Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Onpattro

Active ingredient/s: Patisiran

Sponsor: Alnylam Australia

August 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

List of abbreviations

Abbreviation	Meaning
10-MWT	10 metres walk test
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
ATTR	transthyretin-mediated amyloidosis
CMI	Consumer Medicines Information
CNS	Central nervous system
COMPASS 31	Composite Autonomic Symptom Score 31
COR	Comparable Overseas Regulator
DLP	Data lock point
hATTR	hereditary transthyretin-mediated amyloidosis
hATTR	Hereditary transthyretin-mediated amyloidosis
HCP	Healthcare provider
ICH	International Conference on Harmonization
mBMI	Modified body mass index
mNIS	Modified neuropathy impairment score
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
RMP	Risk management plan
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
TGA	Therapeutic Goods Administration
TTR	Transthyretin

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Onpattro
Active ingredient:	Patisiran
Decision:	Approved
Date of decision:	18 November 2022
Date of entry onto ARTG:	21 November 2022
ARTG number:	380813
, *Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Alnylam Australia Pty Ltd Level 1 60 Martin Place Sydney NSW 2000
Dose form:	Concentrated injection for infusion 10
Strength:	mg/5 mL
Container:	Vial
Pack size:	One
Approved therapeutic use for the current submission:	Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.
Route of administration:	Intravenous infusion
Dosage:	The recommended dose of Onpattro is 300 micrograms per kg body weight administered via intravenous infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg. Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised for patients treated with Onpattro (see section 4.4 Special Warnings and Precautions for Use of the Product Information). For further information refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Alnylam Australia Pty Ltd (the sponsor) to register Onpattro (patisiran) 10 mg/5 mL, concentrated injection for infusion, vial for the following proposed indication:[1]

> *Onpattro is indicated for the treatment of hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy*

Condition

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare, life threatening, autosomal dominant multi-systemic disease caused by mutations in the transthyretin (TTR) gene that results in rapidly progressive, debilitating morbidity and high mortality. The cardinal manifestations of hATTR amyloidosis are polyneuropathy and cardiomyopathy.

Transthyretin, also known as prealbumin, is a tetrameric protein produced by hepatocytes, the choroid plexus and retina. There are more than 120 reported TTR genetic mutations associated with hATTR amyloidosis, and almost all patients are heterozygous for the mutated *TTR* allele. Mutations in the *TTR* gene lead to destabilisation of the tetrameric protein and disassociation of the TTR subunits into dimers and individual mutant and wild type monomers, which subsequently misfold. These misfolded TTR monomers can then self-assemble into oligomers and form amyloid fibrils and plaques in the extracellular space of various tissues including the peripheral nervous system, heart, gastrointestinal tract, kidney, central nervous system (CNS) and eye leading to cellular injury and organ dysfunction with corresponding clinical manifestations.

Current treatment options

The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, gastroenterology, and cardiology specialties. Limited treatment options, namely orthotopic liver transplant and TTR tetramer stabilisers, exist for a small subset of patients.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from European Medicines Agency. The full dossier was submitted to the TGA.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

At the time the TGA considered this submission, a similar submission had been approved in European Union (EU) on 27 August 2018, United States of America (USA) on 10 August 2018, Canada on 7 June 2019, Japan on 18 June 2019, Switzerland on 23 September 2019 and United Kingdom on 26 April 2021.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status of selected countries

Region	Submission date	Status	Approved indications
European Union (Centralised)	15 December 2017	Approved on 27 August 2018	Treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
United States of America	11 December 2017	Approved on 10 August 2018	Treatment of the polyneuropathy of hATTR amyloidosis in adults
Canada	14 November 2018	Approved on 7 June 2019	Treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
Japan	27 September 2018	Approved on 18 June 2019	Treatment of TTR type familial amyloidosis with polyneuropathy
Switzerland	3 December 2018	Approved on 23 September 2019	Treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
United Kingdom;[2]	30 March 2021	Approved on 26 April 2021	Treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

[2] Patisiran-LNP was first approved in the UK on 27 August 2018 via the EU CAP. The EU centrally-authorised Marketing Authorisation was automatically converted to a UK Marketing Authorisation, effective in Great Britain only, and issued with a UK Marketing Authorisation number on 01 January 2021. From 01 January 2021, the existing centrally-authorised Marketing Authorisation issued by the European Medicines Agency will continue in place in Northern Ireland where it remains subject to EU Regulations.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-05675-1-1

Description	Date
Designation (Orphan)	12 October 2021
Submission dossier accepted and first round evaluation commenced	31 January 2022
First round evaluation completed	17 May 2022
Sponsor provides responses on questions raised in first round evaluation	14 July 2022
Second round evaluation completed	21 September 2022
Delegate's Overall benefit-risk assessment	15 November 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	18 November 2022
Administrative activities and registration on the ARTG completed	21 November 2022
Number of working days from submission dossier acceptance to registration decision*	157

* The COR-B process has a 175 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Onpattro is a concentrated injection for infusion containing patisiran sodium (10 mg/5 mL as patisiran) formulated as 'lipid nanoparticles' in phosphate buffered saline. The product is white to off-white, opalescent, homogeneous liquid supplied in a glass vial. Onpattro is supplied in cartons of one vial.

Onpattro is administered by intravenous infusion after dilution in 0.9% saline (to 200 mL); the recommended dose is 300 µg/kg every 3 weeks. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg (that is 3 vials).

The evaluator reviewed the assessment reports prepared by the COR for the same submission and provided to the TGA by the applicant. The evaluator also assessed any Australian-specific data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product and checked for compliance, as applicable, with Australian

legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Nonclinical

The scope and quality of the submitted nonclinical dossier was mostly acceptable, with studies consistent with the principles of ICH guidance for the nonclinical testing of pharmaceuticals.[3] All pivotal safety related studies were conducted according to Good Laboratory Practice.

The animal studies support the proposed clinical dose and dosing regimen. However, effects on TTR mRNA levels in the choroid plexus or retinal pigment epithelium were not assessed. Furthermore, no studies were submitted to determine if Onpattro could suppress disease progression or ameliorate disease symptoms. Therefore, no comment in regard to efficacy can be given based on nonclinical data.

In vivo, Onpattro decreased circulating retinol binding protein, vitamin A and thyroxine, but not triiodothyronine levels in monkeys. This was not associated with signs of vitamin A deficiency or effects on the thyroid.

A specialised safety pharmacology study conducted in cynomolgus monkeys that covered the central nervous system, cardiovascular and respiratory systems did not reveal any treatment-related changes to central nervous system or respiratory function at moderate exposures. Effects on electrocardiography parameters and central nervous system and respiratory function are not expected in patients.

The pharmacokinetic profiles of Onpattro, and the two novel lipids DLin-MC3-DMA and PEG_{2000}-C-DMG in rats and monkeys were qualitatively similar to humans following Onpattro intravenous administration.

Repeat dose toxicity studies using the clinical route (intravenous) were conducted in mice (6 weeks dose range finding study), rats (up to 26 weeks) and cynomolgus monkeys (up to 39 weeks). Dose limiting hepatotoxicity was observed in all species. Aside from the injection site reactions and degenerative hepatic effects, the other findings in toxicity studies were considered of low or no clinical concern.

A carcinogenicity study conducted in transgenic mice (26 weeks in TgRasH2) did not identify treatment related tumour or pre-neoplastic findings, but exposures were low and only a single species for which the drug is not pharmacologically-active was used. The negative results are considered inconclusive.

Studies on fertility, embryofetal development and pre/postnatal development were conducted with Onpattro in rats and/or rabbits. A pregnancy category D;[4] is warranted given the potential adverse embryofetal development effects associated with an imbalance in vitamin A levels.

Dedicated local tolerance studies were not conducted but repeat dose toxicity studies showed injection site reactions (minimal to severe vascular/perivascular inflammation) to Onpattro in mice, rats and monkeys.

Onpattro was not immunotoxic in repeat dose toxicity studies. There was no evidence of immunosuppression by patisiran or Onpattro *in vitro* or *in vivo*.

[3] International scientific guideline: ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. EMA/CPMP/ICH/286/1995.

[4] Pregnancy category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

In summary, the primary pharmacology data lend some support for the proposed indication. The collective toxicity findings with Onpattro of potential clinical relevance include:

- Hepatotoxicity (accompanied by increased liver enzymes), which should be easily monitored;
- Injection site reactions, which could easily be monitored;
- Teratogenicity, which can be mitigated by sufficient warnings and labelling.

The proposed pregnancy category for Onpattro (Category D) is acceptable.

Although some limitations were identified in the nonclinical dossier (low assessed margins, inadequate carcinogenicity assessment), the clinical presentations of hATTR amyloidosis (multiple organs impairment), the disease outcome (fatal), the limited treatment alternatives and the expected treatment benefits, may outweigh any unknown risks. The nonclinical evaluator has recommended approval of Onpattro.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- Two Phase I single ascending dose studies in healthy volunteers (Studies ALN-TTR02-001 and ALN-TTR02-005)
- A Phase II open label, multiple-ascending dose study in patients with hATTR amyloidosis with polyneuropathy (Study ALN-TTR02-002)
- A Phase II open label, single arm, long term follow up extension study in patients with hATTR amyloidosis with polyneuropathy (Study ALN-TTR02-003). This was a long term follow up extension study with a 24 month treatment duration that provided supportive efficacy data to Study ALN-TTR02-004. Patients enrolled in this study had previously participated in Study 002. The dosing gap between Study ALN-TTR02-002 and Study ALN-TTR02-003 was at least six months
- A pivotal Phase III double blind, placebo controlled study in patients with hATTR amyloidosis with polyneuropathy (Study ALN-TTR02-004). The study was an 18 month treatment duration that provided the primary efficacy data for the registration of Onpattro.
- A global open label, single arm, long term follow up extension study (Study ALN-TTR02-006). This is a long term follow up extension study of patients who completed Studies ALN-TTR02-003 and ALN-TTR02-004. An interim analysis with a data cutoff date of 14 July 2017 provides efficacy data on the placebo patients from Study ALN-TTR02-004 who transitioned to Onpattro in Study ALN-TTR02-006, as well as further long term data in support of the persistence of efficacy of Onpattro in patients previously dosed in Studies ALN-TTR02-003 and ALN-TTR02-004with Onpattro.

The core studies providing efficacy and safety data are the pivotal Phase III double blind, placebo controlled Study ALN-TTR02-004 and two open label, single arm studies that evaluated Onpattro at the intended dose and regimen in patients with hATTR amyloidosis (Study ALN-TTR02-003 and Study ALN-TTR02-006).

The clinical development program is considered adequate to assess the clinical efficacy and safety of Onpattro for the proposed indication.

Pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of Onpattro was assessed in five clinical studies with intensive PK sampling (Studies ALN-TTR02-001, -005, -002, and -003) and sparse PK sampling (ALN-TTR02-004). The PK profiles of three Onpattro components, including active drug substance patisiran and the two novel lipids, DLin-MC3-DMA and PEG_{2000}-C-DMG, exhibited multiphasic plasma profiles and were found to be predictable and generally consistent across studies and between healthy subjects and patients with hATTR amyloidosis with polyneuropathy.

The overall conclusions from overseas regulator were:

- The population PK model for Onpattro was considered acceptable
- The exposure to patisiran, DLin-MC3-DMA and PEG_{2000}-C-DMG increased proportional to the dose after single and repeated administration in the dose range 0.01 to 0.3 mg/kg
- After administration of 0.3 mg/kg every 3 weeks in hATTR amyloidosis patients with polyneuropathy, the steady state was observed after Week 24
- Subgroup analyses were performed to evaluate if dose adjustment was needed in Study ALN-TTR02-004. Results indicated that there were no meaningful differences in steady state plasma concentrations of patisiran in any subgroup, age, gender, *V30M* mutation status, mild and moderate renal impairment, and mild hepatic impairment subgroups. PK exposures and transthyretin reduction was similar in patients regardless of age, gender, *V30M* mutation status, mild and moderate renal impairment, or mild hepatic impairment. Therefore, no dose adjustment was deemed necessary in any subgroup
- Onpattro did not induce CYP1A2 or CYP3A4

Pharmacodynamics

ALN-18328,[5] the active ingredient in Onpattro, is a first-in-class silencing RNA that utilises the naturally occurring mechanism of RNA interference to reduce the expression of mutant and wild type TTR mRNA and its corresponding protein. ALN-18328 is formulated as lipid nanoparticle to target delivery to hepatocytes in the liver, the primary source of TTR protein in the circulation.

Two Phase I Onpattro single ascending dose studies in healthy volunteers contributed pharmacodynamic (PD) assessments (for example, TTR levels). In addition, Study ALN-TTR02-002 was a Phase II multiple ascending dose study that contributed PD (for example, TTR levels, safety) in patients with hATTR amyloidosis with polyneuropathy. Dose dependent reductions in serum TTR concentrations were observed in both healthy volunteers, and in patients with hATTR amyloidosis with polyneuropathy (Studies ALN-TTR02-002). Sustained TTR reduction between doses was consistently achieved with 0.3 mg/kg every 3 weeks, where maximum TTR reductions of up to 96% were observed. The 0.3mg/kg was selected as allowing a reduction of 80% of TTR levels, and the frequency of three weekly leads to a more consistent fall over the treatment period without increase of adverse events over the four weekly frequency.

The overseas regulator noted:

> 'Patisiran was shown to be an *in vitro* time dependent CYP2B6 inhibitor and the net effect (TDI and induction) *in vivo* is not possible to be predicted from *in vitro* data. In absence of a DDI study with a CYP2B6 probe and taken into consideration the limited number of substrates metabolized by CYP2B6, it is considered acceptable to reflect the *in vitro* results in the SmPC Section 4.5, that is that the net effect, if any, on a CYP2B6

[5] A novel small interfering ribonucleic acid

substrate co-medicated with Patisiran-LNP *in vivo* is not known and to refer the prescriber to bupropion and efavirenzas as relevant CYP2B6 substrates.

In relation to the pharmacological effect of Onpattro which leads to a decrease in serum vitamin A (retinol) levels, the CHMP considers that the supplementation with 2500 IU vitamin A per day is an appropriate risk minimisation measure.

Overall the pharmacokinetics and pharmacodynamics of patisiran have been thoroughly investigated and well described. The results generally reflect the expected behaviour of a substance belonging to the chemical class of double-stranded oligonucleotides.'

Dose finding for the pivotal studies

The overseas regulator noted:

'Two Phase I patisiran-LNP single ascending dose (SAD) studies in healthy volunteers (ALN-TTR02-001 and ALN-TTR02-005 referenced as 'Study 001' and 'Study 005') contributed pharmacodynamic (PD) assessments (for example, TTR levels). Study ALN-TTR02-002 (referenced as "Study 002") was a Phase II multiple ascending dose (MAD) study that contributed PD in patients with hATTR amyloidosis with polyneuropathy; this study supported the selection of the patisiran-LNP dose and regimen for continued development. It included assessments of serum TTR levels.

In the pooled analysis of Studies 001, 005, and 002, the patisiran-LNP dose of 0.15 mg/kg was on the steep phase of the dose response curve, resulting in less TTR reduction (75.4%) compared with 0.3 mg/kg and greater variability in PD response. The patisiran-LNP dose of 0.5 mg/kg (n = 1) was on the plateau of the dose response curve, resulting in only a marginal increase (4.7%) in TTR reduction compared with 0.3 mg/kg. The 0.5 mg/kg dose was not pursued in clinical studies after Study 001 because of the minimal observed difference in TTR reduction and the occurrence of an acute infusion related reactions at the start of infusion. The maximum percent TTR reduction from Baseline was observed within 10 to 14 days after the first dose. After a single dose of up to 0.5 mg/kg in healthy volunteers, TTR concentrations generally returned to baseline within 70 days. Sustained TTR reduction between doses was consistently achieved with 0.3 mg/kg every 3 weeks, where maximum TTR reductions of up to 96% were observed. A more sustained TTR reduction between doses was observed for a patisiran LNP dose of 0.3 mg/kg given every 3 weeks than every 4 weeks.'

The 0.3 mg/kg every 3 weeks dose was the recommended dose going into the Phase III studies.

Efficacy

Pivotal Study ALN-TTR02-004

Study ALN-TTR02-004 was a multinational, randomised, double blind, placebo controlled, Phase III study designed to demonstrate the efficacy and safety of 0.3 mg/kg Onpattro every 3 weeks in patients with hATTR amyloidosis. The primary objective was to determine the efficacy of Onpattro by evaluating the difference between the Onpattro and placebo groups in the change from Baseline of modified neuropathy impairment score (mNIS)[6] + 7 score at 18 months. The mNIS + 7 is a comprehensive composite assessment that measures the wide range of motor, sensory, and autonomic neurologic impairment experienced by hATTR polyneuropathy patients. The secondary objective was to determine the effect of Onpattro on various clinical parameters

[6] Modified neuropathy impairment score was specifically designed to assess polyneuropathy impairment in patients with hATTR amyloidosis.

by assessing the difference between Onpattro and placebo in the change from Baseline in the following measurements at 18 months.

The mNIS+7, a composite neurologic impairment score, was the primary efficacy variable in the pivotal Study ALN-TTR02-004. Composite neurologic impairment scores have been used previously as endpoints in clinical trials for the assessment of neuropathy progression. In particular, the neuropathy impairment score (NIS) and NIS + 7 (= NIS in addition with seven neurophysiological variables) have been used in clinical trials of diabetic polyneuropathy and chronic inflammatory demyelinating polyneuropathy. These scores have been adopted in clinical studies of hATTR amyloidosis.

All patients received premedication in order to reduce the potential of an infusion related reaction. There was no premedication given in the evening prior to the infusion. Patients received the following premedication on the day of study drug administration at least 60 minutes prior to the infusion:

- Intravenous dexamethasone (10 mg) or equivalent;
- Oral paracetamol/acetaminophen (500 mg) or equivalent;
- Intravenous histamine H2 blocker (for example, ranitidine 50 mg, famotidine 20 mg, or equivalent other histamine H2 blocker dose);
- Intravenous histamine H1 blocker: diphenhydramine 50 mg (or equivalent other intravenous histamine H1 blocker available at the study site). Hydroxyzine or fexofenadine 25 mg orally or cetirizine 10 mg orally may be substituted for any patient who does not tolerate intravenous diphenhydramine or other intravenous histamine H1 blocker.

Results

A total of 323 patients were screened for participation in the study. A total of 225 patients were randomised (148 to the Onpattro group and 77 to the placebo group). All randomised patients were treated with study drug. A total of 56% of patients were included in the predefined cardiac subpopulation. Of the 225 patients randomised and treated, all were included in the modified intent to treat and safety population; patients in the Onpattro group were included in the PK population. A total of 203 (90.2%) patients were included in the per protocol population for efficacy analysis.

Primary endpoint

The global outcome measured in mNIS + 7 at 18 months is shown in Table 3 below. Improvement (change in mNIS + 7 score < 0) was seen in approximately half (56.1%) of Onpattro treated patients at 18 months, compared to 4% in the placebo group.

Table 3: 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 square; max = maximum; min = minimum; MMRM = mixed effect model repeated measure; 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 mean, SEM, differences in LS means, 95% CIs, and Month 18 p-value from MMRM model

The dropout rate in the placebo group was higher than in the Onpattro group, and the reasons provided for withdrawal of consent in a majority of patients in the placebo group was 'worsening of disease' or 'disease progression'. Data suggested that placebo dropouts generally had a worse outcome compared with completers, while some Onpattro dropouts derived benefit from treatment before withdrawal. All sensitivity analyses resulted in a consistent estimate of a positive treatment effect of Onpattro compared to placebo on mNIS + 7.

Secondary and exploratory endpoint measures

To control overall Type I error, these secondary endpoints were tested in a hierarchical order, in the order listed below.

Norfolk QoL-DN Domains

The Norfolk quality of life-diabetic neuropathy is a nerve fibre specific quality of life tool that was developed for patients with diabetic neuropathy. In an observational cross-sectional natural history study it was demonstrated that the Norfolk quality of life-diabetic neuropathy is reliable and valid in assessing quality of life in patients with hATTR amyloidosis. There was a statistically significant difference in quality of life as assessed by Norfolk quality of life-diabetic neuropathy at 18 months favouring the Onpattro group compared to placebo (least square mean Onpattro -6.7, least square mean placebo 14.4, least square mean difference between groups: -21.3 points, $P = 1.103 \times 10^{-10}$). A consistent treatment effect of Onpattro on Norfolk quality of life-diabetic neuropathy was observed across all subgroups.

Statistically significant differences favouring the Onpattro group compared to placebo at 18 months were observed in motor strength (neurologic impairment score weakness), disability (Rasch-built Overall Disability Scale, R-ODS), gait speed (10 metres walk test, 10-MWT), nutritional status (modified body mass index, mBMI) and autonomic symptoms (Composite Autonomic Symptom Score 31, COMPASS 31) (see Table 4).

Rasch-built Overall Disability Scale, is a patient reported disability scale that captures activity and social participation limitations.

The 10-MWT measures the time it takes a patient to walk a distance of 10 metres. In performing this test, patients were allowed to use ambulatory aids such as a cane or walker. Gait speed is commonly studied in patients with neuropathy and is anticipated to be associated primarily with muscle strength but also with sensation. The mean self selected gait speed in healthy subjects ages 10 to 79 years ranged from approximately 1.1 to 1.3 m/s. A walking speed of 1.4 m/s is considered to represent an 'extremely fit' individual whereas a walking speed of < 0.8m/s suggests a patient with more limited community ambulation.

Modified body mass index is a measure of nutritional status calculated as the product of BMI (weight in kilograms divided by the square of height in meters) and serum albumin (g/L). Patients with hATTR amyloidosis often have poor nutritional status and overall weight loss due in part to severe gastrointestinal manifestations and in part due to cardiac disease.

The COMPASS 31 has been used to assess autonomic symptoms in patients with diabetic neuropathy and small fibre polyneuropathy and is considered a valid instrument in these patients. Patients with hATTR amyloidosis often have debilitating autonomic dysfunction, COMPASS 31 was adopted for use in Onpattro clinical studies.

Summary of main efficacy results

Table 4: Summary of efficacy for the single pivotal trial Study ALN-TTR02-004

Titles: APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)			
Study identifier	Pivotal trial ALN-TTR02-004 EudraCT Number: 2013-002987-17		
Design	A Phase 3 multicenter, double-blind, randomized, stratified, placebo controlled study of patisiran in subjects with a diagnosis of FAP with documented TTR mutation, with symptomatic polyneuropathy defined as Impairment Score (NIS) ≥10 and ≤130, PND score of ≤3b and a Karnofsky performance status of ≥60%. Patients with New York Heart Association heart failure classification >2 were excluded. Consented eligible patients will be randomized to receive either patisiran or placebo in a 2:1 ratio. Patients will have baseline efficacy assessments and efficacy assessments at 9 and 18 months.		
	Duration of main phase:		18 months
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		Study 006: ongoing, up to 5 years
Hypothesis	Superiority to placebo		
Treatments groups	Patisiran		0.3 mg/kg IV patisiran every 3 weeks for 18 months, N=148
	Placebo		Placebo IV (with same premedication as patisiran), every 3 weeks for 18 months. N=77
Endpoints and definitions	Primary endpoint	mNIS+7	Compare change from Baseline to month 18 between treatment arms in the modified Neuropathy impairment score +7 (mNIS+7) (0-304 p)
	Secondary endpoint	Norfolk QoL-DN	Compare change from Baseline to Month 18 between treatment arms in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score (-4 to 136 p)
	Secondary endpoint	NIS-W	Compare change from Baseline to Month 18 between treatment arms in the NIS-W (Neuropathy Impairment Score-Weakness Score)(range: 0 to 192 points). Less neurologic impairment = Lower score
	Secondary endpoint	R-ODS	Compare change from Baseline to Month 18 between treatment arms in the R-ODS (Rasch-Built Overall Disability Scale)(range: 0 to 48). Less disability = Higher score
	Secondary endpoint	Timed 10-meter walk test	Compare change from Baseline to Month 18 between treatment arms in the Timed 10-meter walk test. Faster/better gait speed = Higher speed.
	Secondary endpoint	mBMI	Compare change from Baseline to Month 18 between treatment arms in the modified Body mass index (kg/m² x albumin (g/L)). Better nutritional status = Higher mBMI.
	Secondary endpoint	COMPASS 31	Compare change from Baseline to Month 18 between treatment arms in the COMPASS 31 (Autonomic Symptoms Questionnaire [Composite Autonomic Symptom Score]) (0-100 p). Less autonomic neuropathy symptoms = Lower score.
Database lock	Needs to be confirmed (DC).		

Table 4: Continued, Summary of efficacy for the single pivotal trial Study ALN-TTR02-004

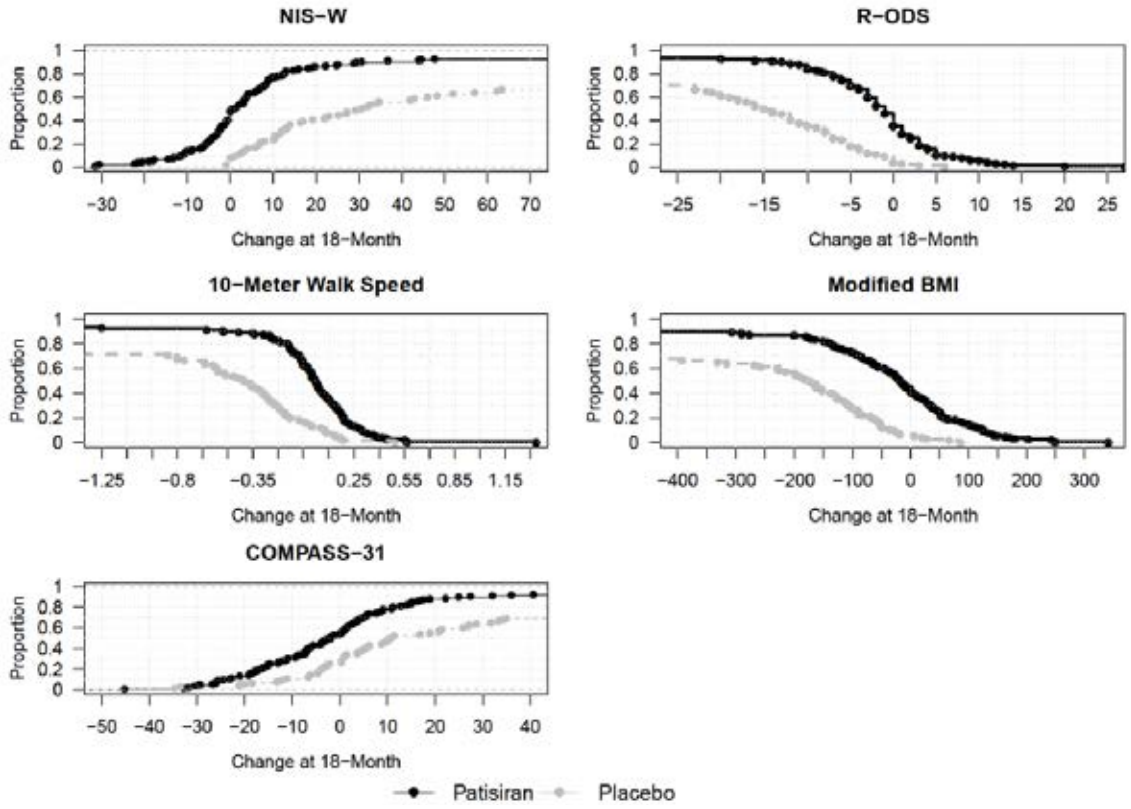
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	mITT, Month 18. The primary efficacy endpoint was the change in mNIS+7 from baseline to Month 18 between treatment arms.		
Descriptive statistics and estimate variability	Treatment group	Patisiran 0.3 mg/kg	Placebo
	Number of subjects (Baseline and mITT)	148	77
	mNIS+7 (MMRM, mITT) Change from baseline, LS mean (SEM)	-6.03 (1.74)	27.96 (2.60)
	95%CI	-9.46, -2.60	22.83, 33.09
	Norfolk QoL-DN (MMRM, mITT) Change from baseline, LS mean (SEM)	-6.7 (1.77)	14.4 (2.73)
	95%CI	-10.2, -3.3	9.0, 19.8
	NIS-W Change from baseline, LS mean (SEM) 95%CI	0.05 (1.31) -2.52, 2.63	17.93 (1.96) 14.07, 21.79
	R-ODS Change from baseline, LS mean (SEM) 95%CI	0.0 (0.59) -1.1, 1.2	-8.9 (0.88) -10.7, -7.2
	Timed 10-meter walk test Change from baseline, LS mean (SEM) 95%CI	0.08 (0.02) 0.03, 0.12	-0.24 (0.04) -0.31, -0.16
	mBMI Change from baseline, LS mean SEM 95%CI	-3.7 (9.57) -22.6, +15.1	-119.4 (14.51) -148.0, -90.8
	COMPASS 31 Change from baseline, LS mean SEM 95%CI	-5.29 (1.30) -7.85, -2.72	2.24 (1.94) -1.59, +6.06

Table 4: Continued, Summary of efficacy for the single pivotal trial Study ALN-TTR02-004

Effect estimate per comparison	mNIS+7	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	-33.99
		95% CI of difference	-39.86, -28.13
		P-value	9.262×10^{-24}
	Norfolk QoL-DN	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	-21.1
		95% CI of difference	-27.2, -15.0
		P-value	1.103×10^{-10}
	NIS-W	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	-17.07
		95% CI of difference	-22.32, -13.43
		P-value	1.404×10^{-12}
	R-ODS	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	9.0
		95% CI of difference	7.0, 10.9
		P-value	4.01×10^{-16}
	Timed 10-meter walk test	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	0.31
		95% CI of difference	0.23, 0.39
		P-value	1.88×10^{-12}
	mBMI	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		LS Mean Difference	115.7
		95% CI of difference	82.4, 149.0
		P-value	8.832×10^{-11}
	COMPASS 31	Comparison groups	Patisiran 0.3 mg/kg vs placebo
		Difference in LSM	-7.53
		95% CI of difference	-11.89, -3.16
		P-value	0.0008

Cumulative distribution curves of change from Baseline at 18 months in all additional secondary endpoints shows separation between Onpattro and placebo treated patients, favouring Onpattro, across all response thresholds (Figure 1).

Figure 1: Study 004 Cumulative distribution plots of secondary efficacy endpoints change from Baseline at Month 18 (modified intent to treat population)



Abbreviation: mBMI = modified body mass index; mITT = modifed intent to treat; NIS = neurologic impairment score; NIS-W = neurologic impairment score weakness; QoL-DN = quality of life-diabetic neuropathy

Cardiac assessment

Cardiac assessment through echocardiogram, troponin I, and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels were included as exploratory endpoints. The analysis of the effect of Onpattro on amyloid cardiomyopathy was focused on a pre-specified cardiac subpopulation (LV wall thickness ≥ 1.3 cm with no history of aortic valve disease or hypertension), which comprised 56% of the overall study population. Among patients in the cardiac subpopulation, 73% had non-*V30M* genotype. The majority (60.3%) had New York Heart Association (NYHA) class II;[7] heart failure.

N-terminal prohormone of B-type natriuretic peptide

In the cardiac subpopulation, at Baseline, geometric mean NT-proBNP levels were 726.92 ng/L and 711.10 ng/L in the Onpattro and placebo groups, respectively. At month 18, geometric mean NT-proBNP decreased to 544.06 ng/L in the Onpattro group and increased to 1116.75 ng/L in the placebo group.

[7] New York Heart Association (NYHA) classification:
Class I: No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic left ventricular dysfunction). Metabolic equivalent (MET) > 7.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild congestive heart failure). MET = 5.
Class III: Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate congestive heart failure). MET = 2–3.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms of congestive heart failure present at rest (severe congestive heart failure). MET = 1.6.

Supportive studies

Study ALN-TTR02-003

Study ALN-TTR02-003 was a multinational, multicentre, Phase II, open label, extension study designed to provide long term (up to two years) Onpattro dosing to patients with hATTR amyloidosis with polyneuropathy who received and tolerated Onpattro in Study ALN-TTR02-002. Patients could continue treatment in Study ALN-TTR02-006 after completion of this study. All efficacy summaries were descriptive and no hypothesis testing was performed.

A total of 27 patients were enrolled and treated in Study ALN-TTR02-003. A total of 25 patients completed the study.

Following administration of Onpattro, the mean (standard error of mean) change from Baseline in the mNIS + 7 at 24 months was -6.95 (2.03) points. The mean (standard error of mean) change from Baseline in mNIS + 7 at 24 months was similar between subgroups analysed.

Overall, NIS and NIS + 7, measures of disability (R-ODS), gait speed (10-MWT), nutritional status (mBMI), autonomic function (COMPASS 31), motor strength (grip strength), and QoL (EQ-5D and EQ-VAS) were stable over the 24 month treatment period.

The mean (standard deviation) dermal amyloid burden at Baseline was 10.91% (9.49%) and 15.78% (14.93%) for distal thigh and distal leg, respectively, and the mean absolute (standard error of mean) change from Baseline to 24 months (Week 110) was -3.81% (1.31%) for distal thigh and -6.38% (2.81%) for distal leg that reached nominal statistical significance.

Echocardiogram measures (left ventricle mass, left ventricle wall thickness, longitudinal strain and left ventricle ejection fraction) and cardiac biomarkers (NT-proBNP and troponin I) performed in the predefined cardiac subgroup were stable over time.

Study ALN-TTR02-006

Study ALN-TTR02-006 is an ongoing multicentre, multinational, open label extension study. Eligible patients who completed either of the two parent Studies ALN-TTR02-003 or -004, were given the option to participate in this study. At the time of the interim Study ALN-TTR02-006 data cutoff date (14 July 2017), Study ALN-TTR02-003 was completed and all 25 patients who completed Study ALN-TTR02-003 had enrolled in Study ALN-TTR02-006. Study ALN-TTR02-004 was ongoing; 163 of the 169 patients who completed Study ALN-TTR02-004 by that time had enrolled in Study ALN-TTR02-006. Patients from Study ALN-TTR02-004 remained blinded to Study ALN-TTR02-004 treatment assignment during participation in Study ALN-TTR02-006 at the time of the interim data cut. Efficacy assessment is presented for the smaller subset of approximately 64 patients who had efficacy assessment at Week 52.

A total of 184 patients were dosed with Onpattro in this study for a mean (standard deviation) of 9 (5.976) months (range 0.7 to 24.6 months). Of the 184 patients who had been treated in this study at the time of the interim data cut, Week 52 mNIS + 7 efficacy data were available for 64 patients (n = 10 from 004 placebo, n = 30 from Study ALN-TTR02-004 Onpattro, and n = 24 from Study ALN-TTR02-003 Onpattro). The results are shown in Table 5 below.

Table 5: Study ALN-TTR02-006 modified neuropathy impairment score + 7 at Week 52

Visit	Actual/ Change	Statistic	004 Placebo (N=43)	004 Patisiran-LNP (N=120)	003 Patisiran-LNP (N=25)
Baseline[a]	Actual	N	43	116	25
		Mean	100.08	77.74	45.66
		SD	43.739	43.695	31.640
		Median	93.88	73.94	40.00
		Min, Max	21.5, 190.1	8.0, 198.9	3.0, 127.8
Week 52	Actual	N	10	30	24
		Mean	99.65	81.53	48.49
		SD	44.389	39.167	37.965
		Median	107.13	78.75	41.75
		Min, Max	15.0, 173.0	17.0, 163.0	1.5, 164.4
	Change	N	10	30	24
		Mean	-1.31	1.48	2.47
		SEM	3.116	2.560	2.751
		Median	-1.13	2.38	2.25
		Min, Max	-17.1, 11.3	-29.8, 44.4	-34.0, 36.6

Abbreviations: mNIS + 7 = modified neuropathy impairment score; SD = standard deviations; SEM = standard error of the mean

Note: At each visit the total scores are calculated as the mean of the two independent assessments.

a The last non-missing measurement on or prior to the first dose of study drug in this study. Per protocol, the last testing visit in the parent study will serve as the baseline unless more than 45 days have elapsed in which cause baseline is the Day 1 value.

At Week 52, mean change from Baseline Norfolk quality of life-diabetic neuropathy was -10.2 points in the Study ALN-TTR02-004 placebo and -1.8 points in the Study ALN-TTR02-004 Onpattro groups. Only one patient from the Study ALN-TTR02-003 Onpattro group performed a Norfolk quality of life-diabetic neuropathy assessment at Baseline (not required in Study ALN-TTR02-003), therefore the change over time cannot be evaluated.

Clinical endpoints assessing disability (R-ODS), ambulatory ability (10 metre walk test), nutritional status (mBMI), autonomic symptoms (COMPASS 31), neuropathy (NIS, NIS+7), motor strength (grip strength), quality of life questionaires (EQ-5D) and overall health (EQ-VAS) were generally stable or improved at Week 52 relative to Study ALN-TTR02-006 baseline.

At Week 52, echocardiogram results were available for only 9 patients in Study ALN-TTR02-004 placebo group, 27 patients (23 patient for left ventricle ejection fraction) in Study ALN-TTR02-004 Onpattro group and 24 patients in the Study ALN-TTR02-003 Onpattro group. Among the group of patients from the Study ALN-TTR02-004 placebo group with Week 52 assessments, there was evidence of stabilisation of cardiac structure and function relative to baseline following transitioning to Onpattro on Study ALN-TTR02-006 according to the applicant. In patients from the Study ALN-TTR02-004 Onpattro and Study ALN-TTR02-003 Onpattro groups who received treatment with Onpattro on the parent studies, continued treatment with Onpattro in Study ALN-TTR02-006 resulted in maintenance of efficacy according to the applicant.

At Week 52, median change from Baseline in NT-proBNP levels were -12.01 ng/L in the Study ALN-TTR02-004 placebo, -15.05 ng/L in Study ALN-TTR02-004 Onpattro, and 33.61 ng/L in the Study ALN-TTR02-003 Onpattro group.

Study ALN-TTR02-006 update report (17 March 2022 – 3 year data)

As of the data cutoff, the median (range) total duration of patisiran exposure in Study ALN-TTR02-006 was 45.11 (1.3, 61.3) months, for a cumulative drug exposure of 733 person-years. The median (range) duration of patisiran administration in Study ALN-TTR02-006 was 40.71 (1.3, 61.3) months in the Study ALN-TTR02-004 Placebo group, 44.68 (1.3, 60.7) months in the Study ALN-TTR02-004 Patisiran group, and 58.22 (45.6, 60.1) months in the Study ALN-TTR02-003 Patisiran group.

> 'In patients from the Study ALN-TTR02-004 Placebo group, there was evidence of disease stabilization relative to baseline across measures of neuropathy impairment, quality of life, and other important disease manifestations 12 months after transitioning to patisiran in Study ALN-TTR02-006; thereafter, the maintenance of the patisiran treatment effect was seen at Years 2 and 3. For patients in the Studies ALN-TTR02-004 and -003 Patisiran groups, who previously received patisiran in the parent studies, continued exposure to patisiran in Study ALN-TTR02-006 resulted in maintenance of the treatment effect observed at Study 006 baseline for up to 3 years. Most patients showed improvement or stability in FAP (familial amyloidotic polyneuropathy) stage and PND (polyneuropathy disability) score over time. Among the FAP Stage III patients who had post-baseline measurements in Study ALN-TTR02-006, the overall clinical picture suggests relative stability over time in measures of neuropathy impairment, quality of life, and disability with patisiran treatment in Study ALN-TTR02-006. Some patients showed meaningful improvement in these measures, and, of particular note, one patient who was previously wheelchair bound (or bedridden) improved with ongoing patisiran treatment such that they were able to walk again with assistance. These findings underscore the potential for treatment with patisiran to benefit patients with the most severe stage of disease.
>
> Changes in serum TTR levels were as expected. In patients from the Study ALN-TTR02-004 placebo group, patisiran treatment resulted in a mean TTR reduction from Baseline of 83.3% at Week 52. For patients in the Studies ALN-TTR02- 004 and -003 Patisiran groups, who had already received patisiran in the parent studies and had low TTR levels at Study ALN-TTR02-006 baseline, continued treatment with patisiran showed stable reductions in serum TTR levels. The maintenance of reduced TTR levels over a total of more than 5 years with patisiran treatment suggests that there is no tachyphylaxis observed with long-term treatment.
>
> The 3-year efficacy and safety data from Study ALN-TTR02-006 are consistent with what has previously been observed with patisiran in clinical studies and confirms the clinical efficacy and acceptable safety profile of patisiran. These data also support early treatment intervention to avoid disease progression and that the effects of patisiran are maintained with continued treatment. No new safety signals emerged in patients with long-term patisiran treatment.'

Study ALN-TTR02-008

Study ALN-TTR02-008 was initiated on 27 March 2019 and completed on 20 October 2020. Twenty four patients enrolled in this study; 23 received Onpattro treatment. Data from this study is summarised below in the Study ALN-TTR02-008 summary report (dated 25 June 2021).

Study ALN-TTR02-008 was a global, Phase III b, open label study designed to evaluate the safety, efficacy, and PK of Onpattro in patients with hATTR amyloidosis with disease progression after orthoptic liver transplant. All patients were treated with Onpattro 0.3 mg/kg Onpattro intravenous every 3 weeks for 12 months. The primary objective was to evaluate the reduction of TTR with patisiran treatment in hATTR amyloidosis patients with disease progression after

orthoptic liver transplant. A total of 24 patients were enrolled, of whom 23 (95.8%) received ≥ 1 dose of patisiran and 22 (91.7%) completed study treatment. The mean age at enrolment was 58 years, and the mean time from liver transplant to the first dose of patisiran in this study was 9.4 years.

> 'The study met its primary endpoint, with patients demonstrating a statistically significant median TTR reduction from Baseline of 91.0% ($p = 4.483 \times 10^{-8}$). The robust and sustained reduction of serum TTR achieved with patisiran in hATTR amyloidosis patients with disease progression after orthoptic liver transplant on this study was similar in magnitude to the reduction observed in Study ALN-TTR02-004,[8] which did not include patients who had undergone orthoptic liver transplant. This indicates that patisiran liver uptake and RNA interference activity remains intact in orthoptic liver transplant patients and is not impacted by the concomitant administration of immunosuppressive agents.
>
> Patients showed improvement or stability at Month 12 in measures of neuropathy impairment (NIS), patient-reported measures of quality of life (Norfolk QoL-DN), autonomic neuropathy symptoms (COMPASS-31), activities of daily living and social participation limitations (R-ODS), and nutritional status (mBMI), which was consistent with the findings of Study 004.[8]
>
> Pharmacokinetics of patisiran in hATTR amyloidosis patients with disease progression after orthoptic liver transplant was consistent with the results of prior patisiran studies.[9],[10] The similarity of the PK profiles of patisiran in non-transplant and post-transplant hATTR amyloidosis patients suggests that the liver uptake of patisiran is not influenced by liver transplantation. In addition, the consistent PK results of the current study relative to past studies also suggest the absence of drug-drug interaction between patisiran and concomitantly administered immunosuppressive drugs in patients in orthoptic liver transplant patients.
>
> Overall, patisiran had an acceptable safety profile in patients with hATTR amyloidosis who had undergone orthoptic liver transplant. The nature and type of AEs were generally consistent with those commonly observed in patients with hATTR amyloidosis and the established safety profile of patisiran.'

In the study hATTR amyloidosis patients with disease progression after orthoptic liver transplant showed robust and sustained TTR reductions during treatment with patisiran, which were consistent with reductions observed in prior patisiran studies. Patients also showed improvement or stability at Month 12 in clinical measures of neuropathy impairment, patient-reported measures of quality of life, autonomic neuropathy symptoms, activities of daily living and social participation limitations, and nutritional status. Safety data indicate that patisiran had an acceptable safety profile in the treatment of hATTR amyloidosis patients with disease progression after orthoptic liver transplant.

The Delegate commented that in this patient population, patisiran demonstrated favourable efficacy and safety consistent with observations in other studies.

[8] Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med*. 2018 July 5;379(1):11-21.

[9] Zhang X, Goel V, Attarwala H, Sweetser MT, Clausen VA,Robbie GJ. Patisiran Pharmacokinetics, Pharmacodynamics, and Exposure-Response Analyses in the Phase 3 APOLLO Trial in Patients With Hereditary Transthyretin-Mediated (hATTR) Amyloidosis. *J Clin Pharmacol*. 2020a Jan;60(1):37-49.

[10] Zhang X, Goel V,Robbie GJ. Pharmacokinetics of Patisiran, the First Approved RNA Interference Therapy in Patients With Hereditary Transthyretin-Mediated Amyloidosis. *J Clin Pharmacol*. 2020b May 2020;60(5):573-85.

Other studies

No dedicated studies in subjects with renal and hepatic impairment were performed with Onpattro.

The Delegate noted that the overseas regulator raised a number of efficacy concerns, including requesting further data to support use in patients with advanced polyneuropathy and further data to support cardiac benefits.

After considering the sponsor's responses to the major objections and other concerns raised during the overseas regulator evaluation, the evaluator concluded that the proposed indication was too broad and should be amended to the current approved indication in the Summary of product characteristics.[11]

Conclusions on clinical efficacy

The overseas regulator noted:

> 'The study population in the pivotal study 004 was limited to subjects with Polyneuropathy Disability (PND) Scores of 0-IIIB hATTR/FDP stage 1 and 2. It is acknowledged that the clinical data from study 004 shows a convincing difference between patisiran and placebo regardless of baseline disease stages at inclusion for the studied population. However, there is only very limited data in patients with more severe disease and it is therefore not found adequate to extrapolate the results from less severe to more advanced stages of the disease (PND stage IV/FAP stage 3 = non ambulatory patients).
>
> Significant effects were seen on the primary and secondary endpoints related to polyneuropathy, but there are a number of other concerns related to these endpoints and the related results (see Limit of Quantitation). In addition, the study population was restricted to subjects with polyneuropathy but still ambulant, that is more severely affected subjects were excluded. Cardiac endpoints were only exploratory and subjects with a severe cardiac involvement were excluded, and since the applicant has proposed a broad indication of 'adult hATTR' this results in a major objection on the indication text, and several other concerns related to the indication.'

The overseas regulator considered that the presented data supports the following indication; 'Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.'

The TGA evaluator agreed with the overseas regulator conclusions that the clinical data available tends to suggest that patisiran is effective for treatment of hATTR amyloidosis patients with stage 1 or 2 polyneuropathy.

Safety

It is noted in overseas regulator report that:

> 'The safety database includes 218 patients with hATTR amyloidosis with polyneuropathy exposed to Onpattro. 179 patients have been dosed for at least 12 months and 101 for at least 24 months. In addition, 48 patients have been exposed in an expanded access program in the United States of America. Overall, the safety database is small, but taking into consideration the rarity of the disease, it is considered acceptable.

[11] Summary of Product Characteristics of Onpattro, available at https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf

> However, long-term safety data are still limited. In this respect, the applicant has committed to conduct, post approval, a prospective observational study to monitor and assess the long-term safety of Onpattro in hATTR amyloidosis patients. The main adverse events were infusion related reactions, which are manageable with premedication and slowing or temporary stopping of infusion if necessary.
>
> In addition consequences of vitamin A deficiency and hepatic disorders are considered potential risks and are appropriately captured in the RMP (risk management plan).'

The TGA evaluator noted that a (post-authorisation safety study) protocol prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real world cohort of hATTR amyloidosis patients has been submitted in this application, which appears to be the study referred to above.

The submission provided the following:

- Post-authorisation safety study protocol prospective observational study to monitor and assess the safety of Onpattro (patisiran) in a real world cohort of hATTR amyloidosis patients, dated 17 August 2020
- Protocol for non-interventional study protocol Study ALN-TTR02-010 patisiran pregnancy surveillance program, dated 6 September 2019
- Post-authorisation safety study protocol assessment report for study protocol ALN-TTR02-010, dated 28 January 2021
- Observational study protocol ALN-TTRr02-013 ConTTRibute: A global observational multicenter long-term study of patients with transthyretin mediated amyloidosis, dated 20 March 2020

Post authorisation safety study

The objective of this study is to assess the safety of Onpattro in real world clinical practice by creating and monitoring a longitudinal cohort of hereditary transthyretin-mediated amyloidosis patients, including both patients treated with Onpattro and comparator patients (treated with a competitor and untreated), following local standard of care.

The primary objective of the study is to characterise the safety of Onpattro under real world conditions using composite measures of protocol specified safety events of interest (for example, hepatic events) in hATTR amyloidosis patients exposed to Onpattro.

The secondary objectives of the study are:

- To characterise the safety of Onpattro in sub-populations (for example, patients administered home infusions, patients with prior liver transplant, hepatic impairment, and renal impairment)
- To describe epidemiological and clinical characteristics of hATTR amyloidosis patients, and patients treated with Onpattro in a real world setting.
- To evaluate information from all pregnancies including pregnancy outcomes and selected infant outcomes.

This is a multinational, non-interventional, observational study conducted over a period of 10 years to evaluate the safety of Onpattro in hATTR amyloidosis patients exposed to Onpattro under real world conditions. This protocol does not recommend the use of any specific treatments. No study medication is provided as part of participation. The study will use epidemiological cohort techniques to describe the epidemiological and clinical characteristics of hATTR amyloidosis patients globally, including Europe (for example, France, Germany, Italy,

Netherlands, Portugal, Spain, Sweden and United Kingdom), and the United States. Patients will be enrolled during a two year period (to be extended if necessary based on actual enrolment).

The study will enrol approximately 300 hATTR amyloidosis patients regardless of their treatment status. This is estimated to result in approximately 150 Onpattro exposed patients. Inclusion criteria are broad: confirmed diagnosis of hATTR amyloidosis and informed consent.

Study ALN-TTR02-010

There are no available data on the use and safety of Onpattro in pregnant women. Onpattro leads to a decrease in serum vitamin A levels. Vitamin A is essential for normal embryofoetal development.

Study ALN-TTR02-010 is an observational program that will collect primary data on pregnant women from the US, the United Kingdom (to Onpattro during the exposure window, defined as 12 weeks prior to their last menstrual period (LMP UK), France, Spain, Italy, and Germany, and other potential countries, who have been exposed) or at any time during pregnancy.

The objectives are:

- To collect and evaluate information from all pregnancies and to estimate the frequency of selected pregnancy outcomes (that is, live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women exposed to Onpattro during the defined exposure window.
- To estimate the frequency of selected foetal/neonatal/infant outcomes (that is, major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through at least the first year of life of infants from pregnancies in women exposed to Onpattro during the defined exposure window.

Data will be collected from patients and their healthcare providers (HCPs) (for example, obstetrician, Onpattro-prescribing physician) about their experiences during pregnancy and through at least 1 year after birth (infant's HCP and/or the patient). The program is voluntary, and any woman exposed to Onpattro during the exposure window, as defined above, and meeting the inclusion criteria will be eligible. The total duration of participation is up to 21 months, and the total duration of the program is approximately 10 years or longer as needed. Inclusion criteria are broad: patient consent (written or verbal per local regulations or ethics committee requirements) obtained prior to enrolment, and documentation that the patient was exposed to Onpattro at any point starting from 12 weeks before last menstrual period or at any point during pregnancy.

No data have been presented from this study.

Study ALN-TTRr02-013

Study ALN-TTRr02-013 also known are ConTTRibute trial is a prospective, global, multicentre, long term observational study designed to document the clinical outcomes of patients with transthyretin-mediated amyloidosis (ATTR) over time. The study protocol does not recommend the use of any specific treatments and no study medication is provided as part of participation. There are no visits or procedures associated with the study, patients will follow routine clinical care. All treatments and/or any changes considered necessary for a patient's welfare will be determined at the discretion of the patient's physician.

The objectives are:

- To describe epidemiological and clinical characteristics, natural history and real world clinical management of ATTR amyloidosis patients.

- To characterise the safety and effectiveness of Onpattro as part of routine clinical practice in the real world clinical setting

Any patient with a diagnosis of ATTR amyloidosis, hereditary or wild type, will be eligible for the study. Given the rare nature of hereditary ATTR amyloidosis, at least 80% of the first 500 patients enrolled must be patients diagnosed with hATTR amyloidosis to ensure that real world management of hATTR amyloidosis patients can be characterised. Of the 400 patients enrolled with hATTR amyloidosis, at least 150 should be treated with patisiran in order to conduct comparative analyses.

Inclusion criteria are broad such as confirmed diagnosis of ATTR amyloidosis and informed consent (if/where applicable). Patients enrolled in another clinical trial of any investigational agent will be excluded.

No data have been presented from this study.

The Australian submission included the following post-market data from:

- Periodic Benefit-Risk Evaluation Report 001 (PBRER 001), for the period 10 Aug 2018 to February 2019, dated 17 April 2019
- PBRER 002, for the period 10 February 2019 to 9 August 2019, dated 16 October 2019
- PBRER 003, for the period 10 August 2019 to 9 February 2020, dated 15 April 2020
- PBRER 004, for the period 10 February 2020 to 9 August 2020, dated 12 October 2020
- PBRER 005, for the period 10 August 2020 to 9 February 2021, dated 12 April 2021
- PBRER 006, for the period 10 February 2021 to 9 August 2021, dated 11 October 2021

Commonly reported serious adverse events for Onpattro from the clinical development program were cardiac failure and cerebrovascular accident, syncope, urinary tract infection and cardiac failure congestive, diarrhoea and pneumonia and cardiac amyloidosis.

Commonly reported serious and non-serious adverse reactions from post-marketing data sources were fatigue, infusion related reactions and somnolence.

The PBRERs confirmed the important identified risk of infusion related reactions, and the important potential risks of consequences of vitamin A deficiency, severe hypersensitivity and hepatic disorders, and missing information for longer term safety (greater than 3 years), use in patients with moderate or severe hepatic impairment, use in patients with severe renal impairment or end stage renal disease, use in patients with prior liver transplantation and use in pregnancy and lactation. No new or important safety-related patterns or trends were observed that would have an impact on the safety profile of Onpattro. The majority of the reported signs and symptoms of infusion related reactions s reported from post-marketing sources were non-serious and consistent with the known safety profile of Onpattro.

Commonly reported infusion related reaction type events included: abdominal discomfort, abdominal pain, abdominal pain upper, back pain, blood pressure decreased, blood pressure increased, chest discomfort, chest pain, cough, dizziness, dyspnoea, erythema, infusion site erythema, fatigue, flushing, headache, hot flush, hypertension, hypotension, musculoskeletal pain, nausea, pain, pain in extremity.

In PBRER 002, a new safety signal for syncope was noted. Hence, syncope was added into the Summary of Product Characteristics;[11] as an infusion related reaction key symptom. These changes have been made to the Australian Product Information (PI).

In PBRER 003, pruritis and syncope were noted as new safety signals. Pruritis was added into the Summary of Product Characteristics;[11] as a key symptom of infusion related reaction. This change has been made to the Australian PI.

In PBRER 004, there were no newly detected safety signals pertaining to Onpattro. In PBRER 5 a safety signal for mild transaminase elevations was noted. In PBRER 006 there were no newly detected safety signals but the signal for mild transaminase elevations was ongoing. The benefit risk profile of Onpattro in its approved indications remains unchanged.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.0 (date 25 July 3018; DLP 14 September 2017) and Australia specific annex (ASA) version 0.1 (date 3 December 2021) in support of this application. The sponsor submitted ASA version 0.2 (14 July 2022) with the sponsor response to TGA questions.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion-related reactions	ü[1]	–	ü	ü[5]
Important potential risks	Consequences of vitamin A deficiency	ü	–	ü	–
	Severe hypersensitivity	ü[1]	–	ü	–
	Hepatic disorders	ü	ü[2,3]	ü	–
Missing information	Longer-term safety (>3 years)	ü	ü[2,3]	ü	–
	Use in patients with moderate or severe hepatic impairment	ü	ü[3]	ü	–
	Use in patients with severe renal impairment or end-stage renal disease	ü	ü[3]	ü	–
	Use in patients with prior liver transplantation	ü	ü[3]		–
	Use in pregnancy and lactation	ü	ü[4]	ü	–

1 Follow-up questionnaires

2 Open-label extension study (ALN-TTR02-006)

3 Prospective observational cohort study (ALN-TTR02-009)

4 Global pregnancy surveillance program (ALN-TTR02-010)

5 Educational materials for healthcare professionals and patients

The summary of safety concerns is acceptable from a risk management perspective.

Routine pharmacovigilance activities are proposed for all safety concerns. Follow up questionnaires are included for the important identified risk 'infusion related reactions' and the important potential risk 'severe hypersensitivity'. Additional pharmacovigilance activities include three studies as outlined in the table above. The pharmacovigilance plan is acceptable.

Routine and additional risk minimisation activities have been proposed. The additional activities include educational materials for healthcare professionals and patients for minimising the risk of infusion-related reactions when Onpattro is administered in the home setting. In the response

to TGA questions, sponsor has updated the ASA to include PI as package insert as a routine risk minimisation activity. The sponsor has agreed to provide all additional risk minimisation materials, the implementation plan and the effectiveness evaluation plan to the TGA prior to launch for review. The acceptability of the risk minimisation plan will be reviewed once the updated ASA with the implementation and evaluation of effectiveness plans is provided. This should not impede registration.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> 'The Onpattro EU-Risk Management Plan (RMP) (version 1.0, dated 25 July 2018, data lock point 14 September 2017), with Australia Specific Annex (version 0.2, dated 14 July 2022), included with submission PM-2021-05675-1-1, to be revised to the satisfaction of the TGA, and any subsequent revisions, will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.'

As Onpattro is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Onpattro (patisiran) is to be included in the Black Triangle Scheme. The PI and CMI for Onpattro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

This is a new chemical entity application to register Onpattro, the active ingredient patisiran.

The proposed indication is:

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

Hereditary transthyretin-mediated amyloidosis is a rare, life threatening, autosomal dominant multi-systemic disease caused by mutations in the TTR gene that results in rapidly progressive, debilitating morbidity and high mortality. There are currently limited treatment options that may alter the course of the hATTR disease, namely orthotopic liver transplant and TTR tetramer stabilisers; these exist for a small subset of patients.

The product provides an alternative treatment for hATTR amyloidosis for which few therapeutic options are available. This is based on data from the pivotal Study ALN-TTR02-004 and supportive Studies ALN-TTR02-003 and -006. Dose dependent reductions in serum TTR concentrations with Onpattro were observed in both healthy volunteers and in patients with hATTR amyloidosis with polyneuropathy. Long term dosing with Onpattro sustained a mean TTR reduction of approximately 80% over two years of treatment. Furthermore, in relation to neurological impairment a statistically significant difference favouring Onpattro group compared to placebo at 18 months was observed for the primary and all secondary endpoints.

Quality

The Delegate noted that the quality evaluator reviewed the assessment reports prepared by the COR for the same submission. All labelling and PI recommendation from the quality evaluator have been accepted by the sponsor.

Nonclinical

The scope and quality of the submitted nonclinical dossier was mostly acceptable, with studies consistent with the principles of ICH guidance;[3] for the nonclinical testing of pharmaceuticals. All pivotal safety-related studies were conducted according to Good Laboratory Practice.

The primary pharmacology data lend some support for the proposed indication.

The collective toxicity findings with Onpattro of potential clinical relevance include:

- Hepatotoxicity (accompanied by increased liver enzymes), which should be easily monitored;
- Injection site reactions, which could easily be monitored;
- Teratogenicity, which can be mitigated by sufficient warnings and labelling.

The proposed pregnancy category for Onpattro (Category D) is acceptable.[4]

Although some limitations were identified in the nonclinical dossier (low assessed margins, inadequate carcinogenicity assessment), the clinical presentations of hATTR amyloidosis (multiple organs impairment), the disease outcome (fatal), the limited treatment alternatives and the expected treatment benefits, may outweigh any unknown risks.

All labelling and PI recommendation from the nonclinical evaluator have been accepted by the sponsor.

The nonclinical evaluator has recommended approval of Onpattro.

Clinical

The core studies providing efficacy and safety data are the pivotal Phase III double blind, placebo controlled Study ALN-TTR02-004 and two open label, single arm studies that evaluated Onpattro at the intended dose and regimen in patients with hATTR amyloidosis (Studies ALN-TTR02-003 and -006).

The clinical development program is considered adequate to assess the clinical efficacy and safety of Onpattro for the proposed indication.

Pharmacology

Overall, the pharmacokinetics and pharmacodynamics of Onpattro have been thoroughly investigated and well described. The results generally reflect the expected behaviour of a substance belonging to the chemical class of double stranded oligonucleotides.
The 0.3 mg/kg every 3 weeks dose was the recommended dose going into the Phase III studies.

Efficacy

Pivotal Study ALN-TTR02-004

Study ALN-TTR02-004 was a multinational, randomised, double blind, placebo controlled, Phase III study designed to demonstrate the efficacy and safety of 0.3 mg/kg Onpattro every 3 weeks in patients with hATTR amyloidosis. The primary objective was to determine the efficacy of Onpattro by evaluating the difference between the patisiran and placebo groups in the change from Baseline of mNIS + 7 score at 18 months.

A total of 323 patients were screened for participation in the study. A total of 225 patients were randomised (148 to the Onpattro group and 77 to the placebo group). All randomised patients were treated with study drug.

Improvement (change in mNIS+7 score < 0) was seen in approximately half (56.1%) of Onpattro treated patients at 18 months, compared to 4% in the placebo group. Results from secondary endpoints also favoured the Onpattro group.

Study ALN-TTR02-003

Study ALN-TTR02-003 was a multinational, multicentre, Phase II, open label, extension study designed to provide long term (up to 2 years) Onpattro dosing to patients with hATTR amyloidosis with polyneuropathy who received and tolerated Onpattro in Study ALN-TTR02-002. Patients could continue treatment in Study ALN-TTR02-006 after completion of this study. A total of 27 patients were enrolled and treated in Study ALN-TTR02-003. Twenty-five patients completed the study.

Study ALN-TTR02-006

Study ALN-TTR02-006 is an ongoing multicentre, multinational, open label extension study. Eligible patients who completed either of the two parent Studies ALN-TTR02-003 or -004, were given the option to participate in this study. At the time of the interim Study ALN-TTR02-006 data cutoff date (14 July 2017), Study ALN-TTR02-003 was completed and all 25 patients who completed Study ALN-TTR02-003 had enrolled in Study ALN-TTR02-006.

The three year efficacy and safety data from Study ALN-TTR02-006 are consistent with what has previously been observed with Onpattro in clinical studies and confirms the clinical efficacy and acceptable safety profile of Onpattro. These data also support early treatment intervention to avoid disease progression and that the effects of Onpattro are maintained with continued treatment. No new safety signals emerged in patients with long term Onpattro treatment.

Efficacy conclusions

The clinical data from Study ALN-TTR02-004 show a convincing difference between Onpattro and placebo regardless of baseline disease stages at inclusion for the studied population. However, there is only very limited data in patients with more severe disease and it is therefore not found adequate to extrapolate the results from less severe to more advanced stages of the disease (polyneuropathy disability stage IV/familial amyloidotic polyneuropathy stage 3 = non ambulatory patients).

Significant effects were seen on the primary and secondary endpoints related to polyneuropathy. However, the study population was restricted to subjects with polyneuropathy but still ambulant, that is more severely affected subjects were excluded. Cardiac endpoints were

only exploratory and subjects with a severe cardiac involvement were excluded, and hence a broader indication of 'adult hATTR' is not supported.

The available data supports the following indication:

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

Safety

In general, study treatment was well tolerated, with most adverse events (AE) being mild or moderate in severity. Common treatment related AEs included mild or moderate infusion related reactions that required no intervention or were easily managed. Deaths, serious adverse event (SAE), severe AEs, and AEs leading to study withdrawal were more frequently reported for the placebo group compared to the Onpattro groups.

The safety profile was consistent across disease stages, across the studies and post-market data.

Overall the favourable effects on neuropathy observed in the studies conducted to date appear to outweigh the unfavourable effects in the population studied, that is hATTR amyloidosis patients with familial amyloidotic polyneuropathy stage I and II. It is notable that there are uncertainties associated with the clinical relevance of results on cardiac parameters, considering the pronounced effect of patisiran on neurological endpoints and the biological plausibility of an effect also on other manifestations of the disease (supported by the mechanism of action of patisiran and the pathophysiology of the condition).

Known important risks include infusion related reactions. Infusion related reactions were shown to occur commonly in the clinical trial program and PBRER's. They can generally be managed with pre-medication and /r slowing or temporarily stopping the infusion.

Important potential risks include vitamin A deficiency and severe hypersensitivity.

The overseas regulator noted that:

> 'Further, the efficacy in patients whose disease is dominated by cardiac manifestations has not been evaluated separately. The results of the pivotal study shows a statistically significant effect on several measured echocardiographic variables as well as on NT-proBNP, favoring Onpattro compared to placebo. However, it is unclear if these surrogate markers are predictive of clinically relevant outcomes.'

The overseas regulator noted that:

> 'The cardiac dysfunction needs to be observed on a long-term way to draw robust conclusion of any beneficial effect considering that the cardiac disease evolves slowly stretched during 4 to 5 years usually.'

The post-market data showed infusion related reactions are a known serious adverse event associated with Onpattro treatment. Further post-market data to the present date, and updated results from all clinical studies should be requested from the sponsor.

Missing information:

- Longer term safety (> 3 years)
- Use in patients with moderate or severe hepatic impairment.
- Use in patients with severe renal impairment or end stage renal disease.
- Use in patients with prior liver transplantation.
- Use in pregnant or lactating women and effects on pregnancy outcomes.

Data have been provided out to 3 years, which supports safety in the medium term.

Following review of the data presented in second round of evaluation, the benefit/risk profile of Onpattro remains positive for the indications proposed.

Conditions of registration:

- Provide updated data from all ongoing studies as they become available.
- Provide updated post-market data in the form of PSUR's /PBRERs as they become available.

Risk management plan

The summary of safety concerns is acceptable from a risk management perspective. Routine pharmacovigilance activities are proposed for all safety concerns. Routine and additional risk minimisation activities have been proposed. The additional activities include educational materials for healthcare professionals and patients for minimising the risk of infusion-related reactions when Onpattro is administered in the home setting.

Proposed action

The Delegate considered that there are sufficient data to support the efficacy of Onpattro for the proposed indication and the overall safety profile is considered acceptable. The benefit/risk profile appears to be positive.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Onpattro (patisiran) 10 mg/5 mL, concentrated injection for infusion, vial indicated for:

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

Specific conditions of registration applying to these goods

- Onpattro (patisiran) is to be included in the Black Triangle Scheme. The PI and CMI for Onpattro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Onpattro EU-RMP (version 1.0, dated 25 July 2018, data lock point 14 September 2017), with ASA (version 0.2, dated 14 July 2022), included with submission PM-2021-05675-1-1, to be revised to the satisfaction of the TGA, and any subsequent revisions, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Provide updated data from all ongoing studies as they become available.
- Provide updated post-market data in the form of PSURs/PBRERs as they become available.

Attachment 1. Product Information

The PI for Onpattro approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #