Summary Report of Benefit-Risk Assessment

AMVUTTRA SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 25MG

NEW DRUG APPLICATION

Active Ingredient	Vutrisiran
Product Registrant	Medison Pharma Singapore Pte. Ltd.
Product Registration Number	SIN17124P
Application Route	Abridged evaluation
Date of Approval	25 October 2024

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A INTRODUCTION

Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

The active substance, vutrisiran, is a second-generation chemically stabilised, double-stranded, small interfering ribonucleic acid (siRNA) that specifically targets variant and 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. Vutrisiran causes the catalytic degradation of *TTR* mRNA in the liver through RNA interference (RNAi), resulting in the reduction of variant and wild-type serum TTR protein levels. It is developed with the same mechanism of action as patisiran with a less frequent dosing regimen and via the subcutaneous route instead of intravenously for convenience of dosing.

Amvuttra is available as solution for injection in a pre-filled syringe containing 25mg/0.5mL vutrisiran as vutrisiran sodium. Other ingredients are sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, sodium chloride and water for injection. Sodium hydroxide and phosphoric acid might be used for pH adjustment.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, vutrisiran sodium, is manufactured at [redacted] The drug product, Amvuttra Solution for Injection in pre-filled syringe 25mg, is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany.

Drug substance

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP) standard.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at -20±5ºC with a re-test period of 36 months. The packaging is high-density polyethylene (HDPE) bottle closed with a polypropylene (PP) screw-top.

Drug product

The manufacturing process involves formulation of the drug product, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A guideline and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a Type 1 glass pre-filled syringe with stainless steel 29-gauge needle with a passive needle safety system.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of vutrisiran in the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy was based on one pivotal study, referred to as the HELIOS-A study. This was a Phase III, multicentre, open-label, randomised study in adult patients with hATTR amyloidosis with polyneuropathy, investigating the efficacy of vutrisiran using patisiran as a reference comparator. An external placebo group was referenced from the patisiran study APOLLO, which was a Phase III, multicentre, randomised, double-bind, placebo-controlled study in hATTR amyloidosis patients with polyneuropathy.

Patients were randomised 3:1 to subcutaneous vutrisiran 25mg every 3 months or intravenous patisiran 0.3mg/kg every 3 weeks. The study was conducted in two parts: an 18-month Treatment Period with an efficacy analysis at Month 9 and additional efficacy analyses at Month 18, followed by an 18-month Treatment Extension Period, during which all patients were treated with vutrisiran.

Efficacy assessments were based on comparison of the vutrisiran arm of the study with an external placebo group (placebo arm of the APOLLO study; n=77), which comprised a similar population of patients with hATTR amyloidosis with polyneuropathy.

The primary efficacy endpoint was the change from baseline to Month 18 in modified Neuropathy Impairment Score +7 (mNIS+7). This was 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 (modified body mass index [mBMI]), and patient-reported ability to perform activities of daily living and social

participation (Rasch-Built Overall Disability Scale [R-ODS], with score ranging from 0 to 48 points). The primary and secondary clinical endpoints were evaluated based on a superiority comparison between vutrisiran and the external placebo control.

In addition, the pharmacodynamic secondary endpoint, percent reduction in serum TTR levels through Month 18 in the vutrisiran arm was compared to the within-study patisiran arm. The TTR percent reduction through Month 18 was evaluated as the average trough TTR percent reduction from Month 6 to 18, which correspond to the steady state period for both vutrisiran and patisiran. Non-inferiority was declared if the lower limit of the 95% CI for the treatment difference in TTR percent reduction (vutrisiran – patisiran) was greater than –10%.

Since both vutrisiran and patisiran were developed using the same RNAi platform, target the same transthyretin gene and have the same mechanism of action (silencing of the *TTR* RNA), a non-inferiority comparison versus patisiran based on a pharmacodynamic endpoint (measurement of the reduction of TTR protein) and the indirect comparison to the placebo arm of the patisiran APOLLO study based on clinical endpoints, could be considered acceptable. The use of an external placebo group from the APOLLO study was considered justified in view of the overlap in baseline characteristics between vutrisiran-treated patients in HELIOS-A and placebo-treated patients in APOLLO with the same efficacy endpoints used in both studies. Historical data has demonstrated predictable disease trajectory patterns across hATTR amyloidosis studies, which allowed for reliable comparison with the external placebo group with similar demographics and baseline disease characteristics. Furthermore, given that hATTR amyloidosis is a life-threatening and rare disease with currently available therapy (patisiran), a concurrent placebo arm was ethically inappropriate.

A total of 164 adult patients with hATTR amyloidosis with stage 1 and 2 polyneuropathy were randomised to receive vutrisiran (n=122) or patisiran (n=42). Of the patients who received vutrisiran, the median patient age at baseline was 60 years (range 26 to 85 years), 38% were ≥65 years old, and 65% of patients were male. A total of 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. A total of 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 left ventricular wall thickness ≥13 mm with no history of hypertension or aortic valve disease).

Treatment with vutrisiran demonstrated statistically significant and clinically relevant improvements in all endpoints measured from baseline to Month 9 and 18, compared to the external placebo group of the APOLLO study ($p<0.0001$). At Month 18, the LS mean difference in mNIS+7 change from baseline was -28.55 (95% CI: -34.00, -23.10; $p<0.0001$) and in Norfolk QoL-DN was -21.0 (95% CI: -27.1, -14.9; $p<0.0001$). Significant improvements were also observed in gait speed, nutritional status and disability scores.

The treatment effect at Months 9 and 18 was consistent across all prespecified subgroups for both the primary endpoint of mNIS+7 and the Norfolk QoL-DN. Notably, for assessments of neuropathy and QOL, improvement relative to baseline was observed in approximately half of vutrisiran-treated patients, demonstrating reversal of disease manifestations.

Summary of clinical efficacy from Study HELIOS-A (mITT)

Endpoint	Baseline, Mean		Change from Baseline, LS Mean		Vutrisiran – Placebo (APOLLO) Treatment difference LS Mean (95% CI)	P value
	Vutrisiran (N=122)	Placebo (APOLLO) (N=77)	Vutrisiran (N=122)	Placebo (APOLLO) (N=77)		
Month 9						
mNIS+7[a]	60.55	74.61	-2.24	14.76	-17.00 (-21.78, -12.22)	<0.0001
Norfolk QoL-DN[a]	47.1	55.5	-3.3	12.9	-16.2 (-21.7, -10.8)	<0.0001
10m walk test (m/s)[b]	1.01	0.79	0	-0.13	0.131 (0.070, 0.193)	<0.0001
Month 18						
mNIS+7[a]	60.55	74.61	-0.46	28.09	-28.55 (-34.00, -23.10)	<0.0001
Norfolk QoL-DN[a]	47.1	55.5	-1.2	19.8	-21.0 (-27.1, -14.9)	<0.0001
10m walk test (m/s)[b]	1.01	0.79	-0.02	-0.26	0.239 (0.154, 0.325)	<0.0001
mBMI[c]	1057.5	989.9	25.0	-115.7	140.7 (108.4, 172.9)	<0.0001
R-ODS[d]	34.1	29.8	-1.5	-9.9	8.4 (6.5, 10.4)	<0.0001

mITT: modified Intent-to-Treat population, which refers to the analysis set of all randomised patients who received any amount of study drug, and analysed according to the treatment to which they were randomised.

[a] A lower number indicates less impairment/fewer symptoms.

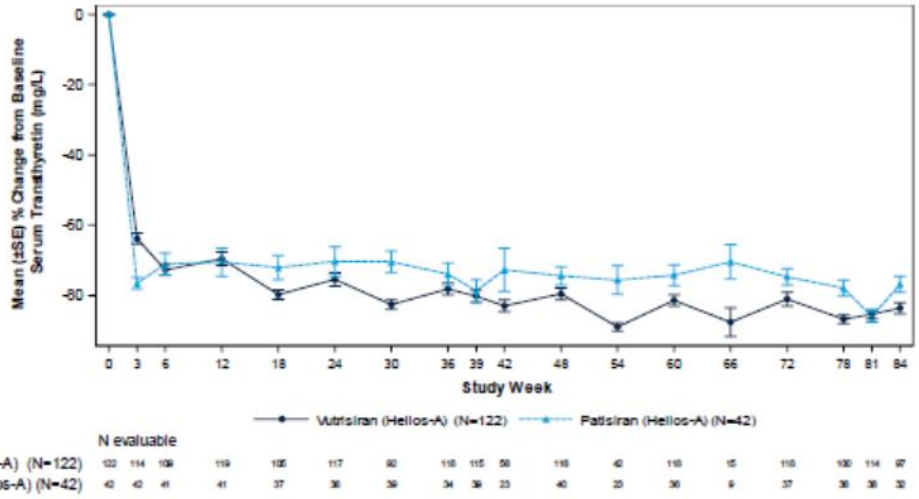
[b] 10m walk test: The time it takes for a patient to walk 10 metres (gait speed); a higher number indicates less disability/less impairment.

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

[d] R-ODS: A 24-item patient-reported measure of activities of daily living and social participation, with scores ranging from 0 to 48; a higher number indicates less disability/less impairment.

Vutrisiran treatment resulted in a rapid and sustained reduction in serum TTR levels over 18 months, similar to what was observed in the within-study patisiran group (see figure below).

Mean TTR percent change from baseline over time during the 18-month treatment period (mITT)



Abbreviations: mITT=modified intent-to-treat; SE=standard error; TTR=transthyretin.
Notes: Month 9 and Month 18 nontrough TTR assessments presented at Weeks 39 and 81, respectively. Presented data ≥5 patients per treatment arm at given study visit.

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%).

The results for the primary and secondary endpoints at Month 18 showing superiority of vutrisiran compared to placebo, together with the demonstration of non-inferiority of vutrisiran to patisiran on the TTR percent reduction, demonstrated the efficacy of vutrisiran in patients with hATTR with stage 1 and 2 polyneuropathy.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of vutrisiran was based primarily on safety data derived from the pivotal Phase III HELIOS-A study. As of the cut-off date of 26 August 2021, a total of 155 patients (122 patients from the Treatment Period and 33 patients in the Treatment Extension Period) with hATTR amyloidosis with polyneuropathy were exposed to vutrisiran in the clinical development program, with a cumulative exposure of 233.0 patient years; 118 patients have overall been exposed for ≥18 months and five subjects have been exposed for ≥27 months.

Overview of safety profile during HELIOS-A Treatment Period and APOLLO placebo group (DCO 26 Aug 2021, Safety population)

Adverse Event (AE)	APOLLO Placebo (N=77) n (%)	HELIOS-A Vutrisiran (N=122) n (%)	HELIOS-A Patisiran (N=42) n (%)
Any AE	75 (97.4)	119 (97.5)	41 (97.6)
Treatment-related AE	30 (39.0)	29 (23.8)	15 (35.7)
Serious adverse event (SAE)	31 (40.3)	32 (26.2)	18 (42.9)
Treatment-related SAE	0	2 (1.6)	5 (11.9)
Discontinuations due to AE	11 (14.3)	3 (2.5)	3 (7.1)
Deaths due to AE	6 (7.8)	2 (1.6)	3 (7.1)

While majority of the patients reported at least one AE, this is expected considering the disease characteristics of hATTR. Most of these AEs were of mild to moderate in severity. AEs occurring in >10% of patients receiving vutrisiran included (vutrisiran vs placebo vs patisiran): falls (18.0% vs 28.6% vs 14.3%), pain in extremity (14.8% vs 10.4% vs 7.1%), diarrhoea (13.9% vs 37.7% vs 16.7%), peripheral oedema (13.1% vs 22.1% vs 9.5%), urinary tract infection (13.1% vs 18.2% vs 19.0%), arthralgia (10.7% vs 0% vs 9.5%), and dizziness (10.7% vs 14.3% vs 0%); all of which, except pain in extremity and arthralgia, occurred at a similar or lower rate than in the external placebo group. In addition, dyspnea was reported in 6.6% of vutrisiran-treated subjects vs none reported in the external placebo group from the APOLLO study.

Treatment-related AEs were reported in 23.8% of patients in the vutrisiran group vs 35.7% in the patisiran group. In the vutrisiran group, treatment-related AEs reported in ≥3 patients were vitamin A decreased (6.6%), injection site reaction (3.3%) and dry eye (2.5%), as compared to 4.8%, 0% and 0% respectively in the patisiran group. There were no treatment-related AEs that led to discontinuation of the study drug.

A reduction of serum vitamin A level is an expected secondary pharmacodynamic effect of reducing serum TTR protein, and the package insert has included warnings and recommendations on vitamin A replacement.

SAEs occurred in 26.2% of patients in the vutrisiran group vs 42.9% in the patisiran group during the Treatment Period. The nature and type of SAEs observed were consistent with those expected in this population and predominantly included infections and cardiac events. Two SAEs (dyslipidaemia and *Escherichia* urinary tract infection) were considered related to treatment by the Investigator. These events resolved with oral atorvastatin and intravenous ceftriaxone treatment respectively, and both patients continued on vutrisiran without interruption. During the Treatment Extension Period, one treatment-related SAE of transaminases increased was reported.

Mortality was numerically lower in the vutrisiran group (1.6%, n=2) than in the external placebo group (7.8%, n=6) or concurrent comparator patisiran group (7.1%, n=3). None of the deaths in the vutrisiran group were considered related to study drug by the Investigators. One patient died from COVID-19 pneumonia. The other patient, who had a history of atrial fibrillation, cardiac amyloidosis, cardiac failure, cerebrovascular accident, and transient ischemic attack, died due to iliac artery occlusion occurred during hospitalisation for heart failure and pneumonia; the cause of death was consistent with the patient's underlying disease.

During the Treatment Extension Period, three additional patients died (two sudden cardiac deaths and a sudden death), none of which were considered related to study drug by the Investigators.

Overall, there were no new safety signals raised with regard to cardiac, hepatic, ocular and renal events. The safety profile of vutrisiran was considered acceptable in the target patient population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

hATTR amyloidosis is a rare, autosomal dominant, rapidly progressive, multi-systemic debilitating disease with high mortality. Amyloid deposits accumulate in multiple organs, particularly the peripheral nervous system, gastrointestinal tract, kidney, and heart, which manifests in progressive polyneuropathy including sensorimotor neuropathy and autonomic neuropathy. Cardiomyopathy, nephropathy, and gastrointestinal dysfunction frequently develop simultaneously. Currently, there are no registered treatments specifically approved for hATTR amyloidosis polyneuropathy, highlighting an unmet medical need for effective therapies to manage this condition.

Vutrisiran is a second-generation RNAi therapeutic developed with the same mechanism of action as patisiran (first generation RNAi) with a less frequent dosing regimen and via the subcutaneous route for convenience of dosing as compared to patisiran.

The efficacy of vutrisiran in adult patients with hATTR amyloidosis with polyneuropathy was assessed in the HELIOS-A study, where it demonstrated significant and clinically relevant improvements in neuropathy as compared to the external placebo group. The LS mean difference in mNIS+7 (vutrisiran – placebo) from baseline to Month 9 and Month 18 was -17.00 (95% CI: -21.78, -12.22) and -28.55 (95% CI: -34.00, -23.10) points, respectively.

Vutrisiran treatment also significantly improved the quality-of-life measurements (Norfolk QoL-DN) as compared with the external placebo group at Month 9 (LS mean difference change from baseline of -16.2 [95% CI: -21.7, -10.8] and Month 18 (LS mean difference of -21.0 [95% CI: -27.1, -14.9]).

Significant improvements with vutrisiran treatment compared with the external placebo group were observed for all other secondary endpoints, including 10-MWT at Months 9 and 18, mBMI at Month 18, and R-ODS at Month 18. The mean changes from baseline for primary and secondary efficacy endpoints in the vutrisiran group were similar with those in the within-study patisiran group.

TTR reduction with vutrisiran was statistically non-inferior to within-study patisiran in the TTR per-protocol population, assessed by mean trough serum TTR levels over 18 months. Improvements in efficacy outcomes with vutrisiran were generally similar to those observed with patisiran, although no statistical testing was conducted as HELIOS-A was not designed to compare the two treatments.

Overall, vutrisiran has an acceptable safety profile, which was mainly characterised by pain in extremity, arthralgia, dyspnea and vitamin A decreased. The overall incidence of AEs was similar to that observed in the external placebo group from the APOLLO study. The majority of the AEs were mild or moderate in severity and generally consistent with those expected as a consequence of hATTR amyloidosis. There were no new or unexpected safety signals detected in the vutrisiran group. Importantly, injection site reactions were reported in low frequencies and without the need for premedication as compared to the intravenously administered comparator patisiran. The decrease in serum levels of vitamin A is an expected secondary pharmacodynamic effect of reducing serum TTR protein, and adequate warnings and recommendations on vitamin A replacement have been included in the package insert.

Overall, the benefits of vutrisiran in the proposed target population outweighed the potential risks and the benefit-risk assessment of vutrisiran is positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Amvuttra for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy was deemed favourable and approval of the product registration was granted on 25 October 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

Amvuttra solution for injection in pre-filled syringe 25mg

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 (injection).

Clear, colourless-to-yellow solution (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-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

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.

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 hepatic impairment (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). Vutrisiran has not been studied in patients with moderate or 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

Summary of the safety profile

During the HELIOS-A 18-month treatment period, the most frequently occurring adverse reactions reported in Amvuttra-treated patients were pain in extremity (15%) and arthralgia (11%).

Tabulated list of adverse reactions

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 categories:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1 000 to <1/100)

Table 1: Adverse reactions reported for Amvuttra

System Organ Class	Adverse reaction	Frequency
Respiratory, thoracic, and mediastinal disorders	Dyspnoea[a]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Pain in extremity	Very common
General disorders and administration site conditions	Injection site reaction[b]	Common
Investigations	Blood alkaline phosphatase increased	Common
[a] Includes dyspnoea, dyspnoea exertional and dyspnoea paroxysmal nocturnal [b] 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

Immunogenicity
During the HELIOS-A 18-month treatment period, 4 (3.3%) Amvuttra-treated patients developed anti-drug antibodies (ADA). 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. Healthcare professionals are asked to report any suspected adverse reactions.

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 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 variant and wild-type serum TTR protein levels.

Pharmacodynamic effects

Mean serum TTR was 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.

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

Clinical efficacy and safety

The efficacy of Amvuttra was studied in a global, randomised, open-label clinical study (HELIOS-A) in adult patients with hATTR amyloidosis with polyneuropathy. 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 amyloidosis with polyneuropathy. 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 analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analyzed using the mixed-effects model for repeated measures (MMRM)

[b] External placebo group from APOLLO randomised controlled study

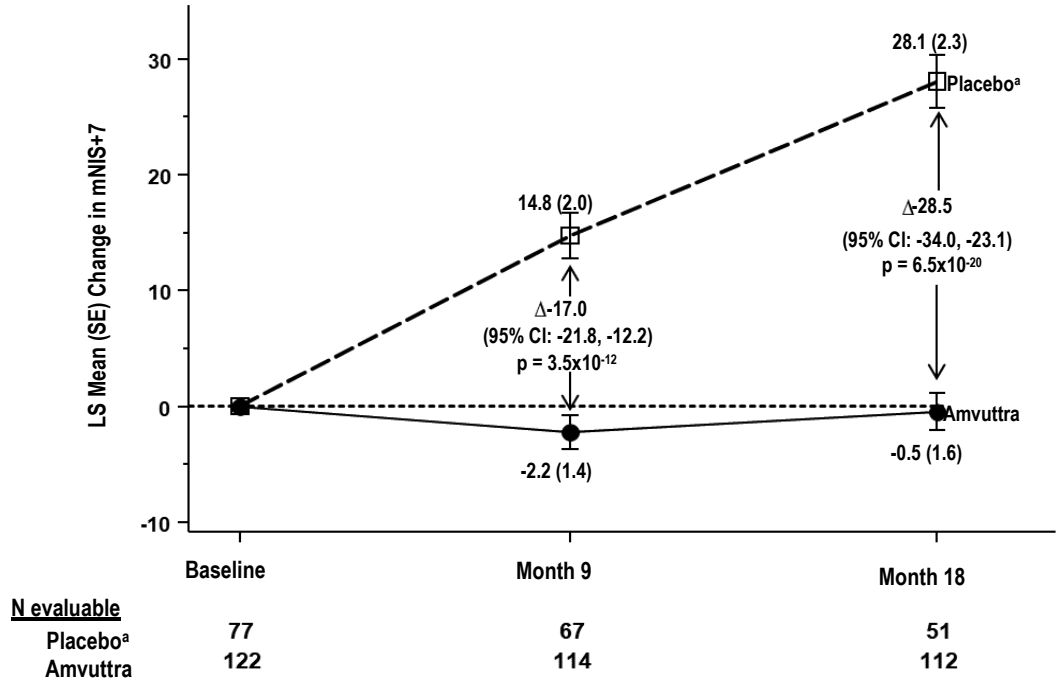
[c] A lower number indicates less impairment/fewer symptoms

[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 analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analyzed 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.

Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed.

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. There were no significant differences in steady state pharmacokinetic parameters or TTR reduction between patients < 65 years old and ≥ 65 years old.

Hepatic impairment
Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild hepatic impairment (total bilirubin ≤ 1 x ULN and AST > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and

any AST) on vutrisiran exposure or TTR reduction compared to patients with normal hepatic function. Vutrisiran has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment
Population pharmacokinetic and pharmacodynamic analyses 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*. Carcinogenicity studies have not been completed.

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 6^{th} 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 dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)
Phosphoric acid (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

3 years.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

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