PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Amvuttra 25 mg

solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains vutrisiran sodium equivalent to 25 mg vutrisiran in 0.5 mL solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (S.C).

Clear, colourless-to-yellow solution for subcutaneous injection, essentially free of particulates. (pH of approximately 7; osmolality 210 to 390 mOsm/kg).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis. Treatment should be started as early as possible in the disease course to prevent the accumulation of disability.

Posology

The recommended dose of Amvuttra is 25 mg administered via subcutaneous injection once every 3 months.

Vitamin A supplementation at approximately, but not exceeding, 2,500 IU to 3,000 IU vitamin A per day is advised for patients treated with Amvuttra (see section 4.4).

The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.

There is limited data with vutrisiran in patients with New York Heart Association (NYHA) Class IV and in patients who have both NYHA Class III and National Amyloidosis Centre (NAC) stage III. However, if patients on vutrisiran progress to these stages, these data suggest that patients can remain on treatment.

Missed dose
If a dose is missed, Amvuttra should be administered as soon as possible. Dosing should be resumed every 3 months, from the most recently administered dose.

Special populations

Elderly patients
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild (total bilirubin ≤ 1 x upper limit of normal (ULN) and aspartate aminotransferase (AST) > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. Vutrisiran has not been studied in patients with severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73 m^2). Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Paediatric population
The safety and efficacy of Amvuttra in children or adolescents < 18 years of age have not been established. No data are available.

Method of administration

Amvuttra is for subcutaneous use only. Amvuttra should be administered by a healthcare professional.

This medicinal product is ready-to-use and for single-use only.

Visually inspect the solution for particulate matter and discolouration. Do not use if discoloured or if particles are present.

Prior to administration, if stored cold, the pre-filled syringe should be allowed to warm by leaving carton at room temperature for about 30 minutes.

- The subcutaneous injection should be administered into one of the following sites: the abdomen, thighs, or upper arms. Amvuttra should not be injected into scar tissue or areas that are reddened, inflamed, or swollen.
- If injecting into the abdomen, the area around the navel should be avoided.

4.3 Contraindications

Severe hypersensitivity (e.g., anaphylaxis) to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Vitamin A deficiency

By reducing serum transthyretin (TTR) protein, Amvuttra treatment leads to a decrease in serum vitamin A (retinol) levels (see section 5.1). Serum vitamin A levels below the lower limit of normal should be corrected and any ocular symptoms or signs due to vitamin A deficiency should be evaluated prior to initiation of treatment with Amvuttra.

Patients receiving Amvuttra should take oral supplementation of approximately, but not exceeding, 2,500 IU to 3,000 IU vitamin A per day to reduce the potential risk of ocular symptoms due to vitamin A deficiency. Ophthalmological assessment is recommended if patients develop ocular symptoms suggestive of vitamin A deficiency, including reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening or corneal perforation.

During the first 60 days of pregnancy, both too high or too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should be excluded before initiating Amvuttra and women of childbearing potential should practise effective contraception (see section 4.6). If a woman intends to become pregnant, Amvuttra and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted. Serum vitamin A levels may remain reduced for more than 12 months after the last dose of Amvuttra.

In the event of an unplanned pregnancy, Amvuttra should be discontinued (see section 4.6). No recommendation can be given whether to continue or discontinue vitamin A supplementation during the first trimester of an unplanned pregnancy. If vitamin A supplementation is continued, the daily dose should not exceed 3,000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 2,500 IU to 3,000 IU per day should be resumed in the second and third trimesters if serum vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

It is not known whether vitamin A supplementation in pregnancy will be sufficient to prevent vitamin A deficiency if the pregnant female continues to receive Amvuttra. However, increasing vitamin A supplementation to above 3,000 IU per day during pregnancy is unlikely to correct plasma retinol levels due to the mechanism of action of Amvuttra and may be harmful to the mother and foetus.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed. Vutrisiran is not expected to cause interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes, or to modulate the activity of transporters. Therefore, vutrisiran is not expected to have clinically significant interactions with other medicinal products.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Treatment with Amvuttra reduces serum levels of vitamin A. Both too high or too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should

be excluded before initiation of treatment and women of childbearing potential should use effective contraception. If a woman intends to become pregnant, Amvuttra and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted (see section 4.4.). Serum vitamin A levels may remain reduced for more than 12 months after the last dose of treatment.

Pregnancy

There are no data on the use of Amvuttra in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Amvuttra should not be used during pregnancy. As a precautionary measure, vitamin A (see section 4.4) and thyroid stimulating hormone levels should be obtained early in pregnancy. Close monitoring of the foetus should be carried out, especially during the first trimester.

Breast-feeding

It is unknown whether vutrisiran is excreted in human milk. There is insufficient information on the excretion of vutrisiran in animal milk (see section 5.3).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Amvuttra, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of Amvuttra on human fertility. No impact on male or female fertility was detected in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Amvuttra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The safety profile of Amvuttra was characterised based on the data from randomised-controlled phase 3 clinical studies. Adverse reactions reported in the pooled dataset of HELIOS-A and HELIOS-B studies are presented in Table 1. The adverse reactions are presented as MedDRA preferred terms and under the MedDRA System Organ Class (SOC). The frequency of the adverse reactions is expressed according to the following category: Common (≥1/100 to <1/10).

Table 1: Adverse reactions reported for Amvuttra

System Organ Class	Adverse Reaction	Frequency
General disorders and administration site conditions	Injection site reaction[a]	Common
Investigations	Alanine transaminase increased	Common
	Blood alkaline phosphatase increased	Common
[a] Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild, transient, and did not lead to treatment discontinuation		

Description of selected adverse reactions

Liver function tests
In the HELIOS-B study, 97 (30%) of patients treated with Amvuttra and 78 (24%) patients treated with placebo had a mild increased alanine aminotransferase (ALT) greater than the ULN and less than or equal to 3×ULN. All patients treated with Amvuttra with mild ALT elevations were asymptomatic and the majority had normalization of ALT levels with continued dosing.

Immunogenicity
In the HELIOS-A and HELIOS-B studies, 4 (3.3%) and 1 (0.3%) Amvuttra-treated patients, respectively, developed anti-drug antibodies (ADA). In both studies, ADA titres were low and transient with no evidence of an effect on clinical efficacy, safety, or pharmacokinetic or pharmacodynamic profiles of vutrisiran.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In case of overdose, it is recommended that the patient be monitored as medically indicated for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Nervous System Drugs; ATC code: N07XX18

Mechanism of action

Amvuttra contains vutrisiran, a chemically stabilized double-stranded small interfering ribonucleic acid (siRNA) that specifically targets variant and/or wild-type transthyretin *(TTR)* messenger RNA (mRNA) and is covalently linked to a ligand containing three *N* - acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

Through a natural process called RNA interference (RNAi), vutrisiran causes the catalytic degradation of *TTR* mRNA in the liver, resulting in the reduction of serum levels of variant and wild-type amyloidogenic TTR protein thus reducing the deposition of TTR amyloid in tissues.

Pharmacodynamic effects

In HELIOS-A, mean serum TTR was rapidly reduced as early as Day 22, with mean near to steady state TTR reduction of 73% by Week 6. With repeat dosing of 25 mg once every 3 months, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 88%, respectively. Similar TTR reductions were observed regardless of genotype (V30M or non-V30M), prior TTR stabiliser use, weight, sex, age, or race.

In HELIOS-B, the mean serum TTR reduction profile was consistent with that observed in HELIOS-A, and similar across all subgroups studied (age, sex, race, body weight, anti-drug antibody [ADA] status, ATTR disease type [wild-type or hereditary], NYHA class, and baseline tafamidis use).

Serum TTR is a carrier of retinol binding protein 4, which is the principal carrier of vitamin A in the blood. In HELIOS-A, Amvuttra decreased serum vitamin A levels with mean steady state peak and trough reductions of 70% and 63%, respectively (see sections 4.4 and 4.5). In HELIOS-B, serum vitamin A reductions were consistent with those observed in HELIOS-A.

In HELIOS-B, NT-proBNP and Troponin I, cardiac biomarkers associated with heart failure, demonstrated relative stability in Amvuttra-treated patients for median change from baseline through Month 30 in the overall population (NT-proBNP: 9% increase; Troponin I: 10% decrease) while levels in placebo patients demonstrated worsening (NT-proBNP: 52% increase; Troponin I: 22% increase). Consistent trends were observed in the monotherapy population.

In HELIOS-B, centrally-assessed echocardiograms showed reduction relative to placebo favouring Amvuttra in LV wall thickness (LS mean difference: -0.4 mm [95% CI -0.8, -0.0]) and longitudinal strain (LS mean difference: -1.23% [95% CI -1.73, -0.73]) in the overall population. Results in the monotherapy population were consistent.

Clinical efficacy and safety

hATTR amyloidosis with polyneuropathy
The efficacy of Amvuttra was studied in a global, randomised, open-label clinical study (HELIOS-A) in adult patients with hATTR-PN. Patients were randomised 3:1 to receive 25 mg of Amvuttra (N=122) subcutaneously once every 3 months, or 0.3 mg/kg patisiran (N=42) intravenously once every 3 weeks. The treatment period of the study was conducted over 18 months with two analyses at Month 9 and at Month 18. Ninety-seven percent (97%) of Amvuttra-treated patients completed at least 18 months of the assigned treatments (vutrisiran or patisiran). Efficacy assessments were based on a comparison of the vutrisiran arm of the study with an external placebo group (placebo arm of the APOLLO Phase 3 study) comprised of a similar population of patients with hATTR-PN. Assessment of non-inferiority of serum TTR reduction was based on comparison of the vutrisiran arm to the within-study patisiran arm.

Of the patients who received Amvuttra, the median patient age at baseline was 60 years (range 34 to 80 years), 38% were ≥ 65 years old, and 65% of patients were male. Twenty-two (22) different TTR variants were represented: V30M (44%), T60A (13%), E89Q (8%), A97S (6%), S50R (4%), V122I (3%), L58H (3%), and Other (18%). Twenty percent (20%) of patients had the V30M genotype and early onset of symptoms (< 50 years old). At baseline, 69% of patients had stage 1 disease (unimpaired ambulation; mild sensory, motor, and autonomic neuropathy in the lower limbs), and 31% had stage 2 disease (assistance with ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk). There were no patients with stage 3 disease. Sixty-one percent (61%) of patients had prior treatment with TTR tetramer stabilisers. According to the New York Heart Association (NYHA) classification of heart failure, 9% of patients had class I and 35% had class II. Thirty-three percent (33%) of patients met pre-defined criteria for cardiac involvement (baseline LV wall thickness ≥ 13 mm with no history of hypertension or aortic valve disease).

The primary efficacy endpoint was the change from baseline to Month 18 in modified Neuropathy Impairment Score +7 (mNIS+7). This endpoint is a composite measure of motor, sensory, and autonomic neuropathy including assessments of motor strength, reflexes, quantitative sensory testing, nerve conduction studies, and postural blood pressure, with the score ranging from 0 to 304 points, where an increasing score indicates worsening impairment.

The change from baseline to Month 18 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score was assessed as a secondary endpoint. The Norfolk QoL-DN questionnaire (patient-reported) includes domains relating to small fibre, large fibre, and autonomic nerve function, symptoms of polyneuropathy, and activities of daily living, with the total score ranging from -4 to 136, where increasing score indicates worsening quality of life.

Other secondary endpoints included gait speed (10-meter walk test), nutritional status (mBMI), and patient-reported ability to perform activities of daily living and social participation (Rasch-Built Overall Disability Scale [R-ODS]).

Treatment with Amvuttra in the HELIOS-A study demonstrated statistically significant improvements in all endpoints (Table 2 and Figure 1) measured from baseline to Month 9 and 18, compared to the external placebo group of the APOLLO study (all $p < 0.0001$).

The time-averaged trough TTR percent reduction through Month 18 was 84.7% for vutrisiran and 80.6% for patisiran. The percent reduction in serum TTR levels in the vutrisiran arm was non-inferior (according to predefined criteria) to the within-study patisiran arm through Month 18 with a median difference of 5.3% (95% CI 1.2%, 9.3%).

Table 2: Summary of clinical efficacy results from the HELIOS-A study

Endpoint[a]	**Baseline, Mean (SD)**		**Change from Baseline, LS Mean (SEM)**		**Amvuttra - Placebo**[b] **Treatment Difference, LS Mean (95% CI)**	***p*-value**
	Amvuttra N=122	**Placebo**[b] **N=77**	**Amvuttra**	**Placebo**[b]		
Month 9						
mNIS+7[c]	60.6 (36.0)	74.6 (37.0)	-2.2 (1.4)	14.8 (2.0)	-17.0 (-21.8, -12.2)	*p*<0.0001
Norfolk QoL-DN[c]	47.1 (26.3)	55.5 (24.3)	-3.3 (1.7)	12.9 (2.2)	-16.2 (-21.7, -10.8)	*p*<0.0001
10-meter walk test (m/sec)[d]	1.01 (0.39)	0.79 (0.32)	0 (0.02)	-0.13 (0.03)	0.13 (0.07, 0.19)	*p*<0.0001
Month 18						
mNIS+7[c]	60.6 (36.0)	74.6 (37.0)	-0.5 (1.6)	28.1 (2.3)	-28.5 (-34.0, -23.1)	*p*<0.0001
Norfolk QoL-DN[c]	47.1 (26.3)	55.5 (24.3)	-1.2 (1.8)	19.8 (2.6)	-21.0 (-27.1, -14.9)	*p*<0.0001
10-meter walk test (m/sec)[d]	1.01 (0.39)	0.79 (0.32)	-0.02 (0.03)	-0.26 (0.04)	0.24 (0.15, 0.33)	*p*<0.0001
mBMI[e]	1057.5 (233.8)	989.9 (214.2)	25.0 (9.5)	-115.7 (13.4)	140.7 (108.4, 172.9)	*p*<0.0001
R-ODS[f]	34.1 (11.0)	29.8 (10.8)	-1.5 (0.6)	-9.9 (0.8)	8.4 (6.5, 10.4)	*p*<0.0001

Abbreviations: CI=confidence interval; LS mean=least squares mean; mBMI=modified body mass index; mNIS=modified Neuropathy Impairment Score; QoL-DN=Quality of Life - Diabetic Neuropathy; SD=standard deviation; SEM=standard error of the mean

[a] All Month 9 endpoints analysed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analysed using the mixed-effects model for repeated measures (MMRM)

[b] External placebo group from APOLLO randomised controlled study

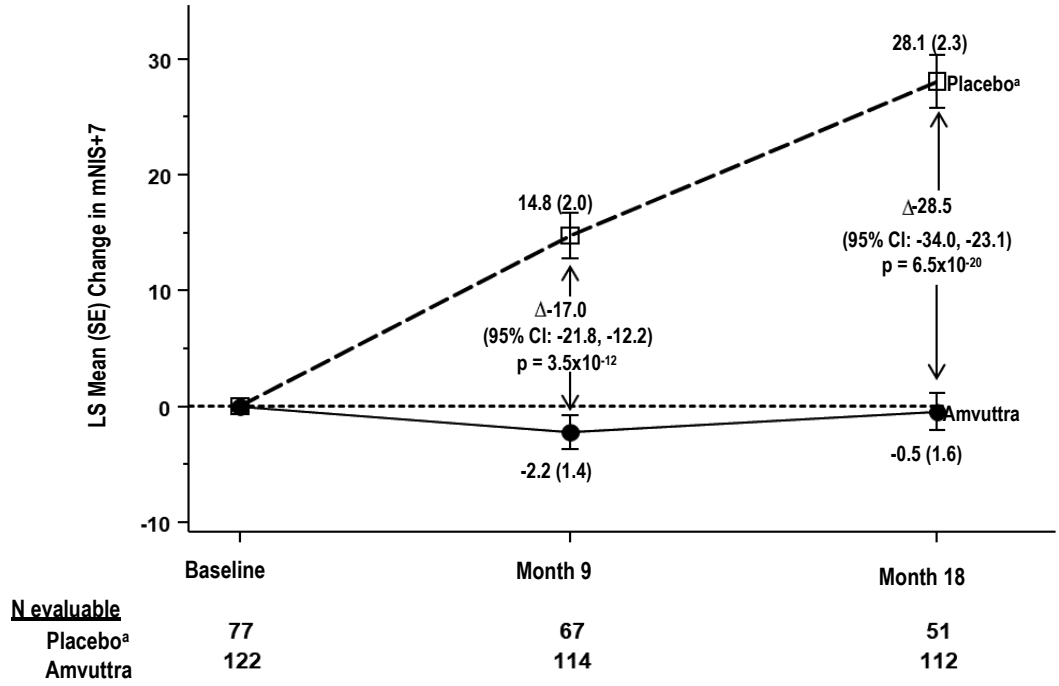
[c] A lower number indicates less impairment/fewer symptoms

[d] A higher number indicates less disability/less impairment

[e] mBMI: body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

[f] A higher number indicates less disability/less impairment.

Figure 1: Change from Baseline in mNIS+7 (Month 9 and Month 18)



A decrease in mNIS+7 indicates improvement

Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA –external placebo

All Month 9 endpoints analysed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analysed using the mixed-effects model for repeated measures (MMRM)

[a] External placebo group from APOLLO randomised controlled study

Patients receiving Amvuttra experienced similar benefit relative to placebo in mNIS+7 and Norfolk QoL-DN total score at Month 9 and Month 18 across all subgroups including age, sex, race, region, NIS score, V30M genotype status, prior TTR stabiliser use, disease stage, and patients with or without pre-defined criteria for cardiac involvement.

The N-terminal prohormone-B-type natriuretic peptide (NT-proBNP) is a prognostic biomarker of cardiac dysfunction. NT-proBNP baseline values (geometric mean) were 273 ng/L and 531 ng/L in Amvuttra-treated and placebo-treated patients, respectively. At Month 18, the geometric mean NT-proBNP levels decreased by 6% in Amvuttra patients, while there was a 96% increase in placebo patients.

Centrally-assessed echocardiograms showed changes in LV wall thickness (LS mean difference: -0.18 mm [95% CI -0.74, 0.38]) and longitudinal strain (LS mean difference: -0.4% [95% CI -1.2, 0.4]) with Amvuttra treatment relative to placebo.

wtATTR or hATTR amyloidosis with cardiomyopathy

The efficacy of Amvuttra was demonstrated in a global, randomised, double-blind, placebo-controlled clinical study (HELIOS-B) 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 (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. According to the NYHA classification of heart failure (HF), 15% of patients had Class I, 77% had Class II, and 8% had Class III and were NAC ATTR disease stage 1 or 2. Patient demographics and baseline disease characteristics were similar between the treatment groups.

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 (Table 3). 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. A Kaplan-Meier curve illustrating time to first CV event or all-cause mortality is presented in Figure 2.

Both components of the primary composite endpoint individually contributed to the treatment effect in the overall population and monotherapy population (Table 3).

In the secondary endpoint analysis of all-cause mortality including data up to Month 42, incorporating the double-blind period and up to an additional 6 months of survival data for all patients, Amvuttra led to a 35.5% reduction in the risk of death relative to placebo in the overall population (hazard ratio: 0.645; 95% CI: 0.463, 0.898; *p*=0.0098), and to a 34.5% reduction in the monotherapy population (hazard ratio: 0.655; 95% CI: 0.440, 0.973; *p*=0.0454).

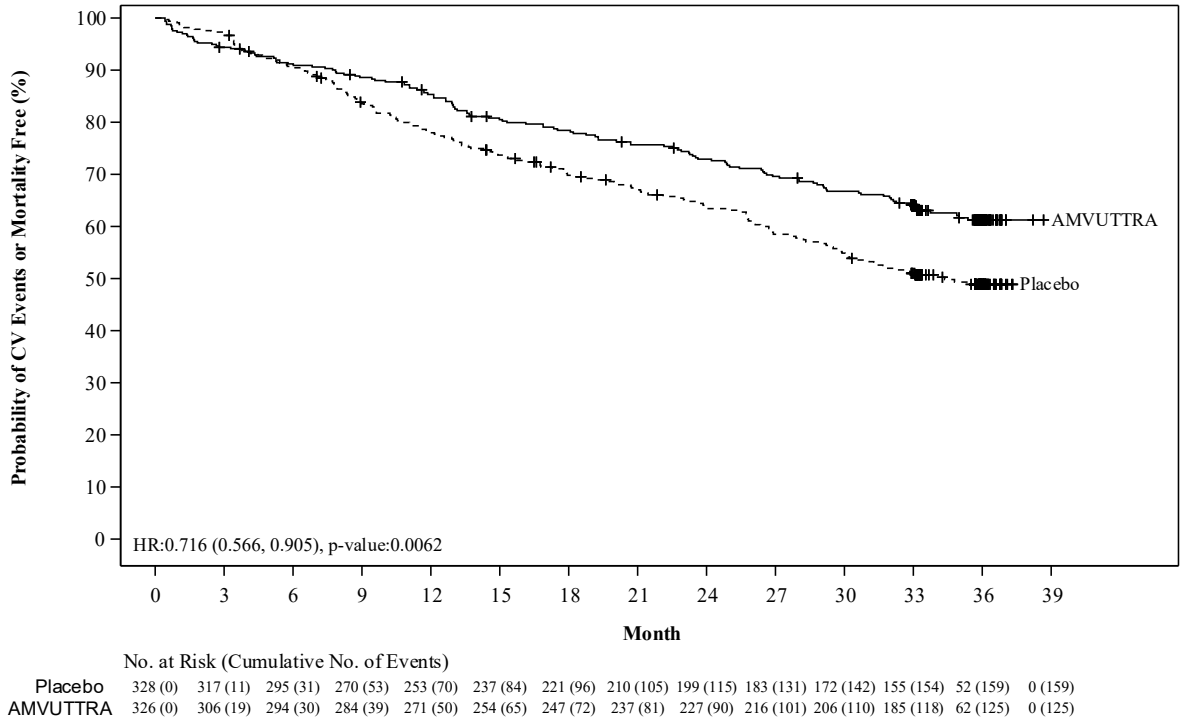
Table 3: Primary composite endpoint and its individual components in HELIOS-B

Endpoint		**Overall population**		**Monotherapy population**	
		Amvuttra (N=326)	**Placebo (N=328)**	**Amvuttra (N=196)**	**Placebo (N=199)**
Primary composite endpoint[a]	Hazard Ratio (95% CI)[b] *p*-value[b]	0.718 (0.555, 0.929) 0.0118		0.672 (0.487, 0.929) 0.0162	
Components of the Primary Composite Endpoint					
All-cause mortality	Hazard Ratio (95% CI)[c]	0.694 (0.490, 0.982)		0.705 (0.467, 1.064)	
CV hospitalisations and UHF visits	Relative Rate Ratio (95% CI)[d]	0.733 (0.610, 0.882)		0.676 (0.533, 0.857)	

Abbreviations: CI=confidence interval; CV=cardiovascular; UHF=urgent heart failure
Heart transplantation and left ventricular assist device placement are treated as death. Deaths after study discontinuation are included in the all-cause mortality component analysis.

[a] Primary composite endpoint defined as: composite outcome of all-cause mortality and recurrent CV events. Primary analysis included at least 33 months (and up to 36 months) follow-up on all patients.
[b] Hazard Ratio (95% CI) and *p*-value are based on a modified Andersen-Gill model.
[c] Hazard Ratio (95% CI) is based on a Cox proportional hazard model.
[d] Relative rate ratio (95% CI) is based on a Poisson regression model.

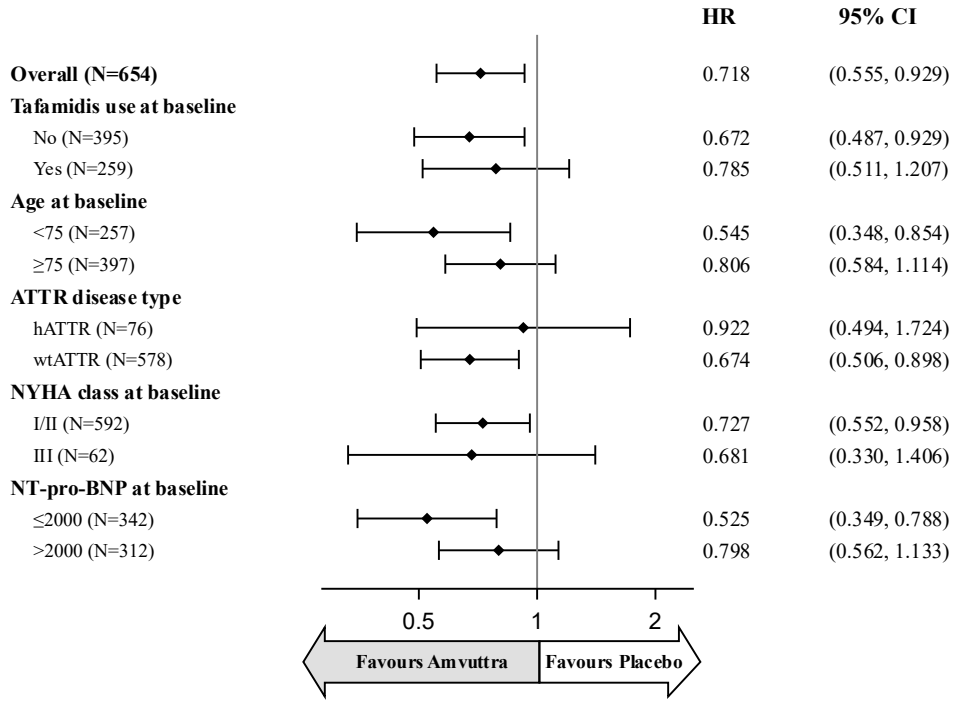
Figure 2: Time to First CV Event or All-Cause Mortality (Overall population)



Abbreviation: CI=confidence interval; CV=cardiovascular; HR = hazard ratio.
Heart transplantation and left ventricular assist device placement are treated as death. Kaplan-Meier curves are adjusted for baseline disease characteristics using the inverse probability of treatment weighting method. HR and 95% CI are based on a Cox proportional hazard model, and *p*-value is based on log-rank test.

Results from the subgroup analysis for the primary composite endpoint favoured Amvuttra across all prespecified subgroups in the overall population and the monotherapy population. In the subgroup of patients on background tafamidis, Amvuttra led to a 21.5% numerical reduction in the risk of all-cause mortality and recurrent CV events relative to placebo (hazard ratio: 0.785; 95% CI: 0.511, 1.207) (Figure 3).

Figure 3: Subgroup Analyses of the Primary Composite Endpoint (Overall Population)



Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; hATTR = hereditary transthyretin amyloidosis; HR = hazard ratio; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; wtATTR = wild-type transthyretin amyloidosis.
HR and 95% CI are based on modified Andersen-Gill model analyses.

The treatment effects of Amvuttra on functional capacity, patient-reported health status and quality of life, and heart failure symptom severity were assessed by the change from baseline to Month 30 in 6-Minute Walk Test (6-MWT), the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score and NYHA class, respectively. The KCCQ-OS is composed of four domains including Total Symptoms (Symptom Frequency and Symptom Burden), Physical Limitation, Quality of Life, and Social Limitation. The Overall Summary score and domain scores range from 0 to 100, with higher scores representing better health status.

A statistically significant treatment effect favouring Amvuttra was observed for 6-MWT distance, KCCQ-OS score, and stable or improved NYHA class, in both the overall population and monotherapy population (Table 4), with consistent results across all subgroups studied. The treatment effect on KCCQ-OS score was consistent across all four domain scores.

Table 4. Change from Baseline in 6-MWT distance, KCCQ-OS score and NYHA class at Month 30

	Overall population		Monotherapy population	
	Amvuttra (N=326)	**Placebo (N=328)**	**Amvuttra (N=196)**	**Placebo (N=199)**
6-MWT (metres)				
Baseline Mean (SD)	372 (104)	377 (96)	363 (103)	373 (98)
Change from baseline to Month 30, LS Mean (SE)[a]	-45 (5)	-72 (5)	-60 (7)	-92 (6)
Treatment Difference from Placebo, LS Mean (95% CI)	26 (13, 40)		32 (14, 50)	
p-value[a,b]	<0.0001		0.0005	
KCCQ-OS (points)				
Baseline Mean (SD)	73 (19)	72 (20)	70 (20)	70 (21)
Change from baseline to Month 30, LS Mean (SE)[a]	-10 (1)	-15 (1)	-11 (2)	-19 (2)
Treatment Difference from Placebo, LS Mean (95% CI)	6 (2, 9)		9 (4, 13)	
p-value[a,b]	0.0008		0.0003	
NYHA Class				
% of patients with stable or improved NYHA class at Month 30	68	61	66	56
Difference from Placebo, (%) (95% CI)[c]	9 (1, 16)		13 (3, 22)	
p-value[c]	0.0217		0.0121	

Abbreviations: 6-MWT = 6-minute walk test; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire, LS = least squares; CI = confidence interval; SD = Standard deviation; SE = Standard Error; NYHA = New York Heart Association

[a] For assessment missing because of death (including heart transplantation and left ventricular assist device placement), and inability to walk as the result of ATTR disease progression (applicable to 6-MWT only), data were imputed from resampling of the worst 10% of observed changes.

[b] Estimated from the MMRM (mixed-effect model repeated measures) model.

[c] Based on Cochran-Mantel-Haenszel method.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Amvuttra were characterised by measuring the plasma and urine concentrations of vutrisiran.

Absorption

Following subcutaneous administration, vutrisiran is rapidly absorbed with a time to maximum plasma concentration (t_{max}) of 3.0 (range: 2.0 to 6.5) hours. At the recommended dosing regimen of 25 mg once every 3 months subcutaneously, the mean (% coefficient of variation [%CV]) steady state peak concentrations (C_{max}), and area under the concentration time curve from 0 to 24 hours (AUC_{0-24}) were 0.12 µg/mL (64.3%), and 0.80 µg·h/mL (35.0%), respectively. There was no accumulation of vutrisiran in plasma after repeated quarterly dosing.

Distribution

Vutrisiran is greater than 80% bound to plasma proteins over the concentration range observed in humans at the dose of 25 mg once every 3 months subcutaneously. Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 µg/mL to 19% at 50 µg/mL). The population estimate for the apparent central compartment

volume of distribution (Vd/F) of vutrisiran in humans was 10.2 L (% Relative standard error [RSE]=5.71%). Vutrisiran distributes primarily to the liver after subcutaneous dosing.

Biotransformation

Vutrisiran is metabolised by endo- and exo-nucleases to short nucleotide fragments of varying sizes within the liver. There were no major circulating metabolites in humans. *In vitro* studies indicate that vutrisiran does not undergo metabolism by CYP450 enzymes.

Elimination

Following a 25 mg single subcutaneous dose, the median apparent plasma clearance was 21.4 (range: 19.8, 30.0) L/h. The median terminal elimination half-life ($t_{1/2}$) of vutrisiran was 5.23 (range: 2.24, 6.36) hours. After a single subcutaneous dose of 5 to 300 mg, the mean fraction of unchanged active substance eliminated in urine ranged from 15.4 to 25.4% and the mean renal clearance ranged from 4.45 to 5.74 L/h for vutrisiran.

Linearity/non-linearity

Following single subcutaneous doses over the 5 to 300 mg dose range, vutrisiran C_{max} was shown to be dose proportional while area under the concentration-time curve from the time of dosing extrapolated to infinity (AUC_{inf}) and area under the concentration-time curve from the time of dosing to the last measurable concentration (AUC_{last}) were slightly more than dose proportional.

Pharmacokinetic/pharmacodynamic relationship(s)

Population pharmacokinetic/pharmacodynamic analyses in healthy subjects and patients with hATTR amyloidosis (n=202) showed a dose-dependent relationship between predicted vutrisiran liver concentrations and reductions in serum TTR. The model-predicted median steady state peak, trough, and average TTR reductions were 88%, 86%, and 87%, respectively, confirming minimal peak-to-trough variability across the 3-month dosing interval. Covariate analysis indicated similar TTR reduction in patients with mild-to-moderate renal impairment or mild hepatic impairment, as well as by sex, race, prior use of TTR stabilisers, genotype (V30M or non-V30M), age and weight.

Special populations

Gender and race
Clinical studies did not identify significant differences in steady state pharmacokinetic parameters or TTR reduction according to gender or race.

Elderly patients
In the HELIOS-A study, 46 (38%) patients treated with vutrisiran were ≥ 65 years old and of these 7 (5.7%) patients were ≥ 75 years old. In the HELIOS-B study, 299 (91.7%) patients treated with vutrisiran were ≥ 65 years old, with a median age of 77.0 years, and of these 203 (62.3%) were ≥75 years old. There were no significant differences in steady state pharmacokinetic parameters or TTR reduction.

Hepatic impairment
Clinical studies indicated no impact of mild (total bilirubin ≤ 1 x ULN and AST > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment on vutrisiran exposure or TTR reduction compared to patients with normal hepatic function. Vutrisiran has not been studied in patients with severe hepatic impairment.

Renal impairment
Clinical studies indicated no impact of mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m^2) on vutrisiran exposure or TTR reduction compared to subjects with normal

renal function. Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease.

5.3 Preclinical safety data

General toxicology

Repeated once-monthly subcutaneous administration of vutrisiran at ≥ 30 mg/kg in monkeys produced the expected sustained reductions of circulating TTR (up to 99%) and vitamin A (up to 89%) without any apparent toxicological findings.

Following once monthly repeated dosing for up to 6 months in rats and 9 months in monkeys, the mild and consistent non-adverse histological changes in liver (hepatocytes, Kupffer cells), kidneys (renal tubules), lymph nodes and injection sites (macrophages) reflected the principal distribution and accumulation of vutrisiran. However, no toxicities were identified at up to more than 1,000- and 3,000-fold higher plasma AUC, when normalised to quarterly dosing and compared to the anticipated exposure at the maximum recommended human dose [MRHD].

Genotoxicity/Carcinogenicity

Vutrisiran did not exert any genotoxic potential *in vitro* and *in vivo*. Vutrisiran was not carcinogenic in rats and in male mice. In female mice dosed once monthly with vutrisiran at 3, 9, or 18 mg/kg, a statistically significant dose-dependent trend for combined hepatocellular adenomas and carcinomas was observed with unknown relevance for humans. The carcinogenic potential of vutrisiran is considered low if all toxicity data are taken into account.

Reproductive toxicity

Vutrisiran is not pharmacologically active in rats and rabbits, which limits the predictivity of these investigations. Nevertheless, a single dose of a rat-specific orthologue of vutrisiran did not impact on fertility and early embryonic development in a combined study in rats.

Weekly subcutaneous administrations of vutrisiran did not affect fertility and early embryonic development at more than 300-times the normalised MRHD In an embryo-foetal study with daily subcutaneous vutrisiran administration in pregnant rats, adverse effects on maternal body weight, food consumption, increased premature delivery and post-implantation loss were observed with a maternal NOAEL of 10 mg/kg/day that was more than 300-times the normalised MRHD of 0.005 mg/kg/day. Based on an adverse reduction in foetal body weights and increased skeletal variations at ≥10 mg/kg/day, the foetal NOAEL of vutrisiran was 3 mg/kg/day which is 97-times the normalised MRHD.

In an embryo-foetal development study in pregnant rabbits, no adverse effects on embryo-foetal development were observed at ≤ 30 mg/kg/day vutrisiran, which is more than 1900-times the normalised MRHD.

In a prenatal-postnatal development study, subcutaneous vutrisiran administration on every 6th day had no effect on growth and development of the offspring with a NOAEL of 20 mg/kg, which was more than 90-times the normalised MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium phosphate dibasic dihydrate
Sodium phosphate monobasic dihydrate
Water for injection
Phosphoric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30 °C. Do not freeze.

6.5 Nature and contents of container

Pre-filled syringe (Type I glass) with stainless steel 29-gauge needle with a needle shield.

Amvuttra is available in packs containing one single-use pre-filled syringe.

6.6 Special precautions for disposal and other handling

Amvuttra is for subcutaneous use only and should be administered by a healthcare professional.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

8. LICENCE HOLDER:

Medison Pharma Ltd. 10 Hashiloach St., POB 7090 Petach Tikva

9. REGISTRATION NUMBER

176-25-37761-99

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