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Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

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)

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 name | Amvuttra |
| International Non-Proprietary Name | Vutrisiran |
| Tradename | Amvuttra |
| Orphan condition | Treatment of transthyretin-mediated amyloidosis |
| Sponsor's details: | Alnylam Netherlands B.V.<br>Antonio Vivaldistraat 150<br>1083 HP Amsterdam<br>Noord-Holland<br>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 | Alnylam UK Limited to Alnylam Netherlands B.V. – EC decision of 21 February 2019 |
| Sponsor's change of address | EC letter of 6 November 2020 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Martina Weise / Bruno Sepodes |
| Applicant | Alnylam Netherlands B.V. |
| Application submission | 10 September 2021 |
| Procedure start | 30 September 2021 |
| Procedure number | EMA/H/C/005852 |
| Invented name | Amvuttra |
| Proposed therapeutic indication | Treatment of hereditary transthyretin-mediated amyloidosis<br><br>Further information on Amvuttra can be found in the European public assessment report (EPAR) on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/amvuttra |
| CHMP opinion | 21 July 2022 |

| COMP review of orphan medicinal product designation procedural history | |
|---|---|
| COMP rapporteur(s) | Armando Magrelli / Elisabeth Johanne Rook |
| Sponsor's report submission | 18 March 2022 |
| COMP discussion and adoption of list of questions | 14-16 June 2022 |
| Oral explanation cancelled | 12 July 2022 |
| COMP opinion (adoption via written procedure) | 25 July 2022 |

# 2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2018 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.

The COMP recommends the designation of this 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 as an orphan medicinal product for the orphan indication: treatment of transthyretin-mediated amyloidosis.

# 3. Review of criteria for orphan designation at the time of marketing authorisation

**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**

Amyloidosis is the general term used to refer to the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as constituents of plasma. These depositions disrupt the structure and thus the function of the affected tissues leading to

a wide range of clinical manifestations. Transthyretin-mediated amyloidosis (ATTR amyloidosis) is characterized by the progressive accumulation of insoluble misfolded transthryetin (TTR) protein deposits (amyloid) in the extracellular matrix of tissues causing progressive dysfunction. It is a rare, systemic disease occurring in adults, resulting from either hereditary (genetic mutation) or acquired (ageing) causes. The hereditary form is referred to as hereditary ATTR (hATTR) amyloidosis and the acquired form is referred to as wild-type ATTR (wtATTR) amyloidosis. hATTR amyloidosis is an autosomal dominant disorder caused by over 120 point-mutations in the TTR gene that leads to the extracellular deposition of amyloid fibrils containing both mutant and wild-type (wt) TTR. The site of amyloid deposition and the particular TTR mutation determine the clinical manifestations of the disease, resulting in a spectrum of disease manifestations consisting of polyneuropathy (hATTR amyloidosis with polyneuropathy also known as familial amyloidotic polyneuropathy or FAP) and cardiomyopathy (hATTR amyloidosis with cardiomyopathy also known as familial amyloidotic cardiomyopathy or FAC) phenotypes. While patients with hATTR amyloidosis may present with predominantly polyneuropathy or cardiomyopathy, most patients with hATTR amyloidosis manifest signs and symptoms of both polyneuropathy and cardiomyopathy over the course of their disease. Normal, non-mutant wild type TTR (wt TTR) alone is also amyloidogenic; this is the basis for the acquired, wtATTR amyloidosis, previously known as senile systemic amyloidosis (SSA). In this variant there are no mutations in the TTR gene and clinically it presents typically as cardiomyopathy in a slowly progressive pattern in the elderly.

Transthyretin-mediated amyloidosis diagnosis can be challenging and is based on the establishment of signs and symptoms of polyneuropathy and/or cardiomyopathy consistent with the known clinical manifestations of the disease, in conjunction with biopsy results, confirmation of a mutant TTR genotype and absence of other known causes of peripheral neuropathy or cardiomyopathy

The intended therapeutic indication "Amvuttra is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy." falls within the scope of the designated orphan condition "Treatment of transthyretin-mediated amyloidosis".

## Intention to diagnose, prevent or treat

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

## Chronically debilitating and/or life-threatening nature

ATTR amyloidosis is a progressive, serious and life-threatening, multisytemic disease that leads to motor, sensory and autonomic neuropathy as well as cardiomyopathy. Following the onset of symptoms, quality of life is severely impacted and the disease proceeds inexorably to death, with life expectancy for hATTR amyloidosis limited to 4.7 years following diagnosis. Median survival after diagnosis of hATTR amyloidosis with cardiomyopathy is approximately 2.5 years for patients affected by the V122I mutation and 3.5 years for those affected by T60A. Median survival after diagnosis of wtATTR amyloidosis has been reported to be approximately 3.5 to 4 years.

It can therefore be acknowledged that ATTR amyloidosis is a chronically debilitating and life-threatening condition.

The COMP concluded that the condition remains chronically debilitating and life-threatening due to the development of polyneuropathy and cardiomyopathy.

## Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be less than 0.2 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 1.84 per 10,000.

The relatively large difference in prevalence estimate is mainly driven by the higher figure proposed for the wtATTR population. This figure was 0.032 at the time of designation but is now proposed to be 1.7 in 10,000.

For the calculation of the prevalence the sponsor has added the calculated prevalence values of hATTR amyloidosis with polyneuropathy, hATTR amyloidosis with cardiomyopathy and wild type ATTR (wtATTR) amyloidosis.

The Sponsor presented a summary of estimated hATTR amyloidosis with polyneuropathy prevalence in the community for 2021/experts' opinion. As neither incidence nor prevalence of hATTR amyloidosis with polyneuropathy have been reported for some countries of the European Community, the sponsor chose the prevalence in France to provide a reasonable extrapolation in agreement with the extrapolation method used by Schmidt et al., 2018, in an analysis of the global epidemiology of hATTR with polyneuropathy.

The results from the sponsor's estimation of prevalence estimated for hATTR amyloidosis with cardiomyopathy is displayed in Table 2. For the "other countries'' for which no data was available on public domain, the same approach that was explained above was followed.

**Table 1** Summary of Estimated hATTR amyloidosis with polyneuropathy prevalence in the community for 2021/experts opinion

| Countries | Prevalence[a] | Population of 2021[b] | Number of cases in 2021 |
|---|---|---|---|
| **Austria** | 0.021/10,000 | 8,932,664 | 19 |
| **Bulgaria** | 0.057/10,000 | 6,916,548 | 39 |
| **Cyprus** | 0.583/10,000 | 896,005 | 52 |
| **France** | 0.076/10,000 | 67,439,599 | 513 |
| **Germany** | 0.015/10,000 | 83,155,031 | 125 |
| **Greece** | 0.041/10,000 | 10,682,547 | 44 |
| **Hungary** | 0.016/10,000 | 9,730,772 | 16 |
| **Ireland** | 0.006/10,000 | 5,006,907 | 3 |
| **Italy** | 0.082/10,000 | 59,257,566 | 486 |
| **Netherlands** | 0.027/10,000 | 17,475,415 | 47 |
| **Portugal** | 1.803/10,000 | 10,298,252 | 1,857 |
| **Spain** | 0.006/10,000 | 47,394,223 | 28 |
| **Sweden** | 0.491/10,000 | 10,379,295 | 510 |
| **All other countries** | 0.076/10,000[c] | 115,241,988 | 876 |
| **Total Community** | **0.102/10,000** | 452,806,812 | 4,614[d] |

[a] Represents point prevalence calculated from published studies or expert opinion
[b] Population as per Eurostat database (24 January 2022)
[c] Estimate for other countries (with no published reports/expert opinions) uses France point prevalence estimate
[d] Number obtained with exact values

**Table 2** Summary of estimated hATTR amyloidosis with cardiomyopathy prevalence in the community for 2021/experts opinion

| Countries | Prevalence[a] | Population of 2021[b] | Number of cases in 2021 |
|---|---|---|---|
| **Austria** | 0.027/10,000 | 8,932,664 | 24 |
| **Denmark** | 0.011/10,000 | 5,840,045 | 6 |
| **France** | 0.009/10,000 | 67,439,599 | 61 |
| **Hungary** | 0.005/10,000 | 9,730,772 | 5 |
| **Italy** | 0.008/10,000 | 59,257,566 | 47 |
| **All other countries** | 0.009/10,000[c] | 320,269,602 | 271 |
| **Total Community** | **0.009/10,000** | 452,806,812 | 415 |

[a] Represents point prevalence calculated from published studies or expert opinion (detailed in Table 7)
[b] Population as per Eurostat database (24 January 2022)
[c] Estimate for other countries (with no published reports/expert opinions) uses French point prevalence estimate

For the calculation of wtATTR amyloidosis, since no data were available in the literature for the European countries, the sponsor used the Japanese prevalence and made adjustments as summarized in Table 3 to translate the directly observed Japanese prevalence to an estimate of European prevalence.in JapaninJapan

**Table 3** Table estimation of European wtATTR amyloidosis prevalence from directly observed Japanese prevalence estimate

| Step Number | Description | Numerical Output | Assumptions |
|---|---|---|---|
| **1** | Determine total number of wtATTR amyloidosis cases in Japan: Observed prevalence rate in Japan ([Winburn 2019]) ´ total Japanese population size (Statistical Handbook of Japan 2021) | 0.861 wtATTR amyloidosis cases / 10,000 ´ 125,708,000 = 10,823 wtATTR amyloidosis cases | True prevalence of wtATTR in Japan falls on higher end of observed prevalence rate; all prevalent cases of wtATTR amyloidosis in database population are diagnosed |
| **2** | For total number of prevalent cases of HF in Japan, [Okura 2008; Tsutsui 2019] determine percentage of cases attributable to wtATTR amyloidosis: Total number of wtATTR amyloidosis cases in Japan (Step 1) / total number of prevalent cases of HF in Japan [Okura 2008; Tsutsui 2019] | 10,823 wtATTR amyloidosis cases / 1,248,000 HF cases = 0.8672% of HF cases attributable to wtATTR amyloidosis | No prevalent cases of HF in Japanese adults <45 years of age |
| **3** | Determine wtATTR amyloidosis prevalence rate in European Economic Area (EEA): Percentage of prevalent HF cases attributable to wtATTR amyloidosis x HF prevalence rate in EEA [McDonagh 2021] | 0.8672% of HF cases attributable to wtATTR amyloidosis ´ 200 HF cases per 10,000 population = **1.734 cases per 10,000 population** | European prevalence of HF falls on higher end of accepted prevalence range (1% - 2% of adults) [McDonagh 2021] Percentage of prevalent HF cases attributable to ATTRwt in Europe is equal to that in Japan |

Based on the above data the estimated prevalence of transthyretin-mediated amyloidosis is 1.84 per 10,000 persons.

The COMP agreed that a prevalence of 1.8 is quite conservative and accepted the proposal, taking into account the potential sources of uncertainty in the estimation.

**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 sponsor presented the products which are authorized in the European Union for the treatment of hATTR amyloidosis with polyneuropathy (Table 4).

**Table 4** EC approved therapies for hATTR amyloidosis with polyneuropathy

| | **Date of Authorization** | **Therapeutic Indication** |
|---|---|---|
| ONPATTRO (patisiran) | 27 August 2018 | Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy |
| TEGSEDI (inotersen) | 06 July 2018 | Treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR) |
| VYNDAQEL (tafamidis) | 16 November 2011 (under exceptional circumstances) | Treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment |

Therefore, for the significant benefit Onpattro (patisiran) and Tegsedi (inotersen) should be considered as satisfactory methods.

The sponsor considered also Vyndaqel (tafamidis) as satisfactory method.

However, tafamidis is for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment therefore, vutrisiran covers a broader patient population including patients with stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR), which is not covered by tafamidis.

## Significant benefit

Protocol Assistance (EMEA/H/SA/3876/1/2018/PA/III, 26 Sep 2018) was sought regarding the planned Phase 3 study design where demonstration of significant benefit of vutrisiran for the maintenance of orphan designation at the time of MAA filing was discussed with the COMP. Significant benefit of vutrisiran was proposed to be demonstrated over patisiran, inotersen and tafamidis, the three treatments which were expected to have been approved in the EU at the time of the vutrisiran MAA filing:

- for the demonstration of significant benefit over patisiran, it was proposed to show major contribution to patient care due to a more convenient quarterly SC dosing of vutrisiran compared to patisiran. The COMP advised that this should be demonstrated by adequate quality of life or patient centered outcomes that show a meaningful reduction in treatment burden. It was also

stated that potentially a more favourable safety profile could also support the demonstration of significant benefit;

- regarding the other authorised products inotersen and tafamidis, the COMP recommended that significant benefit be demonstrated with direct or methodologically adequate indirect comparisons showing improved efficacy, improved safety or a major contribution to patient care.

In conclusion, the COMP agreed that the proposed clinical development of vutrisiran could be sufficient to demonstrate significant benefit when taking into consideration above recommendations on evidence generation.

However, as it was mentioned above, regarding the comparison to tafamidis, since vutrisiran covers a broader patient population including patients with stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR), which is not covered by tafamidis, there was need for the sponsor to provide data on this comparison.

The efficacy of Amvuttra was studied in a 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. The primary efficacy endpoint was the change from baseline to Month 18 in modified Neuropathy Impairment Score +7 (mNIS+7). The change from baseline to Month 18 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score was assessed as a secondary endpoint. 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 measured from baseline to Month 9 and 18, compared to the external placebo group of the APOLLO study (all $p < 0.0001$).

- *Significant benefit of vutrisiran over inotersen*

The sponsor claims demonstration of significant benefit of vutrisiran over inotersen based on the criterion of improved safety and major contribution to patient care.

The safety profile of inotersen is characterized by the risks of thrombocytopenia, glomerulonephritis and renal function decline, which are listed as warnings in the Summary of Product Characteristics (SmPC) [Akcea Therapeutics; Benson 2017]. Inotersen is associated with reductions in platelet count, which may result in thrombocytopenia (a very common ADR per Tegsedi SmPC). In the Phase 3, NEURO-TTR trial, platelet count reductions to below normal (140 x 109/L) were observed in 54% of patients treated with inotersen and 13% of placebo patients; reductions to below 100x109/L were observed in 23% of patients treated with inotersen and 2% of the patients receiving placebo; confirmed platelet counts of <75x109/L were observed in 10.7% of inotersen-treated patients. Three (3%) patients developed platelet counts <25x109/L; one of these patients experienced a fatal intracranial haemorrhage (Tegsedi SmPC). Therefore, there is a requirement for monitoring of platelet

counts every 2 weeks during treatment with inotersen and for 8 weeks following discontinuation of treatment. Recommendations for dosing adjustments are provided in the posology section of the inotersen SmPC in case of reduction in platelet count. In addition, inotersen is contraindicated in patients with a platelet count less than $100x10^9$/L.

Renal function monitoring recommendations are also provided in the SmPC since glomerulonephritis has occurred in patients treated with inotersen. This includes monitoring of urine protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) every 3 months or more frequently, as clinically indicated, based on history of chronic kidney disease and/or renal amyloidosis. UPCR and eGFR should also be monitored for 8 weeks following discontinuation of treatment. Inotersen is contraindicated in patients with UPCR ≥113 mg/mmol (1 g/g) prior to treatment and eGFR<45 ml/min/1.73m$^2$.

In contrast, the SmPC for vutrisiran does not have these contraindications, thus broadening the patient population addressable by vutrisiran compared to inotersen. Vutrisiran SmPC also does not require monitoring since there were no effects seen on platelet counts or any evidence of renal toxicity in the HELIOS-A study, which included 4 patients with eGFR 30-45 mL/min/1.73m$^2$ at baseline.

The difference in safety and tolerability profile between inotersen and vutrisiran was also reflected in the discontinuation rate from the pivotal studies. In Study NEURO-TTR, inotersen had a higher treatment discontinuation rate (22% of patients) compared to placebo (13%), with the main reasons being adverse events (AEs) or serious adverse events (SAEs) (14.2% vs. 1.7%). In the inotersen group, over one-third of the AEs that led to permanent discontinuation of study treatment were associated with thrombocytopenia (4) or glomerulonephritis (2), which are known to be associated with inotersen treatment [Tegsedi EPAR EMA/411876/2018]. Contrary to this observation, in the 18-month treatment period of HELIOS-A, vutrisiran had a lower treatment discontinuation (4.1%) compared to the external placebo (APOLLO, 37.7%). Of the 5 (4.1%) vutrisiran treatment discontinuations, 1 was due to an unrelated AE, 2 due to death of the patient unrelated to study treatment (COVID-19 pneumonia and iliac artery occlusion), 1 due to physician decision for a patient who did not comply with study visits and was considered lost to follow up, and 1 due to withdrawal of consent to treatment by the patient.

Regarding the major contribution to patient care the sponsor argued that vutrisiran treatment does not require frequent laboratory monitoring as does inotersen, which constitutes a significant reduction in the burden of patient care compared to inotersen. It is estimated that the laboratory monitoring of inotersen contributes to approximately 26 blood draws per patient per year. Additionally, vutrisiran administration every three months is less frequent than the weekly injection of inotersen, which substantially decreases the number of healthcare encounters (from 52 to 4 dosing visits) and the amount of time associated with the weekly visit to a healthcare setting. This is consistent with global trends toward decreased healthcare encounters, the importance of which has recently been highlighted by the COVID-19 pandemic.

Following the COMP's request, the sponsor submitted an indirect treatment comparison (ITC) for efficacy between vutrisiran and inotersen. This ITC was performed using standard, well-accepted methods for estimating the relative efficacy of two treatments that have not been studied in a head-to-head trial, including Bucher and matching-adjusted indirect comparison (MAIC) methods. According to the sponsor the results showed more favorable efficacy outcomes with vutrisiran as compared with inotersen in patients with hATTR amyloidosis with polyneuropathy (see Table 5).

**Table 5.** Mean differences between vutrisiran and inotersen on 15-month changes from baseline on mNIS+$7_{Ionis}$, Norfolk QoL-DN, and BMI in the Bucher and MAIC analyses(primary analyses)

| **Mean Difference[1]** | **Directionality of Change on Measure** | **Bucher Method[2,3]** | | **MAIC Method[2]** | |
|---|---|---|---|---|---|
| | | Estimate (95% CI) | *P* | Estimate (95% CI) | *P* |
| Change from baseline on mNIS+$7_{Ionis}$ score | Lower scores indicate less neurological impairment | -9.2 (-18.8, 0.4) | 0.061 | -4.6 (-13.8, 4.7) | 0.334 |
| Change from baseline on Norfolk QoL-DN score | Lower scores indicate better quality of life | -10.9 (-19.8, -2.0) | 0.016* | -7.9 (-17.1, 1.2) | 0.088 |
| Change from baseline on BMI | Higher values indicate better nutritional status | 0.5 ( -0.2, 1.1) | 0.146 | 0.5 (-0.1, 1.1) | 0.106 |

Abbreviations: BMI = body mass index; CI = confidence interval; MAIC = matching adjusted indirect comparison; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy.
*indicates p-value <0.05.
[1] For mNIS+$7_{Ionis}$ and Norfolk-QoL-DN, mean differences< 0 favor vutrisiran and mean differences > 0 favor inotersen. For BMI, mean differences > 0 favor vutrisiran.
[2] Missing data for change from baseline on mNIS+7Ionis, Norfolk-QoL-DN, and BMI were imputed using jump-to-reference approach.
[3] In the Bucher analysis, the treatment effect for vutrisiran was adjusted using propensity scores estimated from the HELIOS-A study to account for the differences in characteristics between the vutrisiran group and the external placebo group from APOLLO.

In addition, the sponsor claimed that vutrisiran covers a broader patient population (i.e., patients with eGFR <45 mL/min/1.73m$^2$) that can be treated with vutrisiran compared to inotersen. Four patients with baseline eGFR 30-45 mL/min/1.73m$^2$, which would constitute a labeled contraindication to inotersen, were treated on the vutrisiran arm of HELIOS-A. At month 18, 2 of the 4 patients demonstrated substantial improvement from baseline in mNIS+7 (change form baseline of -10.1 and -17.5 points for the two patients respectively). Among these 4 patients, there were no treatment related AEs and no AEs leading to treatment discontinuation. All 4 patients completed the 18-month treatment period and are continuing treatment in the randomized treatment extension.

Finally, the sponsor claimed that patients treated with vutrisiran are observed to have more favorable outcomes in terms of polyneuropathy-related quality of life as measured by Norfolk-QOL-DN. In addition, data from the comparison of vutrisiran with patisiran within HELIOS-A are directionally consistent with the hypothesis that vutrisiran (administered once every 3 months) should yield benefits in terms of general health-related quality of life over treatments with a more frequent administration schedule (such as inotersen which is administered weekly).

The COMP considered that regarding the claim on improved efficacy and based on the ITC results there is a quite large difference in baseline measurements for the mNIS+7 endpoint. This is probably because the treatments vutrisiran and inotersen are actually from different trials and not a randomised comparison. But mNIS+7 mean values of approximately 60 and 75 constitute a fairly large difference, whereas for the NEURO-TTR trial it looks much more balanced for mNIS+7 with approximately 75 and 79. In Table 5, indirect treatment effects of -9.2 (Bucher) and -4.6 (MAIC) for mNIS+7 are reported. This reassures that the treatment effect is not overestimated however, the difference between the two methods is not that small. In addition, no details are provided on the models that have been used. Mixed models and propensity scores are vaguely mentioned, but the sponsor didn't provide any details. Finally, no sensitivity analyses or details on missing data are provided.

In summary, the COMP considered that based on the missing information (e.g. detailed description of the models, missing data, baseline comparisons, etc.) the claim on significant benefit based on the improved efficacy is not acceptable.

Regarding the claim on the broader population, the COMP concluded the clinical data in 4 patients with baseline eGFR 30-45 mL/min/1.73m$^2$, showed that vutrisiran is efficacious in a subset of patients with moderate-severe renal impairment for whom inotersen is contraindicated. Therefore, the significant benefit of vutrisiran versus inotersen is acceptable.

- *Significant benefit of vutrisiran over patisiran*

Based on the results from HELIOS-A, vutrisiran demonstrated non-inferiority compared to within-study patisiran as the 95% CI of the median treatment difference in TTR percent reduction (vutrisiran – patisiran) was 1.17, 9.25, in which its lower limit was above -10%. Since HELIOS-A was not designed to show superiority, the sponsor claimed demonstration of significant benefit of vutrisiran over patisiran based on major contribution to patient care by utilizing a new, infrequent method of administration (subcutaneous [SC] injection every 3 months), which is considered a clinically significant enhancement in delivery of patient care by the sponsor.

The vutrisiran dosing yields better treatment compliance and decreased burden of care while not compromising efficacy or safety as demonstrated by the results from the 18-month treatment period of the HELIOS-A study. More specifically, the reduction in serum TTR levels with vutrisiran (84.7%) was determined to be non-inferior to the within-study patisiran arm (80.6%) based on the prespecified criteria. Accordingly, consistent treatment effects were observed in the vutrisiran and patisiran groups of HELIOS-A at Month 18 time point. Collectively, these results support the clinical interpretation of comparable efficacy of vutrisiran and patisiran.

The key features of vutrisiran and patisiran that are considered relevant to demonstrate major contribution to patient care are provided in Table 6.

**Table 6** Key features of vutrisiran and patisiran considered relevant to demonstrate major contribution to patient care

| | **Patisiran** | **Vutrisiran** |
|---|---|---|
| **Formulation** | LNP | ESC GalNAc conjugate |
| **Method of administration** | Intravenous infusion | Subcutaneous injection |
| **Frequency of administration** | Every 3 weeks | Every 3 months |
| **Requires premedication** | Yes | No |
| **Potential complications from administration** | Infusion related reactions (Important identified risk)<br>Extravasation | Mild, transient ISRs |
| **Number of healthcare visits per year associated with drug administration** | 16 – 18 visits | 4 visits |
| **Time associated with administration** | 80-minutes for IV infusion<br>60 min for administration of premedication and subsequent wait time before dose administration<br>Travel time every 3 weeks to and from specialized infusion center and infusion chair time for patients as well as active HCP time for administering an IV infusion | SC administration usually takes a few seconds<br>No premedication needed<br>Travel every 3 months to and from one of a variety of outpatient settings |
| **Administration setting** | Specialized infusion centers<br>Limited availability of homecare for patients on patisiran in EU | Variety of hospital and outpatient settings |

| | Patisiran | Vutrisiran |
|---|---|---|
| **Number of patients who missed a dose of study drug in HELIOS-A (M9 period)** | 22 (52.4%) patients | 1 (0.8%) patient |

Patisiran is administered by IV infusion every 3 weeks. Each patisiran infusion must be preceded (at least 60 minutes prior to the start of infusion) by a premedication regimen of corticosteroids, antihistamines (H1 and H2 blockers) and paracetamol. The infusion takes approximately 80 minutes, which may even be extended in the event of infusion-related reactions (patisiran SmPC), a recognized complication from intravenous infusions listed as an important identified risk in the patisiran Risk Management Plan. Infusion-related reactions have been reported and continue to be reported in clinical studies of patisiran. While the majority of patients have placement of a peripheral IV catheter for each patisiran infusion and the infusions occur without events, as with any intravenously administered therapy, patients may have complications at the site of the peripheral IV catheter, such as extravasation or phlebitis. In a few instances, reports have been made of indwelling catheters being placed for delivery of regular patisiran infusions. In one case in a clinical trial of patisiran (ALN-TTR02-006), a patient had a serious adverse event (SAE) of vascular device infection necessitating removal of the catheter and discontinuation from further dosing with patisiran due to poor peripheral venous access. These data illustrate some of the clinically significant challenges in administering an IV product for a life-long therapy for a serious medical condition.

In contrast, vutrisiran is administered by SC injection once every three months and as with any SC injection, the administration is quick and typically takes only a few seconds. No premedications, such as the ones required prior to patisiran infusion (including corticosteroids), are required. Mild, transient injection site reactions have been reported with vutrisiran in 5 patients (4.1%), corresponding to 0.6% of the 836 total doses administered during the 18 Month Treatment Period of the HELIOS-A study. Vutrisiran SC administration obviates the risk of complications from intravenous infusions (e.g., IRRs, extravasation) and the potential need for indwelling catheters and the associated risks.

In addition to the advantages of the SC dosing of vutrisiran compared with IV infusion, the infrequent dosing of vutrisiran every 3 months substantially decreases the number of healthcare encounters (from 18 to 4 dosing visits per year). Given that the travel time associated with a visit every three weeks to a specialized infusion center for patisiran administration as well as time required for administering the premedications can be significant, a substantial number of person-hours per year are estimated to be lost on IV infusion care, including travel time and time required for premedication. While home infusion of patisiran by a healthcare professional (HCP) is allowed per the SmPC, in practice it is not permitted or not available in many EU countries. As of the date of this report, the sponsor estimated that only 30% of the patients currently receiving commercial patisiran in the EU have access to home care and these patients reside in only 9 of the 27 Member States. In contrast, vutrisiran can be administered in a variety of hospital and outpatient settings, which enables patients to travel to the closest and most convenient clinic to get their SC injection.

Importantly, vutrisiran, with its infrequent SC administration, is expected to yield improved treatment compliance and resiliency to disruptions in dosing. This has been demonstrated by the results from the HELIOS-A study, where only 1 (0.8%) vutrisiran-treated patient missed a dose of study drug, despite the considerable disruption caused by the ongoing COVID-19 global pandemic. In comparison, 22 (52.4%) patisiran-treated patients missed 1 or more doses.

As a real-world example of the overall burden of care posed by patisiran treatment outlined above, the sponsor argued that at least 2 patients in the EU discontinued treatment with patisiran. One of them,

after approximately 3 years of continuous therapy, despite benefiting from patisiran and showing disease stabilisation, started to experience difficulties with the IV infusion especially related to lack of venous access due to prolonged infusions with patisiran, which led to the implantation of an intravenous chamber device. Soon after, due to concerns about the risk of chamber-related infections and about continued IV treatment requiring premedications and associated fatigue, the patient refused to receive further doses of patisiran. The sponsor is also aware that at least 5 additional patients have expressed substantial concerns with regard to treatment fatigue related to patisiran infusions, drowsiness due to the premedication, and that the frequency of administration interferes with their professional and personal lives. While some of these patients receive home infusions, others have to travel long distances to their local hospital to receive patisiran infusion.

When considering all of the aspects associated with receiving an IV dose every 3 weeks, such as travel time and additional care for both the patient and their caregivers, and including the need for premeditations and a peripheral IV catheter placement, the difference in the delivery of care to patients is substantial and strongly favors vutrisiran.

The COMP considered the above arguments, however, no patient reported outcomes or patient preference data have been provided to support the claim for major contribution to patient care. The sponsor was requested to provide a data driven analysis preferably based on patient reported outcome including quality of life data in order to support the significant benefit of vutrisiran over patisiran.

Based on the above request, the sponsor provided an analysis of data from a 'Patient Experience Survey' administered to patients with hATTR amyloidosis at baseline, at Month 9 and Month 18 of the HELIOS-A treatment period. This analysis comprises 2 questions, to assess the impact of (1) frequency of dosing and (2) the duration of each individual dose administration on patients' perceived experience receiving treatment with vutrisiran or patisiran. The results showed that larger percentages of patients rated the dosing schedule as being "quite convenient" or "extremely convenient" in the vutrisiran arm (71.4% - 86.1%, depending on the assessment time point) than in the patisiran arm (41.7% - 53.8%). In addition, larger percentages of patients rated the duration of dosing as being "quite a bit convenient" or "extremely convenient" in the vutrisiran arm (68.7% - 83.2%, depending on the assessment time point) than in the patisiran arm (35.9% - 50.0%). Further in line with these findings suggesting strong favorability for vutrisiran, patients in the vutrisiran arm reported markedly unfavorable ratings of treatment convenience less commonly than did patients in the patisiran arm. No more than 3.0% of patients at any time point in the vutrisiran arm, but up to 12.5% of those in the patisiran arm, rated the dosing schedule as being "not at all convenient". Similarly, no more than 3.0% of patients at any time point in the vutrisiran arm, but up to 8.3% of those in the patisiran arm, rated the treatment administration time as being "not at all convenient".

The sponsor also provided analysis of data from a 'Patient Preference Survey' administered to patients with hATTR amyloidosis who received patisiran during the treatment period of HELIOS-A, then switched to treatment with vutrisiran during the randomized treatment extension (RET) period. This analysis comprises 3 questions, as outlined further below, to determine (1) the patients' overall preference for vutrisiran or patisiran, (2) how strongly they feel about that preference, and (3) the reason for their preference. The survey included 37 patients who were initially assigned to patisiran during the treatment period of pivotal trial, and then switched to vutrisiran in the extension phase of the study. Data from Month 9 on the RTE period were available for 17 of these patients. Fifteen out of 17 patients (88%) indicated that they prefer the method of administration with vutrisiran to that of patisiran, while 2 (12%) preferred patisiran. The time needed to receive one administration, and the frequency of administration were the two most frequent reasons given as the reason for this

preference. In addition, one third of patients cited less emotional anxiety or distress with the SC injections.

Real word evidence data were submitted of patients who experienced substantial difficulties with the IV infusion due to lack of venous access and complications like lymphangitis, and were successfully converted to vutrisiran in a compassionate use program.

Considering the above data, the COMP concluded that a major contribution to patient care of vutrisiran compared to patisiran has been demonstrated. This together with the clinical data which showed that vutrisiran is of comparable efficacy with patisiran are sufficient to demonstrate significant benefit of vutrisiran versus patisiran.

# 4. COMP position adopted on 25 July 2022

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.