28 August 2018
EMA/564536/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Onpattro (Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA)

Treatment of transthyretin-mediated amyloidosis

EU/3/11/857 (EMA/OD/142/10)

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	
Active substance	Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA
International Non-Proprietary Name	Patisiran
Orphan indication	Treatment of transthyretin-mediated amyloidosis
Pharmaceutical form	Concentrate for solution for infusion
Route of administration	Intravenous infusion
Pharmaco-therapeutic group (ATC Code)	N07XX12 (proposed)
Sponsor's details:	Alnylam Netherlands B.V. Strawinskylaan 3051 1077ZX Amsterdam The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting S.A.R.L.
COMP opinion date	12 January 2011
EC decision date	15 April 2011
EC registration number	EU/3/11/857
Post-designation procedural history	
Change of designated condition COMP opinion date	19 January 2017
Change of designated condition EC decision date	6 April 2017
Transfer of sponsorship	Transfer from Voisin Consulting S.A.R.L. to Alnylam UK Limited – EC decision of 11 November 2014 Transfer from Alnylam UK Limited to Alnylam Netherlands B.V. – EC decision 28 May 2018
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Kristina Dunder, Alexandre Moreau
Applicant	Alnylam Netherlands B.V.
Application submission date	18 December 2017
Procedure start date	25 January 2018
Procedure number	EMA/H/C/004699/0000
Invented name	Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA
Therapeutic indication	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy Further information on Onpattro can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports
CHMP opinion date	26 July 2018
COMP review of orphan medicinal product designation procedural history	

COMP Co-ordinators	M. Možina - D. Matusevicius
Sponsor's report submission date	19 December 2017 and 9 February 2018
COMP discussion and adoption of list of questions	19- 21 June 2018
COMP opinion date	30 July 2018

2. Grounds for the COMP opinion at the designation stage

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

- familial amyloid polyneuropathy (hereinafter referred to as "the condition") was estimated to be affecting approximately less than 0.1 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating due to the progressive neuropathy inducing muscular weakness and in later stages impaired mobility, gastrointestinal problems, orthostatic hypotension, and bladder dysfunction.
  The condition is fatal, with a life expectancy of 9-13 years from symptom onset. The main life threatening events are related mainly to the deposition of amyloid in the cardiac tissue, inducing myocardial infarction and fatal arrhythmias;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

2.2. Amendment of an existing orphan medicinal product designation

The COMP opinion that was the basis for the amendment of the orphan medicinal product designation in 2017 was based on the following grounds:

- the intention to treat the amended condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA was considered justified based on preliminary clinical data showing sustained reduction of transthyretin serum levels over 24 months of treatment and stabilization of parameters of neurologic and cardiac damage;
- the condition is life-threatening and chronically debilitating due to the development of neuropathy and cardiomyopathy. Life expectancy is 3 to 15 years from symptom onset, depending on the transthyretin mutation;
- 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;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing an effect of the proposed product on the cardiac manifestations of the condition, which are not targeted by the currently authorized treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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

Transthyretin-mediated amyloidosis *(*hATTR amyloidosis*)* is a rare, systemic disease occurring in adults, resulting from either hereditary (genetic mutation) or acquired (ageing) causes.

The hereditary forms are commonly sub-classified into two syndromes: hATTR amyloidosis with polyneuropathy, also known as familial amyloidotic polyneuropathy (FAP), and hATTR amyloidosis with cardiomyopathy, also known as familial amyloidotic cardiomyopathy (FAC). They are caused by autosomal dominant mutations in the gene coding for transthyretin (TTR, also known as prealbumin), a 127 amino acid protein produced predominantly by hepatocytes, with a minimum fraction produced by the choroid plexus and retina. Mutations in the TTR protein lead to destabilization of the tetrameric form and to dissociation into dimers and monomers; misfolding of mutated monomers from the α-helical to the β-pleated sheet structure results in tissue deposition of oligomers and amyloid fibrils.

The site of amyloid deposition and the particular TTR mutation determine the clinical manifestations of the disease, which include sensory and motor neuropathy, autonomic neuropathy, and/or cardiomyopathy. There are over 100 reported TTR genetic mutations, resulting in a continuum of hATTR amyloidosis with polyneuropathy or hATTR amyloidosis with cardiomyopathy phenotypes.

The granted therapeutic indication “Onpattro is indicated for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy*”* falls within the scope of the designated orphan indication “treatment of transthyretin-mediated amyloidosis”.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified (reference is made to the European public assessment report of Onpattro).

Chronically debilitating and/or life-threatening nature

There have been no significant changes in the serious and chronically debilitating nature of the condition since the time of initial orphan designation.

hATTR amyloidosis is a progressive and fatal multi-symptom disease that may present with peripheral (sensory and motor) neuropathy, autonomic neuropathy and/or cardiomyopathy. The age of symptoms onset ranges between the second and ninth decades of life, with great variability across different populations. hATTR amyloidosis with polyneuropathy characteristically begins with sensory neuropathy involving legs and arms and then progresses to disabling motor neuropathy characterized by leg weakness and inability to walk, and autonomic neuropathy causing severe gastrointestinal pathology, orthostatic hypotension, and bladder dysfunction with recurring urinary tract infections. Cardiac involvement is common in late stage hATTR amyloidosis with polyneuropathy patients due to amyloid infiltration of the sinus node and atrioventricular conduction system, and infiltration of the

myocardium. Involvement of the conduction system can lead to sudden death due to heart block or tachyarrhythmias, and myocardial infiltration can lead to diastolic dysfunction and heart failure.

Life expectancy is usually to 3 to 15 years from symptom onset, depending on the TTR mutation and clinical picture. Patients with cardiac involvement usually have a shorter life expectancy, while the prognosis is more variable in patients with polyneuropathy.

Number of people affected or at risk

The sponsor provided a comprehensive update of the prevalence of the condition, taking into account different definitions of the condition of the past (with separation of the forms characterised by polyneuropathy from those with cardiomyopathy). There have been no significant changes in the prevalence of the condition between the time of the amendment of the designation (2017) and today.

The sponsor conducted a literature search to retrieve published articles providing epidemiologic data on the prevalence of hATTR amyloidosis; hATTR amyloidosis with polyneuropathy, hATTR amyloidosis with cardiomyopathy, and wtATTR amyloidosis in the European Union, and consulted additional sources, including patients' organizations, research consortia, and registries. From a critical appraisal of the literature and the other sources, the sponsor derived the current prevalence estimates for each of the ATTR forms reported above (hATTR amyloidosis; hATTR amyloidosis with polyneuropathy, hATTR amyloidosis with cardiomyopathy, and wtATTR amyloidosis) and concluded with a proposed overall prevalence of ATTR amyloidosis of 0.14 per 10,000 persons in the EU. The COMP considered this estimate to be acceptable.

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

At the time of this review on orphan designation maintenance, Vyndaqel (tafamidis) is the only pharmacotherapeutic treatment available. Tafamidis is indicated for "treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment"; its use is therefore limited to early stage patients with mild disease.

Since many of the systemic manifestations of the disease are caused by liver-derived circulating TTR, two treatment approaches aimed at reducing the amount of circulating amyloidogenic protein are currently used to treat patients with hATTR amyloidosis: (1) orthotopic liver transplantation (OLT), which essentially eliminates mutant TTR from the circulation but does not affect the hepatic production of WT TTR by the transplanted liver, and (2) TTR tetramer stabilizers (e.g. tafamidis), which act by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers.

Significant benefit

The efficacy of Onpattro was mainly studied in the APOLLO (ALN-TTR02-004) trial, which was a phase 3 multicentre, multinational, randomised, double-blind, placebo-controlled study in 225 patients with hATTR amyloidosis with a TTR mutation and symptomatic polyneuropathy. The primary efficacy variable was the modified Neuropathy Impairment Score +7 (mNIS+7) at 18 months. It is a composite neurologic impairment score that was developed specifically for monitoring progression of neurologic

impairment in hATTR amyloidosis patients. It measures motor, sensory, and autonomic polyneuropathy including assessments of motor strength and reflexes, quantitative sensory testing, nerve conduction studies, and postural blood pressure, with the score ranging from 0 to 304 points, where a higher score indicates more pronounced impairment. The change from baseline in mNIS+7 compared to placebo across all subgroups (age [<65; ≥65], gender, race [white, non-white], region [North America, Western Europe, Rest of World], NIS [< 50; ≥ 50], genotype [V30M; non-V30M], genotype class [Early onset V30M; Other], previous tetramer use, FAP stage [I& II] and cardiac subpopulation) shows a consistent difference in favour of Onpattro (table 1, full study outcomes in Onpattro EPAR).

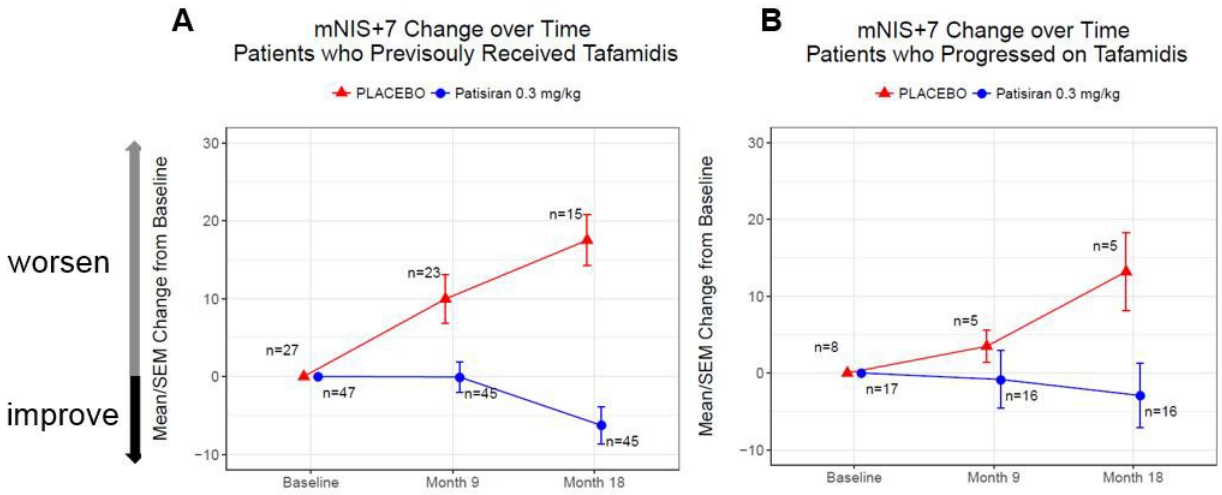
Table 1. Primary efficacy endpoint mNIS+7 at 18 months

Statistic[a,b]	**Placebo** N = 77	**Patisiran-LNP** N = 148
Baseline Scores, Mean (SD)	74.61 (37.04)	80.93 (41.51)
Month 18 Scores, Mean (SD)	101.09 (45.35)	75.13 (43.18)
Change from Baseline, LS Mean (SEM) 95% CI	27.96 (2.602) 22.83, 33.09	-6.03 (1.739) -9.46, -2.60
LS Mean (SEM) Difference Treatment Difference (Patisiran-LNP – Placebo) **95% CI, p-value**	-	**-33.99 (2.974)** **-39.86, -28.13, P=9.262E-24**

Abbreviations: CI=confidence interval; LS=least squares; max=maximum; min=minimum; MMRM=mixed-effect model repeated measures; mNIS + 7=Modified Neurologic Impairment Score + 7; SD=standard deviation; SEM=standard error of the mean.
Note: In the MMRM model, the outcome variable is change from baseline in mNIS + 7. The model includes baseline mNIS + 7 score as covariate and fixed-effect terms including treatment group, visit, treatment-by-visit interaction, genotype, age at hATTR symptom onset, previous tetramer stabilizer use, and region.
[a] Baseline and Month 18 are the averages of 2 assessments performed at least 24 hours but no more than 7 days apart.
[b] LS means, SEM, differences in LS means, 95% CIs, and Month 18 p-value from MMRM model

Significant benefit versus tafamidis is claimed based on the pivotal APOLLO clinical trial of Onpattro in familial amyloid neuropathy (FAP) showing favourable responses in patients that had previously discontinued tafamidis due to disease progression. APOLLO enrolled patients (n=74; 32.9%) that had previously received tafamidis for a mean duration of 13.5 months prior to study start. Of these patients, 25 discontinued tafamidis due to disease progression. These patients were of specific interest regarding the demonstration of significant benefit, because Onpattro led to a relevant improvement of the mNIS+7, the primary endpoint of the study, at 9 and 18 months of treatment (end of the study; figure 1B). The COMP considered that the claim of a significant benefit based on a clinically relevant advantage in patients who did not respond to previous treatment with tafamidis was sufficiently demonstrated.

Figure 1. APOLLO study: benefit of Onpattro to patients who previously received tafamidis



Panel A shows change in mNIS+7 for all patients who discontinued tafamidis treatment for any reason prior to entry into patisiran-LNP Study 004. Panel B shows the change in mNIS+7 for all patients who discontinued tafamidis due to disease progression prior to entry into patisiran-LNP.

Also indirect comparisons were provided between the pivotal trials of Onpattro and tafamidis. The results showed a bigger effect size of Onpattro vs. tafamidis on endpoints related to peripheral neuropathy, even though the overall patient population enrolled in the Onpattro trial was substantially more severe than the one in the tafamidis trial, as shown by baseline NIS-LL (Neurologic Impairment Score-Lower Limb; mean 36.8 at baseline in the Onpattro arm versus 8.4 in the tafamidis arm in the respective trials). When the comparison was limited to only stage I FAP, Onpattro showed a higher effect than tafamidis in reducing NIS-LL (– 8.2 points in patients treated with Onpattro *versus* -2.7 in patients treated with tafamidis). Similar results were shown for the other endpoints related to peripheral neuropathy. The COMP was of the opinion that the data discussed above, related to endpoints of peripheral neuropathy, demonstrated a significant benefit based on better efficacy of Onpattro versus tafamidis.

The sponsor also claimed a benefit on the basis that the therapeutic indication of Onpattro includes stage II FAP, for which no medicinal product was so far authorised. Subgroup analyses of the primary and secondary efficacy endpoints show a consistent benefit of patisiran-LNP versus placebo across patients with stage 1 and stage 2 (table 2). The enlargement of the condition to include stage II was considered relevant but it was not highlighted as one of the main grounds for significant benefit.

In conclusion, the COMP was of the opinion that sufficient evidence has been provided to conclude that Onpattro is of significant benefit over authorised tafamidis in the granted therapeutic indication.

Table 2. Change in mNIS+7 and Norfolk QOL-DN at 18 Months for Onpattro versus placebo

Endpoint/Group	Treatment	Baseline score (mean)	LS Mean (SEM) CFB at 18 months	LS mean (SEM) difference
mNIS+7				
Overall	Patisiran-LNP	80.93	- 6.03 (1.74)	-33.99 (2.97)
	Placebo	74.61	+ 27.96 (2.60)	95% CI: -39.86, -28.13
FAP Stage I	Patisiran-LNP	52.02	- 5.17 (2.17)	-29.65 (3.90)
	Placebo	45.47	+ 24.48 (3.22)	95% CI: -37.40, -21.91
FAP Stage II/III	Patisiran-LNP	104.85	- 4.18 (2.39)	-38.24 (4.42)
	Placebo	101.58	+ 34.06 (3.71)	95% CI: −47.00, −29.49
Norfolk QOL-DN				
Overall	Patisiran-LNP	59.6	- 6.7 (1.77)	-21.1 (3.10)
	Placebo	55.5	+ 14.4 (2.73)	95% CI: -27.2, -15.0
FAP Stage I	Patisiran-LNP	45.5	- 3.2 (2.31)	-18.3 (4.18)
	Placebo	43.7	+ 15.1 (3.47)	95% CI: -26.6, -10.0
FAP Stage II/III	Patisiran-LNP	71.3	- 3.3 (2.49)	-24.2 (4.78)
	Placebo	66.8	+ 20.9 (4.07)	95% CI: -33.6, -14.7

Note: Only one patient had FAP stage III in this study. This patient 020-0001 (placebo) had Month 9 mNIS+7 assessment then discontinued treatment and did not have Month 18 assessment. This patient was included in the MMRM analysis.

4. COMP position adopted on 30 July 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication 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 approximately 0.14 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 neuropathy and cardiomyopathy. Life expectancy is 3 to 15 years from symptom onset, depending on the transthyretin mutation;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Onpattro may be of potential significant benefit to those affected by the orphan condition is confirmed. Indirect comparison with tafamidis, currently authorized for stage I familial amyloid neuropathy, showed better efficacy of patisiran in the primary and in all secondary endpoints measuring different aspects of neuropathy. In addition the sponsor presented data showing clinical efficacy with patisiran in patients who had discontinued treatment with tafamidis due to disease progression. The committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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 Onpattro, synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA, patisiran, EU/3/11/857 for treatment of transthyretin-mediated amyloidosis is not removed from the Community Register of Orphan Medicinal Products.