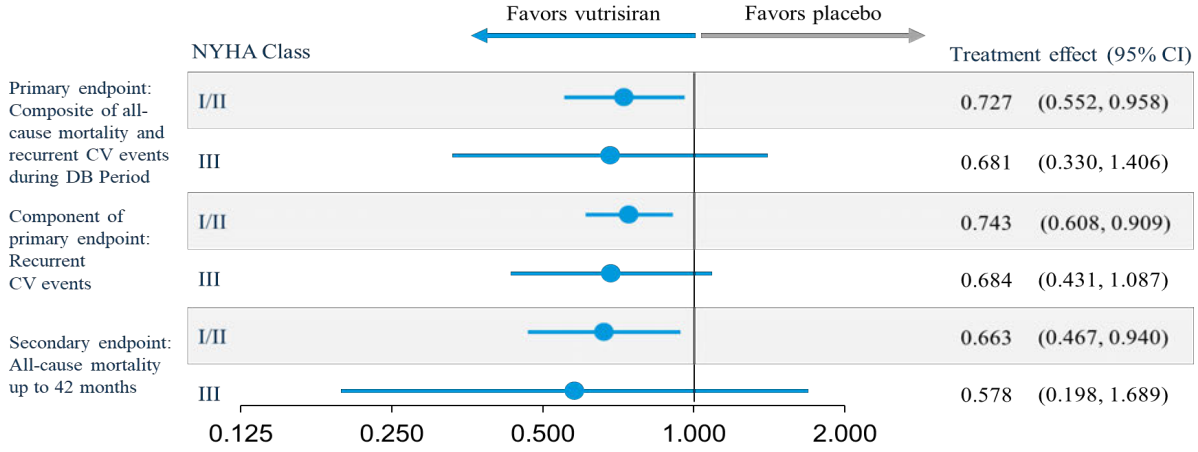
selected baseline variables and postbaseline NYHA Class assessments. For each imputed dataset, common risk difference and standard error were based on CMH method stratified by baseline NT-proBNP.

Finally, the sponsor claimed treatment effect for vutrisiran in a broader population including not only NYHA Class I and II, but also NYHA Class III. In the Phase 3 ATTR-ACT study of tafamidis, in patients with NYHA Class III, the rates of CV-related hospitalisations were higher among patients receiving tafamidis than among those receiving placebo (total number (%) of subjects with CV-related hospitalisations: 76.9% vs 58.7%, relative risk ratio 1.4114 [1.0484, 1.9000]) and CV-related mortality tended to be higher with tafamidis compared to placebo (51.3% vs 49.2%). Accordingly, Section 4.2 of VYNDAQEL SmPC currently includes a recommendation that "when amyloid-related cardiac damage is more advanced, such as NYHA Class III, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy". The European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend use of tafamidis for the treatment of hereditary and wild-type ATTR amyloidosis with cardiomyopathy only in patients with NYHA Class I or II symptoms (McDonagh 2021).

The HELIOS-B study of vutrisiran enrolled patients with NYHA Class III; while patients with both NYHA Class III and ATTR Amyloidosis Disease Stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 ml/min) at baseline were excluded from HELIOS-B, this exclusion criterion resulted in the screen failure of a very small number of patients (N=3).

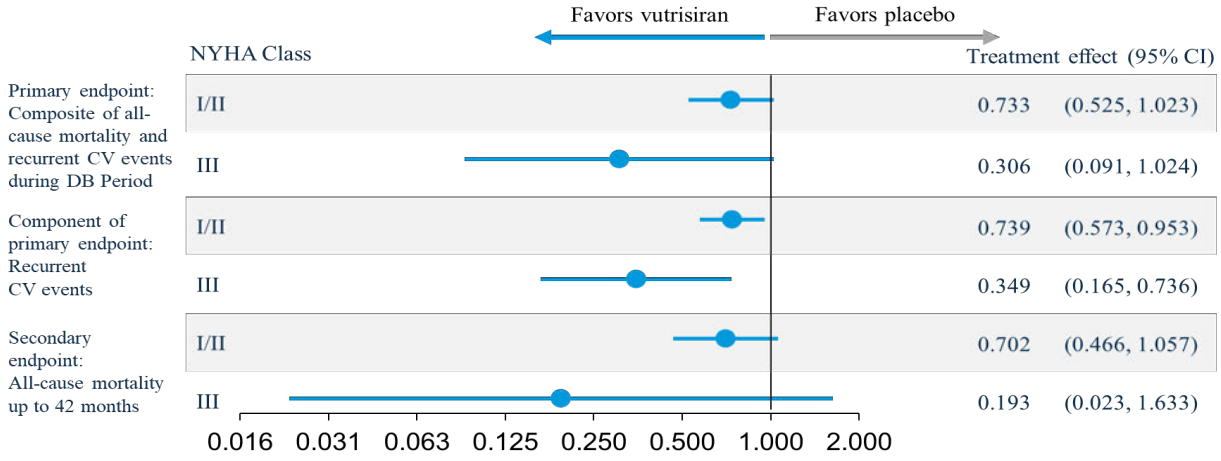
Subgroup analyses by NYHA Class (NYHA I/II vs. III) were performed for the composite endpoint of all-cause mortality and recurrent CV events and the endpoints of 6-MWT, KCCQ-OS, all-cause mortality through 42 months, NYHA class, and recurrent CV events (component of the composite endpoint) in both the overall population and vutrisiran monotherapy subgroup. Forest plots of the subgroup analyses of the primary endpoint, the component of recurrent CV events and the secondary endpoint of all-cause mortality are presented in Figure 1 and Figure 2.

Figure 1. HELIOS-B: Subgroup analysis by NYHA class (overall population)



Abbreviations: CI=confidence interval; CV=cardiovascular; DB=double-blind; LWYY=Lin Wei Ying Yang; NYHA=New York Heart Association. Note: Hazard ratio is presented for primary endpoint based on Lin Wei Ying Yang (LWYY) model and for all-cause mortality endpoint based on Cox proportional hazard model. Relative rate ratio is presented for recurrent CV events based on Poisson regression model.

Figure 2. HELIOS-B: Subgroup analysis by NYHA class (vutrisiran monotherapy subgroup)



Abbreviations: CI=confidence interval; CV=cardiovascular; DB=double-blind; LWYY=Lin Wei Ying Yang; NYHA=New York Heart Association. Note: Hazard ratio is presented for primary endpoint based on LWYY model and for all-cause mortality endpoint based on Cox proportional hazard model. Relative rate ratio is presented for recurrent CV events based on Poisson regression model.

COMP discussion

The sponsor argued that treatment with tafamidis cannot prevent disease progression in the whole group of patients. However, the sponsor did not provide additional evidence to show whether treatment with vutrisiran can prevent disease progression. This is not justified therefore the argument of improved efficacy based on the prevention of disease progression is not valid.

The second argument is the improved efficacy based on HELIOS-B in the subgroup of patients with background tafamidis treatment. While tafamidis has demonstrated established benefits in patients with ATTR amyloidosis in terms of mortality and cardiovascular hospitalization rates, the efficacy of adding vutrisiran to tafamidis (compared to placebo) showed numerically consistent results with tafamidis monotherapy, though effect sizes were smaller (except for the all-cause mortality analysis), and no statistically significant or clinically relevant superiority was observed across primary, secondary, and exploratory endpoints. The analysis was not pre-planned in a confirmatory testing strategy, making it difficult to conclude whether vutrisiran offers a significant benefit in the add-on setting. Even with slightly better efficacy observed in the group receiving vutrisiran with background therapy, it remains unclear if this reflects a true advantage of vutrisiran alone or an additive effect with tafamidis. Differences in baseline characteristics between groups and the time lag for efficacy outcomes further complicate the analysis. The benefits of vutrisiran might take some time to show, which makes it difficult to accurately assess its effectiveness, especially when used alongside tafamidis. The median time of tafamidis therapy was 10.84 months (9.18 in the vutrisiran arm). Considering that the effect of tafamidis on mortality is not expected before month 18 after initiation of therapy, in many of these patients there may be an overlap of efficacy of tafamidis with efficacy of vutrisiran in both the vutrisiran and the placebo arm.

Finally, the sponsor claimed treatment effect for vutrisiran in a broader population including not only NYHA Class I and II, but also NYHA Class III. However, patients with both NYHA Class III and ATTR Amyloidosis Disease Stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 ml/min) at baseline were excluded from HELIOS-B. Furthermore, although there were 27 patients with NYHA III treated with vutrisiran, in 18 of these the effect of tafamidis in the combination cannot be excluded.

In the 9 patients with NYHA III remaining in vutrisiran monotherapy, which is a very limited number of treated patients to perform an analysis, the results were not statistically significant and were associated with big margins of error. Therefore, superiority of vutrisiran in NYHA III could not be established by the COMP.

Based on the above, the COMP considered that a statistically significant and clinically relevant superiority of efficacy of vutrisiran in the add-on setting to tafamidis cannot be justified.

- **Significant benefit of Amvuttra (vutrisiran) over Beyonttra (acoramidis)**

The sponsor claimed significant benefit of Amvuttra (vutrisiran) over Beyonttra (acoramidis) based on the potential to treat the broadest population within the orphan condition of ATTR amyloidosis (acoramidis is only authorised for the treatment of ATTR-CM, while vutrisiran is already authorised for the treatment of hATTR amyloidosis with stage 1 and stage 2 polyneuropathy and, once the current type II variation is approved, it will also be authorised for ATTR-CM); and based on the following claims of significant benefit in the target population of ATTR-CM:

1. Efficacy of vutrisiran in the subpopulation of patients with mild to moderate hepatic impairment. Acoramidis has not been studied in patients with hepatic impairment and is not recommended for use in this population.
2. Consistent treatment effect favouring vutrisiran across the primary composite endpoint of all-cause mortality (ACM) and cardiovascular events (CV) events, the components, ACM and CV events, and all secondary endpoints in the subgroup of patients with NYHA Class III, who did not benefit from acoramidis.
3. Demonstration of statistically significant benefit on ACM (analysed as type 1 error-controlled secondary endpoint) by vutrisiran compared to placebo in HELIOS-B. On the other hand, the treatment effect of acoramidis on ACM was not statistically significant for the pre-specified type 1 error-controlled secondary endpoint of ACM.

1. Hepatically impaired patients

The sponsor argues that acoramidis has not been studied in patients with hepatic impairment and, since reduced hepatic function is also expected to affect its PK [BEYONTTRA EPAR], acoramidis is not recommended for use in this population [BEYONTTRA EU Product Information].

Fifty-five patients with mild hepatic impairment and 11 with moderate hepatic impairment, for whom treatment with acoramidis would not be recommended, were treated with vutrisiran in the HELIOS-B study. Efficacy results observed in this subgroup of patients of the primary composite endpoint were consistent with the overall study population; specifically, there were fewer ACM and CV events among vutrisiran-randomized compared with placebo-randomized patients (HR 0.718, 95% CI 0.397-1.297 in the overall population), and treatment related AEs and SAEs were either comparable or lower in vutrisiran-randomized compared with placebo-randomized patients.

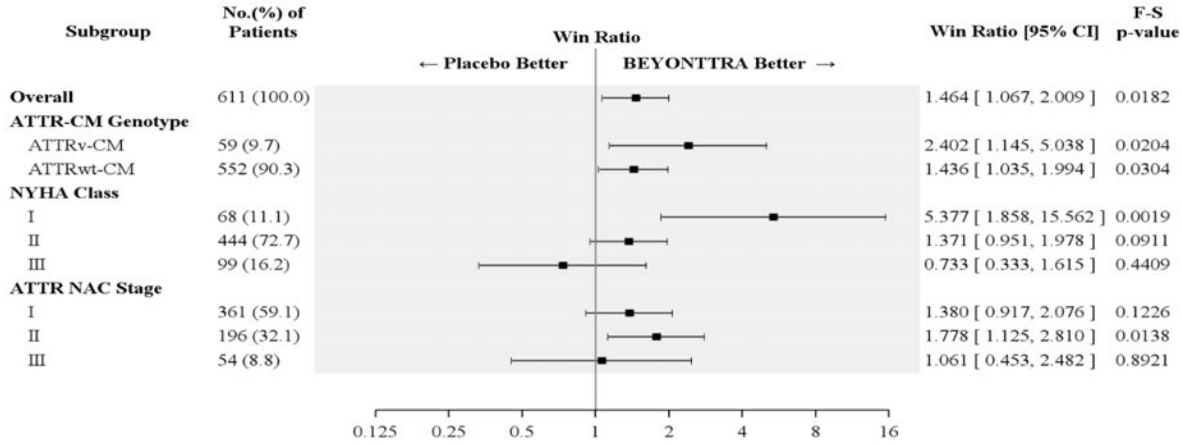
2. Patients with NYHA Class III

Patients with NYHA Class III comprise a subgroup of interest for establishing significant benefit of vutrisiran over acoramidis, as the win ratio analysis of all-cause mortality and CV-related hospitalization numerically favoured placebo (win ratio 0.733) in this subgroup in the ATTRibute-CM study of acoramidis (Figure 3). As further outlined in the EPAR of Beyonttra, "For the primary 4-fold efficacy endpoint and for the 6-MWD, HRs did not indicate efficacy in patients with NYHA III and only limited efficacy was observed for the cumulative frequency of CV hospitalisations. For all-cause mortality, the point estimate of the HRs was even in favour of placebo (Figure 4) with an early shift

favouring placebo around month 12 which is reversed by month 19. The latter finding was further analyzed and the Kaplan - Meier curves for mortality by NYHA category were provided. A continuous trend to lower efficacy was consistent when comparing NYHA I over II to III".

By contrast, in the subgroup of 62 patients with NYHA Class III in the HELIOS-B study, across all primary and secondary endpoints, results consistently favoured vutrisiran over placebo with the point estimates of effect in NYHA Class III being similar to those in NYHA Class I/II. Showing treatment effect in a broader population including not only NYHA Class I and II, but also NYHA Class III, constitutes a significant benefit for vutrisiran over acoramidis.

Figure 3. ATTRibute-CM: Hierarchical combination of all-cause mortality and CV-related hospitalization, Finkelstein-Shoenfeld and win ratio results overall and by subgroup (mITT population)

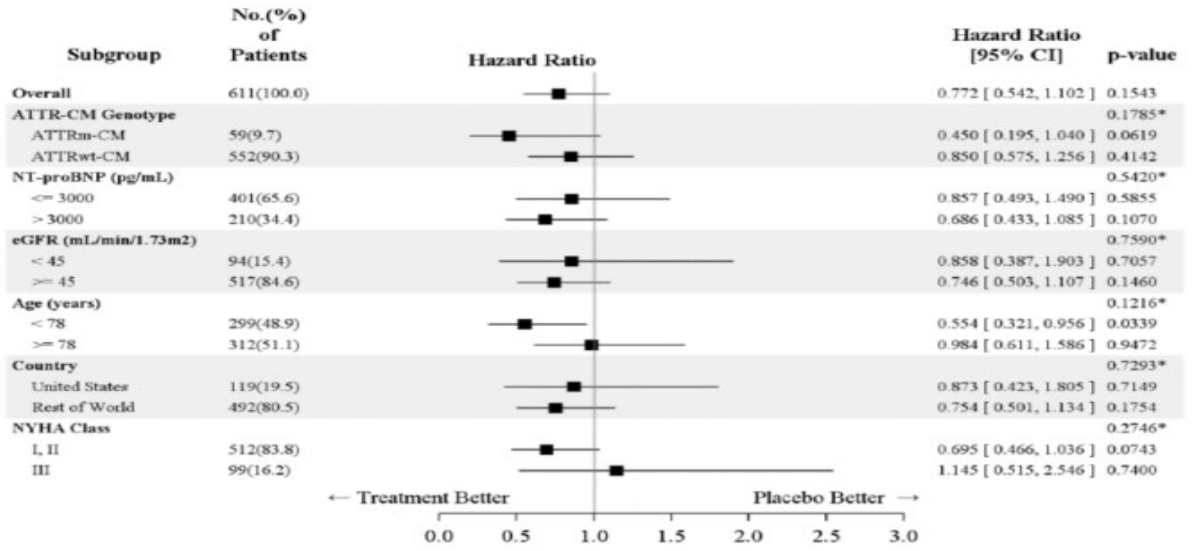


Abbreviations: ACM = all-cause mortality; ATTRwt-CM = wild-type ATTR-CM; ATTRv-CM = variant ATTR-CM; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; NAC = National Amyloidosis Centre (London, UK); NYHA = New York Heart Association; NAC Stage I (NT-proBNP $\leq$ 3 000 pg/mL and eGFR $\geq$ 45 mL/min/1.73 m^2), Stage II (NT-proBNP $\leq$ 3 000 pg/mL and eGFR $<$ 45 mL/min/1.73 m^2 or NT-proBNP $>$ 3 000 pg/mL and eGFR $\geq$ 45 mL/min/1.73 m^2), Stage III (NT-proBNP $>$ 3 000 pg/mL and eGFR $<$ 45 mL/min/1.73 m^2)

[1] The win ratio is the number of pairs with acoramidis treated-participant "wins" divided by number of pairs with placebo-treated participant "wins."

Source: BEYONTTRA EU Product Information

Figure 4. ATTRibute-CM: Forest Plot for Hazard Ratio of all-cause mortality by overall and subgroup analysis, mITT Population



Abbreviations: 6MWD = 6-minute walk distance; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRm-CM = mutant ATTR-CM (ie, ATTRv-CM); ATTRwt CM = wild-type ATTR-CM; CI = confidence interval; CMAD = cardiac mechanical assist device; eGFR = estimated glomerular filtration rate; LS = least squares; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association
All-cause Mortality includes heart transplant, CMAD and all-cause death. * Hazard ratio and p value results are from stratified Cox proportional hazard model with model terms: treatment, baseline 6MWD, subgroup of interest, subgroup x treatment, subgroup x baseline 6MWD. If subgroup variable itself is stratification factor, then it will be removed from stratification variable list. ** P values with * are from testing the interaction of subgroup x treatment, and other p values are for testing the treatment difference at a given value of subgroup variable.
Source: Figure 14.2.1.53

Source: BEYONTTRA EPAR

3. Benefit on all-cause mortality

The sponsor discusses that in the Phase 3 study of acoramidis ATTRibute-CM, the result of a pre-specified, type I error-controlled analysis of ACM as a secondary endpoint was not statistically significant (Table 6) (Poulsen 2024). This finding was clearly reflected in the EPAR of Beyonttra: "Numerically, mortality was lower in patients receiving acoramidis, but no significant improvement was observed for all-cause mortality. The results were consistent for the ITT population. The analysis of CV mortality showed similar non-significant results."

Table 6. Acoramidis (ATTRibute-CM): All-cause mortality as a secondary endpoint

	ATTRibute-CM through 30 months **mITT population**	
	Acoramidis **N=409**	**Placebo** **N=202**
All-cause mortality, n(%)	79 (19.3)	52 (25.7)
Hazard ratio (vs placebo) [a] 95% CI p value	0.772 (0.542, 1.102) **0.1543**	

[a]Based on Cox proportional hazard model
Source: [Poulsen 2024]

In HELIOS-B, on the other hand, vutrisiran demonstrated statistically significant reduction of all-cause mortality when analysed as a pre-specified type I error-controlled secondary endpoint (Table 7). The results of the analysis were consistent in both the overall population and the vutrisiran monotherapy subgroup, defined as patients not on tafamidis at baseline.

Table 7. Vutrisiran (HELIOS-B): All-cause mortality as a secondary endpoint

	HELIOS-B through 33-42 months			
	Overall population		**Monotherapy subgroup**	
	Vutrisiran N=326	**Placebo N=328**	**Vutrisiran N=196**	**Placebo N=199**
All-cause mortality, n(%)	60 (18.4)	85 (25.9)	43 (21.9)	58 (29.1)
Hazard ratio (vs placebo) 95% CI p value	0.645 (0.463, 0.898) 0.0098		0.655 (0.440, 0.973) 0.0454	

Note: Hazard Ratio was based on Cox proportional hazard model, including treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class, and age group as covariates. P-values from log-rank tests were stratified by baseline NT-proBNP (≤3000 ng/L versus >3000 ng/L). For vutrisiran monotherapy subgroup, the analysis was based on the subgroup data only. For overall population, the model was also stratified by baseline tafamidis use.

Other clinically relevant advantages of vutrisiran over acoramidis were claimed by the Sponsor as follows. Acoramidis was shown to be an inhibitor of CYP2C8 and CYP2C9 in vitro, and no in vivo study of effects on these enzymes has been performed. Therefore, as per the Beyonttra SmPC (Section 4.5), "concomitant CYP2C8 and CYP2C9 substrates with narrow therapeutic index should be used with caution".

By contrast, based on in vitro data (and, as expected, given its chemical composition, relatively high molecular weight, and drug disposition as an siRNA-conjugate), vutrisiran is not a substrate, inhibitor, or inducer of CYP enzymes or transporters. In an in-vitro study using pooled human liver microsomes, vutrisiran was not a substrate and did not inhibit any of the major CYPs at concentrations up to 612 µM (10,000 µg /mL). CYP induction and transporter substrate /inhibition studies have not been performed with vutrisiran; however, in vitro DDI data from similar GalNAc-siRNA conjugate molecules that share similar physicochemical properties with vutrisiran indicated that they are not substrates, inhibitors, or inducers of major CYPs and are not substrates or inhibitors of transporters (Ramsden 2019). Overall, the data suggests a low potential for DDI with CYPs or transporters.

Drug-drug interactions are relevant to the population of patients with ATTR-CM, given their demographics commonly associated with polypharmacy (the median age in HELIOS-B was 77 years) and since management of cardiomyopathy comorbidities often requires administration of antidysrhythmics and anticoagulants (Dasgupta 2024; Holcman 2024).

COMP discussion

Regarding the first argument on the hepatic impairment subgroup, the COMP acknowledges the text of the SmPCs but considered that this statics wording is not the only aspect that has to be considered but that the background for this wording also needs to be assessed.

In the clinical studies for acoramidis (including in the ATTRibute-CM pivotal study), ALT and AST ≤ 3 × ULN and total bilirubin ≤ 3 × ULN (≤ 2 × ULN in Phase 2 Study AG10-201) were required at screening.

In HELIOS-B a more granular definition of hepatic impairment was used and patients with mild or moderate hepatic impairment were allowed to be included in the study. Mild hepatic impairment was defined as total bilirubin (TBILI) > 1.0×ULN to ≤1.5×ULN and any AST for the participants without Gilbert's syndrome or (AST > ULN) for those with Gilbert's syndrome. Moderate hepatic impairment is defined as (TBILI > 1.5xULN to ≤3.0×ULN and any AST) for those without Gilbert's syndrome.

Considering the differences in the definition of hepatic impairment, there might be patients enrolled into ATTRibute-CM with mild and moderate hepatic impairment in line with what was done in HELIOS-B. Only hepatically impaired patients with a definition in accordance with the ATTRibute-CM trial should not receive Beyonttra, or rather, there is no data on those patients, and this is not considered a strong enough argument for significant benefit.

In line with the claims of significant benefit over tafamidis, the sponsor claimed treatment effect for vutrisiran in a broader population including not only NYHA Class I and II, but also NYHA Class III. However, patients with both NYHA Class III and ATTR amyloidosis disease stage 3 (defined as NT-proBNP >3000 ng/L and eGFR <45 ml/min) at baseline were excluded from HELIOS-B (N=0) and only 62 patients NYHA Class III and ATTR amyloidosis stage 1 or 2 were included in the study. Due to the substantial uncertainty associated with estimates from limited size subgroup, these data should be interpreted with caution, and no meaningful conclusions can be drawn.

The significant benefit can be based on a clinically relevant advantage (i.e. better efficacy or safety) or a major contribution to patient care (MCPC). The fact that one product is metabolized in a different way and therefore would allow combinations with other medicinal products is per se not a significant benefit, unless it can be shown that this results in a clinically relevant benefit for the patients. No such data has been provided. Additionally, no data was provided to allow a proper comparison of the effect in all-cause mortality.

4. COMP list of issues

- Prevalence

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should justify the inclusion and choice of sources selected for the prevalence estimation and describe the methodology used for these calculations. The sponsor should consider recently published studies, particularly those reflecting increased prevalence rates following advancements in scintigraphy use, as these provide more direct and updated prevalence calculations.

Due to significant uncertainties surrounding many of the underlying assumptions, the sponsor should elaborate on the prevalence estimate for the proposed orphan condition. This recalculation should be grounded in up-to-date and relevant epidemiological studies and registries that accurately reflect the target population. Furthermore, the sponsor is asked to conduct a sensitivity analysis to assess the potential impact of these assumptions on the prevalence estimate. This analysis should consider variability across demographic factors such as age groups, particularly those that may disproportionately contribute to an over- or underestimation. Emphasis should be placed on data sources that align with current diagnostic practices to ensure a more reliable and representative estimate.

- Significant benefit

The significant benefit over tafamidis and acoramidis has not been demonstrated. The applicant should further elaborate on the arguments for improved efficacy considering the limitations of the subgroup analysis.

Comments on sponsor's response to the COMP list of issues

- Prevalence

Regarding the prevalence, the sponsor recalculated the prevalence with updated literature data reporting increases in prevalence over the respective study periods up to 2018 (Table 8).

Table 8. Reported increase in prevalence of ATTR-CM

Article	Geography	Data source	Reported increase	Study period
[Lauppe 2021]	Sweden	National registers	Prevalence: 0.29 to 0.50 per 10,000	2008-2018
[Damy 2020]	France	Nationwide claims (SNDS)	Prevalence: 0.08 to 0.42 per 10,000	2011-2017

The sponsor provided a more conservative estimated prevalence assuming that the increase in the rate observed in the years before 2018 is maintained in the following years up to 2024. The calculation is summarized in Table 9.

This estimate represents an upper bound value, considering that if the same re-calculation approach was applied to Lauppe 2021 (i.e. 0.5 per 10,000 in 2018, increased from 0.29 in 2008), the resulting 2024 estimate in Sweden would be 0.69 per 10,000. Further, if the prevalence-increase from Damy et al., 2020 (533%) is applied to that of Lauppe et al., 2021, the resulting prevalence estimate would be 2.7 per 10,000 which is also below the threshold of 5 per 10,000.

Table 9. Re-calculation of ATTR-CM (hereditary and wild-type) prevalence in 2024

Step number	Description	Numerical Output	Assumptions and rationale
1	Calculate the percentage increase as reported by Damy et al. over the 6-year period from 2011 to 2017	(4.2-0.8)/0.8 * 100 = 425%	While the point estimates reported by Lauppe (year 2018) and Cappelli (year 2022) were higher than that reported by Damy (year 2017), The increase in prevalence rate reported by Damy et al. was chosen for the re-calculation as it was larger than the increase reported by Lauppe et al., in an effort to produce the most conservative estimate.
2	Calculate the compounded per year increase	4.25^(1/6) =1.27; (1.27 – 1)*100= 27%	Assuming a compounded rate of increase.
3	Calculate a 7-year increase for the period 2018-2024	1.27^7 = 5.33 *100 = 533% growth	

Step number	Description	Numerical Output	Assumptions and rationale
4	Calculate prevalence increase based on the projected 533% increase using the calculated increase from step 3 and applying to the prevalence reported in 2017 (0.42 in 10,000)	(0.42 * 5.33) cases per 10,000 = 2.24 cases per 10,000 people in EU	Assuming that the prevalence of ATTR-CM in France is equal to that in the whole EU. The Damy 2020 study population is deemed sufficiently representative to provide a reasonable estimate of a prevalence rate in the EU population because [Damy 2020] relies on the SNDS nationwide database which collects health insurance claims and hospital discharge information from 99% of the French population. France implemented a national referral network and had a relatively high level of disease awareness among physicians. These attributes make it more likely that national summaries identify, and capture patients and the number of undiagnosed cases would be minimal, thus providing a more conservative prevalence estimate.

COMP discussion

Regarding the calculation of prevalence, the COMP considered that, in addition to the publications mentioned from the sponsor, the publication by Ney et al. (2023) should also be taken into account: Ney S, et al. Epidemiology of cardiac amyloidosis in Germany: a retrospective analysis from 2009 to 2018. Clin Res Cardiol. 2023. Based on this publication, the adjusted prevalence of cardiac amyloidosis with a median survival of 6.73 years (according to recent publications which take into account improvement in survival due to approved treatments for ATTR-CM and generally better standard-of-care for heart failure) is 7.8 per 10,000 persons. In comparison, the adjusted prevalence from the studies by Lauppe (2021) and Damy (2020) with the same median survival are 0.89 and 2.42 per 10,000 persons, respectively.

Taking the average of the figures calculated based on the three publications (0.89, 2.42 and 7.8), it gives a mean prevalence of 3.70 per 10,000 persons for ATTR cardiomyopathy. If the prevalence of ATTR-PN is also considered — estimated at 0.12 per 10,000 — then the total prevalence of ATTR amyloidosis (including both cardiomyopathy and polyneuropathy) becomes 3.82 per 10,000 persons.

- **Significant benefit of Amvuttra (vutrisiran) over Vyndaqel (tafamidis)**

1. HELIOS-B within-study propensity score-weighted comparison

The sponsor argued that unbiased cross-study indirect comparison of ATTR-ACT and HELIOS-B is not feasible. The HELIOS-B phase 3 trial was not specifically designed to directly compare vutrisiran and tafamidis within the study, but its structure allows for a comparison within a similar patient population. Patients were randomly assigned to receive either vutrisiran or a placebo, with some continuing prior tafamidis treatment. This created two key subgroups for comparison: one receiving vutrisiran alone and another receiving tafamidis alone. To address imbalances in patient characteristics, and thus minimize confounding, propensity score weighting (stabilized inverse probability of treatment weighting [IPTW]) was applied to patient-level data from the vutrisiran monotherapy and tafamidis

monotherapy groups in HELIOS-B to yield reweighted treatment groups that were balanced in terms of key characteristics. The following baseline parameters were included in the propensity score model for this purpose: age category, ATTR disease type, NYHA class, troponin I (log-transformed), NT-proBNP (log-transformed), KCCQ-OS, average peak longitudinal strain, eGFR, sex, race category, history of antithrombotic agents, PND score, and 6-MWT.

According to the sponsor, after propensity score weighting, most parameters were balanced. In addition, sample size was only minimally impacted (effective sample size after weighting: vutrisiran monotherapy, 188.0; tafamidis monotherapy, 130.6), indicating good overlap between the two groups being compared.

The results are presented in Table 10.

Table 10. Estimates of treatment effect with vutrisiran monotherapy versus tafamidis monotherapy: results from propensity score weighted comparison of the vutrisiran monotherapy and tafamidis monotherapy groups within HELIOS-B

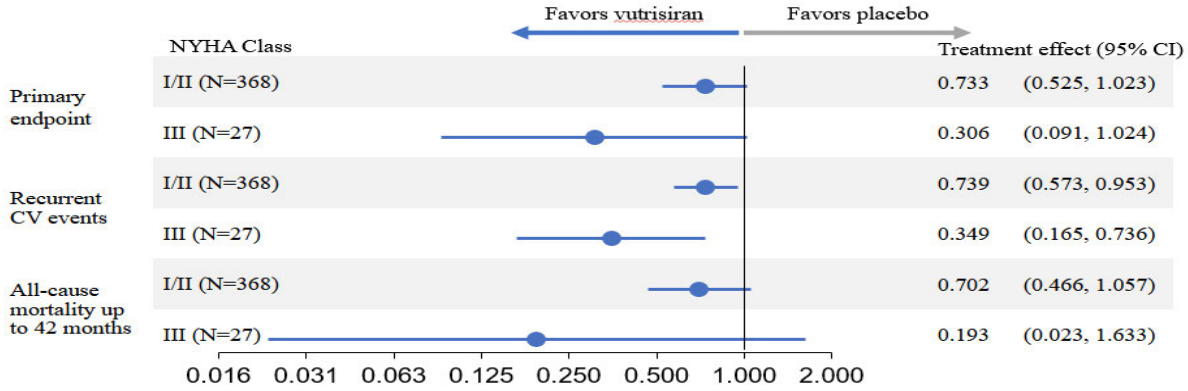
Outcome	**Measure of Treatment Effect**	**Result (Vutrisiran vs. Tafamidis)**
Composite of ACM and recurrent CV events (primary endpoint)[a]	Hazard ratio (95% CI)	0.831 (0.536, 1.287)
CV events (component analysis of primary composite endpoint)[b]	Relative rate ratio (95% CI)	0.82 (0.62, 1.08)
ACM (secondary endpoint)[c]	Hazard ratio (95% CI)	0.814[d] (0.494, 1.340)

Abbreviations: 6-MWT=6-minute walk test; ACM=all-cause mortality; CI=confidence intervals CV=cardiovascular; HR=hazard ratio; NT-proBNP=N-terminal pro-brain natriuretic peptide; RRR=relative risk ratio
[a]Based on data collected over up to 36 months of follow-up in HELIOS-B, with application of propensity score weights (stabilized inverse probability of treatment weighting). HR was derived from a modified Andersen-Gill model that includes treatment, baseline log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT distance as covariates.
[b]Based on data collected over up to 36 months of follow-up in HELIOS-B, with application of propensity score weights (stabilized inverse probability of treatment weighting). RRR was derived from a Poisson regression model that includes treatment, baseline log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT distance as covariates, along with log-transformed follow-up time as an offset variable.
[c]Based on data collected over up to 42 months of follow-up in HELIOS-B, with application of propensity score weights (stabilized inverse probability of treatment weighting). HR was derived from a modified Andersen-Gill model that includes treatment, baseline log-transformed NT-proBNP, log-transformed troponin I, and 6-MWT distance as covariates.
[d]Absolute risk reduction = 5.02%.

2. *Efficacy in sub-population: patients with NYHA Class III*

The sponsor claimed that based on the sample size of N=62 which is relatively sizeable in the context of a rare disease, and the fact that subgroup analyses by NYHA Class (I/II v III) were pre-specified in the protocol of the HELIOS-B study, the efficacy results of vutrisiran in patients with NYHA Class III are deemed sufficient to inform on the consistency of effect across disease severities from NYHA Class I to NYHA Class III, suggesting that patients with NYHA Class III are more likely to receive clinical benefit from treatment with vutrisiran than with a TTR stabilizer like tafamidis.

Figure 5. HELIOS-B: Subgroup analysis by NYHA Class I/II vs III (Vutrisiran Monotherapy Population)



Note: Hazard ratio is presented for primary endpoint based on LWYY model and for all-cause mortality endpoint based on Cox proportional hazard model. Relative rate ratio is presented for recurrent CV events based on Poisson regression model.

In addition, the sponsor presented the efficacy results in patients progressing to NYHA Class III+NAC III or NYHA Class IV during the DB period (Table 11). According to the sponsor, the results were indicative of a beneficial effect of vutrisiran on mortality and recurrent CV events in patients who progressed to NYHA Class III+NAC III or NYHA Class IV. Similarly, vutrisiran led to a numerical reduction in the risk of ACM among these patients.

Table 11. Analyses of primary endpoint (DB period) and all-cause mortality (through 42 months) following progression to NYHA III+NAC III or NYHA IV

	Overall population (N=62)	**Vutrisiran Monotherapy subgroup (N=38)**	**Background tafamidis subgroup (N=24)**
Primary endpoint			
Vutrisiran vs placebo Hazard Ratio(95% CI) [1]	0.644 (0.307, 1.348)	0.542 (0.240, 1.223)	0.441 (0.120, 1.621)
All-cause mortality through 42 months			
Vutrisiran vs placebo Hazard Ratio(95% CI) [2]	0.442 (0.148, 1.323)	0.226 (0.054, 0.940)	0.745 (0.083, 6.585)

Abbreviations: ATTR amyloidosis=transthyretin-mediated amyloidosis; CI=confidence interval; DB=double-blind; NAC=National Amyloidosis Centre; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PH=proportional hazards.
Source: Table 90.q2.2, Table 90.q2.3
Only events occurred on or after the initial advancement to NYHA III + NAC Stage III or NYHA IV were included, and the follow-up time started at the first occurrence of the advancement.
Based on the modified Andersen-Gill model [1] and Cox PH model [2] including treatment group and the following baseline covariates: log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group. For subgroups, the analysis is based on the subgroup data only. For overall population, the model is stratified by baseline tafamidis use.

3. Efficacy in sub-population: patients whose disease progresses on tafamidis

The sponsor claimed that vutrisiran's observed efficacy in patients who experienced disease progression whilst on tafamidis therapy is a significant benefit over tafamidis.

In this subset of the background tafamidis subgroup, treatment with vutrisiran was associated with numerically favourable results compared to placebo including reduction in the composite endpoint of all-cause mortality and recurrent CV events of 41.2% and reduction in all-cause mortality of 56.0%. Trends were consistently favouring vutrisiran across endpoints, except for the proportion with stable or improved NYHA class. While being a small subgroup of the study population not powered to show statistically significant difference, vutrisiran's observed efficacy in patients who experienced disease progression whilst on tafamidis therapy is a significant benefit over tafamidis.

Table 12. Summary of efficacy analyses in tafamidis progressors in the background tafamidis subgroup

	Tafamidis Progressors in the Background Tafamidis Subgroup	
Endpoint	**Treatment Effect Estimation**	**Treatment Effect (95% CI)**
Outcome endpoints		

Primary endpoint: Composite outcome of all-cause mortality and recurrent CV events during the DB Period	Hazard ratio[a]	0.588 (0.218, 1.584)
Secondary endpoint: All-cause mortality through 42 months	Hazard ratio[b]	0.440 (0.131,1.478)
Other secondary endpoints		
6-MWT change from baseline at Month 30	LS mean difference[c]	8.96 (-34.29, 52.20)
KCCQ-OS change from baseline at Month 30	LS mean difference[c]	5.48 (-4.71, 15.67)
Proportion with stable or improved NYHA Class at Month 30	Adjusted % difference[d]	-3.2 (-29.2, 22.8)

Abbreviations: 6-MWT=6-minute walk test; ATTR=transthyretin-mediated (amyloidosis); CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CV=cardiovascular; DB=double-blind; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire – Overall Summary; LS=least squares; LVAD=left ventricular assist device; MCMC=Markov Chain Monte Carlo; MMRM=mixed model repeated measures; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; NYHA=New York Heart Association; PH=proportional hazard.
Notes: Based on events as adjudicated by the Clinical Events Committee and determined by Investigators. Analyses were based on subgroup data only.
[a] Deaths after study withdrawal were not included in analysis. All-cause mortality included heart transplantation and LVAD placement. Based on modified Andersen-Gill model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA Class, and age group as covariates.
[b] Deaths after end of study were included in the analysis. All-cause mortality included heart transplantation and LVAD placement. Based on Cox PH model including treatment group, log-transformed baseline NT-proBNP, ATTR amyloidosis type, NYHA class, and age group as covariates.
[c] Missing change values due to amyloidosis disease progression (for 6-MWT only) and death were imputed using 20 random samples with replacement from the worst 10% of observed change from baseline of all patients at the same visit from the same treatment group and baseline tafamidis use group, capped by 0-baseline distance (for 6MWT)/baseline domain score (for KCCQ-OS). Based on MMRM analysis with baseline 6MWT/KCCQ-OS as a covariate and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, type of ATTR amyloidosis, and age group.
[d] Derived from multiple imputation procedure by combining estimates per Rubin's rules based on 100 datasets where missing NYHA Class values due to death, heart transplantation, and LVAD placement were imputed as Class IV and the other missing NYHA Class values were imputed using an MCMC procedure including selected baseline variables and postbaseline NYHA Class assessments. For each imputed dataset, common risk difference and standard error were based on CMH method stratified by baseline NT-proBNP.

- **Significant benefit of Amvuttra (vutrisiran) over Beyonttra (acoramidis)**

1. Improved efficacy: Ability to treat both the polyneuropathy and cardiomyopathy manifestations in patients with hATTR amyloidosis with cardiomyopathy

According to the authorized therapeutic indications, acoramidis covers the treatment of wild-type or variant ATTR-CM whereas vutrisiran covers both cardiomyopathy but also polyneuropathy disease symptoms (stage 1 and 2) in hereditary patients.

Based on this, the sponsor claimed both a clinically relevant advantage and a major contribution to patient care (MCPC) since vutrisiran could be used as a single medication to treat both their polyneuropathy and cardiomyopathy manifestations of the same disease (ATTR), whereas patients treated with acoramidis would require addition of a second medication to treat polyneuropathy.

2. Certainty of effect on all-cause mortality

The sponsor argued that since the pre-specified, type I error-controlled analysis of all-cause mortality was not statistically significant in the ATTRibute-CM study of acoramidis (p=0.1543) there is no robust evidence of its efficacy on all-cause mortality and insufficient evidence to reject the null hypothesis that acoramidis provides no survival advantage over placebo. Conversely, vutrisiran demonstrated statistically significant reduction of all-cause mortality when analysed as a pre-specified type I error-controlled endpoint in HELIOS-B, which provides relevant evidence of its mortality benefit.

3. Efficacy in patients with NYHA Class III

The sponsor highlighted that in the Phase 3 ATTRibute-CM study of acoramidis, in patients with NYHA Class III, the treatment effect of acoramidis was not consistent across all endpoints tested, with a "continuous trend to lower efficacy" when comparing NYHA I over II to III [European Public Assessment Report (EPAR) of BEYONTTRA] including some point estimates favoring placebo over acoramidis. Conversely, pre-specified subgroup analyses showed that in the subgroup of patients with NYHA Class III of HELIOS-B, across the primary and secondary endpoints, results consistently favoured vutrisiran over placebo, as above with regards to the significant benefit of vutrisiran over tafamidis, suggesting that patients with NYHA Class III are more likely to receive clinical benefit from treatment with vutrisiran than with a TTR stabilizer like acoramidis.

4. Indirect treatment comparison: feasibility assessment

The sponsor highlighted that based on the design of the studies and the different definition of outcomes, the event-based outcomes could not feasibly be compared across the HELIOS-B and ATTRibute-CM trials in an indirect treatment comparison.

COMP discussion

The questions have been addressed by the sponsor and additional analyses were provided regarding the significant benefit of Amvuttra (vutrisiran) over Vyndaqel (tafamidis) and Beyonttra (acoramidis). The justifications were, however, not sufficient for the COMP to be able to conclude on a significant benefit based on a clinically relevant advantage over either of the products based on this data and in line with the initial assessment.

In light of the foregoing, the COMP performed an assessment of the broader therapeutic indication of the relevant products for ATTR amyloidosis, as the designated orphan condition. The sponsor has noted the mixed nature of the cardiac and neuropathy clinical manifestations in this multisystem disease, with around 25% of patients being affected by symptoms of cardiomyopathy as well as polyneuropathy, and Amvuttra being the only product to be authorised for patients with both hATTR-

PN stage 1-2 and ATTR-CM. In this respect, the COMP established that whereas the target population of Amvuttra would include patients with hATTR-PN stage 1-2 and ATTR-CM, the target population of Vyndaqel would only cover patients with hATTR-PN stage 1 and ATTR-CM, while the target population of Beyonttra would only cover patients with ATTR-CM. Therefore, the COMP concluded that when considering the broader therapeutic indication, Amvuttra covers a broader target population than both Vyndaqel and Beyonttra.

5. COMP position adopted on 15 May 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of transthyretin-mediated amyloidosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 3.82 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Amvuttra.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Amvuttra, Synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues, Vutrisiran for treatment of transthyretin-mediated amyloidosis (EU/3/18/2026) is not removed from the Community Register of Orphan Medicinal Products.

6. Appendix 1

Divergent position expressed by some members of the COMP

The orphan criterion of rarity requires the condition to occur in less than 5 in 10.000 in the EU at the time that the application is made. An up-to-date assessment of prevalence is therefore necessary. The epidemiology of ATTR amyloidosis is currently changing rapidly, however.

The recent increase in the use of non-invasive diagnostics for ATTR-amyloidosis and the introduction of treatment options not only increases the proportion of patients with better prognosis compared to the literature predating these developments, but also raises awareness of the condition in clinical practice. All these factors have contributed to a recent steep increase in prevalence, as reported in the literature. In addition, a recent screening study is compatible with prevalence estimates higher than 5.

The undersigned members are of the opinion that the prevalence criterion is no longer met for ATTR amyloidosis at the present time.

COMP members expressing divergent position:

Brigitte Schwarzer-Daum name (Austria)

Frauke Naumann-Winter name (Germany)

Elisabeth Johanne Rook name (Netherlands)