Long-term efficacy and safety of patisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy: Interim 1-year results from an open-label extension study

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Summary

Background Hereditary transthyretin (ATTRv) amyloidosis is a rare, inherited, progressive disease caused by mutations in the transthyretin (*TTR*) gene. We aimed to assess the efficacy and safety of long-term treatment with patisiran, an RNA interference therapeutic that inhibits TTR production, in patients with ATTRv amyloidosis with polyneuropathy.

Methods This multi-country, multi-centre, open-label extension (OLE) trial enrolled patients at 43 sites in 19 countries as of 24 September 2018. Patients were eligible if they had completed the phase 3 APOLLO (randomised, double-blind, placebo-controlled [2:1], 18-month study) or phase 2 OLE (single-arm, 24-month study) parent studies and tolerated the study drug. Eligible patients from APOLLO (APOLLO-patisiran [received patisiran during APOLLO] and APOLLO-placebo [received placebo during APOLLO] groups) and the phase 2 OLE (phase 2 OLE patisiran group) studies enrolled in this Global OLE trial and receive patisiran 0·3 mg/kg by intravenous infusion every 3 weeks for up to 5 years. Efficacy assessments include measures of polyneuropathy (modified Neuropathy Impairment Score +7 [mNIS+7]), quality of life, autonomic symptoms, nutritional status, disability, ambulation status, motor function, and cardiac stress. Patients included in the current efficacy analyses are those who had completed 12-month efficacy assessments as of the data cut-off. Safety analyses included all patients who received ≥1 dose of patisiran up to the data cut-off. The Global OLE is ongoing with no new enrolment, and current findings are based on the 12-month interim analysis. The study is registered with ClinicalTrials.gov, NCT02510261.

Findings Between 13 July 2015 and 21 August 2017, 211/212 patients were enrolled: 137, 49, and 25 patients from the APOLLO-patisiran, APOLLO-placebo, and phase 2 OLE patisiran groups, respectively. At the data cut-off on 24 September 2018, 126/137 (92%), 38/49 (78%), and 25/25 (100%) patients in the APOLLO-patisiran, APOLLO-placebo, and phase 2 OLE patisiran groups, respectively, had completed 12-month assessments. At 12 months, improvements in mNIS+7 with

patisiran in parent studies were sustained from parent study baseline with treatment in the Global OLE (mean change [95% CI], –4·0 [–7·7 to −0·3] APOLLO-patisiran; –4·7 [–11·9 to 2·4] phase 2 OLE patisiran). Mean mNIS+7 score improved from Global OLE enrolment in the APOLLO-placebo group (mean change from Global OLE enrolment [95% CI] −1·4 [–6·2 to 3·5]). Overall, 204/211 (97%) patients reported adverse events (AEs), 82/211 (39%) reported serious AEs, and there were 23/211 (11%) deaths. Serious AEs were more frequent in the APOLLO-placebo group (28/49 [57%]) than in the APOLLO-patisiran (48/137 [35%]) or phase 2 OLE patisiran (6/25 [24%]) groups. The most common treatment-related AE was mild or moderate infusion-related reactions. The frequency of deaths in the Global OLE was higher in the APOLLO-placebo group (13/49 [27%]), who had greater disease burden at Global OLE enrolment, than the APOLLO-patisiran (10/137 [7%]) and phase 2 OLE patisiran (0/25 [0%]) groups.

Interpretation Patisiran demonstrates maintained efficacy with an acceptable safety profile in patients with ATTRv amyloidosis with polyneuropathy. Those receiving delayed treatment accumulated greater disease burden while untreated but benefited after initiating treatment, highlighting the need for early treatment to prevent deterioration. The continued long-term follow-up of patients in this Global OLE study will be important for the overall assessment of the efficacy and safety with patisiran.

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Introduction

Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv (v for variant) amyloidosis, is a rare, inherited, progressive disease caused by mutations in the transthyretin (*TTR*) gene that result in misfolded TTR accumulating as amyloid deposits in multiple organs and tissues, including somatic and autonomic nerves and the heart.[1-3] The majority of patients develop a mixed

phenotype of both polyneuropathy and cardiomyopathy,[4-7] and experience rapid progression after clinical disease onset.[1] The median survival for untreated patients is 4·7 years following diagnosis, with reduced survival (median 3·4 years)[8] for patients presenting with cardiomyopathy.[9] Risk factors for poor prognosis include advanced polyneuropathy, non-V30M (*p.* V50M) genotype with late-onset disease (>50 years), and cardiac involvement.[8,9] Treatments such as orthotopic liver transplantation (OLT)[10] and TTR stabilisers (tafamidis,[11] diflunisal[12]) may slow the natural progression of ATTRv amyloidosis in the early stages of the disease, yet worsening of neurological function and quality of life (QOL) are often observed[11] (due to continuing deposition of wild-type [wt] TTR in the case of OLT).[10]

Patisiran is a lipid nanoparticle RNA interference (RNAi) therapeutic that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing mutant and wt TTR proteins,[13] thereby reducing the source of amyloid fibrils. The phase 3 placebo-controlled APOLLO study and the phase 2 open-label extension (OLE) study demonstrated that patisiran achieved robust, rapid, and sustained reduction of serum TTR levels from baseline in patients with ATTRv amyloidosis with polyneuropathy.[6,14] In the 18-month APOLLO study, patients treated with patisiran 0·3 milligrams/kilogram (mg/kg) intravenous (IV) infusion every 3 weeks (q3w) compared with placebo improved in autonomic, sensory, and motor neuropathy as measured by the primary endpoint modified Neuropathy Impairment Score +7 (mNIS+7) as well as across all secondary endpoints including QOL, motor strength, disability, gait speed, nutritional status,[6,15] and exploratory cardiac structure/function endpoints in the pre-specified cardiac sub-population.[16] Patisiran also improved endpoints related to polyneuropathy and QOL, such as mNIS+7 and Norfolk QOL-Diabetic Neuropathy questionnaire (Norfolk QOL-DN), at 18 months compared with baseline in the majority (56% and 51%, respectively) of patients, suggesting reversal of the polyneuropathy of the disease.[6] In APOLLO, the majority of adverse events (AEs) observed were mild or moderate in intensity and the frequency of severe AEs and serious adverse events (SAEs) were similar between the patisiran and placebo groups.[6] The primary objective of the 24-month phase 2 OLE was to evaluate the safety

and tolerability of patisiran, and the study demonstrated both safety and secondary efficacy results consistent with those reported in APOLLO.[14] Eligible patients who completed APOLLO (patisiran or placebo arm) or the phase 2 OLE were able to enrol into the Global OLE which aims to assess the long-term efficacy and safety of patisiran in patients with ATTRv amyloidosis with polyneuropathy. Here, interim efficacy and safety data from the ongoing Global OLE are discussed.

Methods

Study design and participants

The Global OLE (NCT02510261) is a multi-country, multi-centre, ongoing OLE trial which enrolled patients at 43 sites in 19 countries as of 24 September 2018 (appendix, p 3). Eligible patients included patients who completed the APOLLO or phase 2 OLE studies,[6,14] and, in the opinion of the investigator, tolerated the study drug.

This study is being conducted according to the guidelines of the International Conference on Harmonization, the World Health Organization Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996. Written informed consent was obtained from all patients before undergoing any protocol-specific tests or procedures that are not part of routine care. The study protocol (appendix, p 2) and all amendments were approved by the local Institutional Review Boards and Ethics Committees.

Randomisation and masking

Due to the nature of an OLE study, there was no randomisation or masking in the Global OLE study. However, the patients in the Global OLE came from one of the following three groups: APOLLO-placebo (received placebo in APOLLO; started patisiran in the Global OLE); APOLLO-patisiran (received patisiran in APOLLO; continued patisiran in the Global OLE); and phase 2 OLE patisiran (received patisiran in the phase 2 OLE; continued patisiran in the Global OLE).

APOLLO was a randomised, double-blind, placebo-controlled study in which patients were randomly assigned (2:1) to receive patisiran 0·3 mg/kg or placebo administered by IV infusion q3w for 18 months.[6] Patients were randomised via an interactive response system and treatment arms were further balanced at entry for Neurologic Impairment Score (NIS), early-onset V30M *vs* all other variants, and previous TTR stabiliser use. Further details of the randomisation and blinding process are described in the previously published APOLLO protocol (appendix, p 2). Key eligibility criteria for the APOLLO study included being 18–85 years of age; documented pathogenic *TTR* variant; diagnosis of ATTRv amyloidosis with polyneuropathy; a NIS of 5–130; and polyneuropathy disability (PND) score of IIIB or lower with adequate liver and renal function.[6] Patients with prior liver transplantation or who were New York Heart Association (NYHA) class III or IV were excluded.[6]

In the phase 2 OLE, multi-centre, international study,[14] patients who had previously received and tolerated patisiran in the phase 2 study (NCT01961921)[17] received 0·3 mg/kg patisiran via IV infusion q3w for 24 months.[14] Key eligibility criteria included Karnofsky Performance Status ≥60% and adequate liver and renal function. Patients with prior liver transplantation or who were NYHA class >II were excluded.[14]

Procedure

Patients enrolled in the Global OLE study receive patisiran 0·3 mg/kg IV q3w. The first dose was administered approximately 3 weeks after the last dose in the parent study, either APOLLO or the phase 2 OLE, to maintain the dosing schedule. Treatment is provided either at the study site or via home infusion by a trained healthcare professional where applicable country and local regulations allowed. All patients receive premedication (appendix, p 2) to reduce the potential of infusion-related reactions (IRRs) and continue to take vitamin A supplementation based on the US recommended daily allowance or, at the discretion of the investigator, the local recommended daily allowance of vitamin A.

Efficacy endpoints are measured at the study site or through a central assessment site and include assessments of polyneuropathy (mNIS+7); QOL (Norfolk QOL-DN); autonomic symptoms (Composite Autonomic Symptom Score 31 [COMPASS-31]); nutritional status (modified body mass index [mBMI]; kg/m^2 × albumin level in g/L); disability (Rasch-built Overall Disability Scale [R-ODS]); PND score; familial amyloid polyneuropathy (FAP) stage; motor function (10-metre walk test [10-MWT]; gait speed; grip strength); and cardiac stress (N-terminal prohormone of B-type natriuretic peptide [NT-proBNP] levels). Ranges for scored measures are given in the appendix, p 4. The outcomes listed above are included in this interim 12-month analysis; however, a full list of outcome measures to be collected during the 5-year study is provided in the appendix, p 5.

Serum TTR levels are measured before patisiran administration and were recorded at baseline, at month 6, and at each annual visit. Antidrug antibodies (serum immunoglobulin [Ig] G/IgM antibodies specific to α-(3-{[1,2-di(myristyloxy)proponoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene) are evaluated using a validated ELISA method[6] at month 6 and each annual visit.

AEs are recorded and clinical laboratory testing (haematology, blood chemistry, urinalysis), vital signs, physical examination, Columbia-Suicidality Severity Rating Scale, and ophthalmology testing are being conducted throughout the study. AEs are coded according to the Medical Dictionary for Regulatory Activities Version 18·0, and deaths are adjudicated as described in the appendix, p 6.

Outcomes

The Global OLE does not have pre-specified primary or secondary outcomes as part of the protocol (appendix, p 2). One-year efficacy outcomes included mean change from parent study baseline or Global OLE enrolment to after 12 months in the Global OLE in mNIS+7, Norfolk QOL-DN, COMPASS-31, mBMI, R-ODS, PND score, FAP stage, 10-MWT, grip strength, and NT-proBNP levels. Serum TTR

levels were measured as a pharmacodynamic outcome. Safety assessments included AE monitoring as well as clinical laboratory testing.

Statistical analysis

The sample size for this study was not pre-specified; all patients who completed the APOLLO or phase 2 OLE studies could enrol if they met the eligibility criteria. Efficacy analyses included data from patients who completed the 12-month efficacy assessment. Efficacy data are described either as integrated change from parent study baseline to Global OLE 12 months and/or change from Global OLE enrolment to Global OLE 12 months. Safety analyses included data for patients who received ≥1 dose of patisiran up to the data cut-off, including data beyond the 12-month assessment.

In a post hoc analysis, the integrated exposure-adjusted mortality rate (using pooled data for all patisiran-treated patients from the parent and Global OLE studies) was calculated overall and by treatment group as the total number of deaths per total patient-years of exposure ×100. Deaths occurring between the first patisiran dose and up to 90 days after the last dose were included in the calculation. Additional details are described in the appendix, p 2.

Categorical variables were reported as the number and percentage of patients. For continuous variables, mean, median, standard deviation (SD), standard error of the mean (SEM), 95% confidence intervals (CIs), interquartile range, and range were calculated. No formal significance tests were performed as this study did not include a comparator arm. SAS version 9.4 was used to conduct the statistical analyses. A data monitoring committee was not assigned to oversee this study. This trial is registered as NCT02510261.

Role of the funding source

Alnylam Pharmaceuticals funded the study and collaborated with authors during study design, collection, analysis, interpretation of data, and drafting/reviewing the article. The corresponding author had full access to all data in the study and final responsibility over the decision to submit for publication.

Results

Between 13 July 2015 and 21 August 2017, 211/212 patients (figure 1) enrolled at 43 sites in 19 countries. As of the data cut-off (24 September 2018), 34/211 (16%) patients had withdrawn from the study. Primary reasons for withdrawal (investigator determined) included death (21/211 [10%]), AEs (9/211 [4%]), physician decision (2/211 [1%]), and withdrawal (2/211 [1%]) (figure 1). The proportion of withdrawals in the APOLLO-placebo group (16/49 [33%]) was higher than in the APOLLO-patisiran (18/137 [13%]) and phase 2 OLE patisiran (0/25 [0%]) groups.

Twelve-month efficacy assessments were available for 189/211 (90%) patients (126/137 [92%], 38/49 [78%], and 25/25 [100%] patients in the APOLLO-patisiran, APOLLO-placebo, and phase 2 OLE patisiran groups, respectively). Patients had received patisiran for a mean (SD) of 20·5 (8·0) months and had a cumulative drug exposure of 359·6 patient-years (PY); 133/211 (63%) patients received all planned doses and 49/211 (23%), 16/211 (8%), and 13/211 (6%) patients missed 1, 2, and ≥3 doses, respectively. A total of 577/6005 (10%) infusions of patisiran were received at home by 26/211 (12%) patients**.**

At Global OLE enrolment, patients in the APOLLO-placebo group had higher NT-proBNP levels and more severe disease than patients in the APOLLO-patisiran and phase 2 OLE patisiran groups, as shown by mNIS+7, Norfolk QOL-DN, PND scores, COMPASS-31, and R-ODS (table 1). The phase 2 OLE patisiran group had a higher proportion of patients with the V30M genotype and less severe disease at Global OLE enrolment than patients in either APOLLO group.

The improvement in polyneuropathy with patisiran treatment, demonstrated by a negative change in mean mNIS+7 score relative to APOLLO and phase 2 OLE baseline, was maintained at Global OLE 12 months (mean change [95% CI], −4·0 [−7·7 to −0·3] APOLLO-patisiran; −4·7 [−11·9 to 2·4] phase 2 OLE patisiran) (figures 2A and 2B). The rapid polyneuropathy progression observed among APOLLO-placebo patients halted upon patisiran treatment in the Global OLE, with an improvement in mNIS+7 at Global OLE 12 months from Global OLE enrolment (mean change [95% CI], −1·4 [−6·2 to 3·5]). However, mean mNIS+7 score did not return to APOLLO baseline, likely due to the deterioration on placebo during APOLLO (mean change [95% CI] from APOLLO baseline to Global OLE 12 months +24·0 [15·4–32·5]).

Maintained improvement in QOL, shown by Norfolk QOL-DN, was observed in the APOLLO-patisiran group at Global OLE 12 months relative to APOLLO baseline (mean change [95% CI] –3·9 [–8·1 to 0·3]) (figure 2C). Among APOLLO-placebo patients, patisiran treatment in the Global OLE improved Norfolk QOL-DN (mean change [95% CI] from Global OLE enrolment to Global OLE 12 months –4·5 [–9·6 to 0·7]), halting the deterioration seen during APOLLO. As with the mNIS+7 score, QOL did not return to APOLLO baseline values in the Global OLE (mean change [95% CI] from parent baseline to Global OLE 12 months, +15·0 [8·1–21·9]).

Maintained improvement in autonomic function in the APOLLO-patisiran group (mean change [95% CI], –4·0 [–6·9 to –1·1]) and stabilisation in the phase 2 OLE patisiran group (mean change [95% CI], +0·1 [–4·2 to 4·4]), as measured by COMPASS-31, was seen at Global OLE 12 months compared with parent study baselines (figures 2D and 2E). Consistent with worsening disease, patients who received placebo experienced deterioration in autonomic function during APOLLO, but improvement was seen once they switched to patisiran in the Global OLE (mean change [95% CI] from Global OLE enrolment to Global OLE 12 months –3·7 [–8·0 to 0·6]). Nutritional status (mBMI) was maintained (APOLLO-patisiran and phase 2 OLE patisiran) from parent study baseline or improved (APOLLO-placebo) from Global OLE enrolment (figures 2F and 2G). However, COMPASS-31

and mBMI values did not return to APOLLO baseline in the APOLLO-placebo group due to deterioration experienced on placebo.

The R-ODS score declined slightly compared with parent study baseline in both the APOLLO-patisiran and phase 2 OLE patisiran groups (figures 2H and 2I). However, this decline was modest compared with the substantial worsening observed in the APOLLO-placebo group during APOLLO. Disability among the APOLLO-placebo patients stabilised once they started receiving patisiran.

Compared with parent study baselines, the majority of patients in the APOLLO-patisiran and phase 2 OLE patisiran groups had an improved or stable PND score at Global OLE 12 months (89/148 [60%] APOLLO-patisiran, 17/27 [63%] phase 2 OLE patisiran) (appendix, p 7). The majority of patients in the APOLLO-placebo group demonstrated stable or improved scores at Global OLE 12 months after receiving patisiran treatment in the Global OLE. Similar results were observed with FAP stage (appendix, p 7). Additional clinical and functional parameters, including 10-MWT and grip strength, either improved or stabilised at Global OLE 12 months from the initiation of patisiran treatment among the three groups (appendix, p 8).

NT-proBNP levels were stable in both groups previously treated with patisiran from Global OLE enrolment to Global OLE 12 months. In the APOLLO-placebo group, NT-proBNP levels worsened during APOLLO, but improved once patisiran treatment was initiated (appendix, p 8).

Robust, sustained reduction in mean serum TTR levels was observed in the APOLLO-placebo group upon patisiran treatment in the Global OLE, with a mean (SD) percent TTR reduction of 78·7% (17·1%) at month 6 (appendix, p 19). Serum TTR reductions in APOLLO-patisiran and phase 2 OLE patisiran groups were maintained with continued patisiran in the Global OLE. Antidrug antibody incidence was low (1/211 patient [<1%] at week 26 only) and transient.

Safety outcomes as of the data cut-off of 24 September 2018 are shown in table 2. In total, 204/211 (97%) patients reported AEs. The majority of AEs were mild or moderate in severity. The

most common treatment-related AE was mild or moderate IRRs (eg, back pain, flushing, or rash), which occurred in 25/211 (12%) patients (appendix, p 9); the incidence of IRRs decreased over time. The proportion of patients experiencing IRRs was higher in those newly treated with patisiran in the Global OLE (APOLLO-placebo, 13/49 [27%]) than those who previously received patisiran (APOLLO-patisiran, 10/137 [7%]; phase 2 OLE patisiran, 2/25 [8%]). There were no serious IRRs or discontinuations due to IRRs. IRRs occurred in 4/26 (15%) patients who had home infusions and were generally mild, transient, and readily managed without interruption of the infusion due to the IRR.

SAEs were reported for 82/211 (39%) patients and were most frequent among patients in the APOLLO-placebo group (28/49 [57%]) (table 3). Two out of 211 patients (1%), both in the APOLLO-placebo group, had SAEs that were considered treatment-related, 1 patient with abdominal discomfort and 1 patient with two events associated with extravasation of study drug and reported as phlebitis, cellulitis, hypotension, bacteraemia, and systemic inflammatory response syndrome. Cardiac AEs and SAEs were reported in 44/211 (21%) and 31/211 (15%) patients, respectively; no cardiac AEs were considered related to study drug. Frequencies of cardiac AEs (16/49 [33%]) and cardiac SAEs (11/49 [22%]) were higher in the APOLLO-placebo group compared with other groups.

No clinically relevant safety concerns were identified related to hepatic events, renal events, malignancies, ocular events, metabolic events, and thyroid disorders. No clinically relevant changes were observed in laboratory values (including platelet count), vital signs, and physical examination findings (including ophthalmology examinations) during the Global OLE study.

The frequency of deaths in the Global OLE was higher in the APOLLO-placebo group (13/49 [27%]) than the APOLLO-patisiran (10/137 [7%]) and phase 2 OLE patisiran (0/25 [0%]) groups. Causes of death were consistent with the natural history of ATTRv amyloidosis, with most patients who died having known risk factors for poor prognosis (non-V30M genotype, advanced age, advanced disease status, long duration of disease, advanced neuropathic and cardiac involvement)

and marked disease burden at Global OLE enrolment (17/23 [74%] patients had PND ≥IIIA, including 14/23 (61%) PND ≥IIIB, and 20/23 [87%] patients had NT-proBNP ≥600 pg/mL, including 10/23 [43%] patients with NT-proBNP ≥3000 pg/mL). Investigator-reported causes of death (n=1 for each event unless otherwise specified) include acute myocardial infarction (n=3), cardiac arrest (n=3), amyloidosis (n=3), acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, arrhythmia, atrial flutter, cardiogenic shock, cardiopulmonary failure, cerebrovascular accident, chronic kidney disease, death (cause unknown), dehydration, electrolyte imbalance, hip fracture, haemorrhagic shock, hypovolaemic shock, neurogenic shock, pancreatitis, and septic shock (appendix, p 6). None of the 23/211 (11%) deaths during the Global OLE reporting period were considered treatment-related by investigators.

Across the three studies (phase 2 OLE, APOLLO, and Global OLE), a total of 224 patients received ≥1 dose of patisiran, with some patients receiving ≥4 years of patisiran treatment. Overall mean (SD) exposure was 34·0 months (14·5) with 104/224 (46%) patients treated for ≥3 years and 35/224 (16%) for ≥4 years. As of the data cut-off, the overall exposure-adjusted mortality rate for all patisiran-treated patients was 4·8 per 100 PY (95% CI 3·3–6·7), based on 30 deaths and 629·4 PY cumulative exposure (appendix, p 10). In a post hoc analysis, the exposure-adjusted mortality rate was lowest for patients from the phase 2 OLE, who were treated the longest and from the earliest stage of disease, and lower in APOLLO-patisiran compared with APOLLO-placebo patients (appendix, p 10).

In the APOLLO study, the exposure-adjusted mortality rate was lower in patients who received patisiran (3·2 per 100 PY [95% CI 1·4–6·2]) than placebo (6·2 per 100 PY [95% CI 2·5–12·7]). A post hoc analysis to account for the effect of important imbalances between treatment groups showed that exposure-adjusted mortality rates remained consistently lower in patients who received patisiran versus placebo (appendix, p 20).

Discussion

Patients in this study represent those with the longest treatment duration with an RNAi therapeutic to date. The Global OLE enrolled patients with ATTRv amyloidosis with polyneuropathy with a wide range of disease severity who had previously received either patisiran or placebo in APOLLO, or patisiran in the phase 2 OLE study. The beneficial effects of patisiran on polyneuropathy, QOL, autonomic symptoms, nutritional status, motor function, disability, and cardiac stress were sustained at Global OLE 12 months, demonstrating maintenance of patisiran efficacy with continued treatment. Additionally, patisiran continued to demonstrate an acceptable safety profile.

Patients who received placebo during APOLLO had accumulated greater disease burden compared with those who had received patisiran. Despite disease progression in APOLLO, these patients exhibited stabilisation or improvement compared with Global OLE enrolment in mean mNIS+7, Norfolk QOL-DN, COMPASS-31, mBMI, and NT-proBNP levels following 12 months of patisiran treatment in the Global OLE. However, their neurological disability and mortality rate remained higher than in patients who received patisiran in the parent studies, underscoring the importance of treatment at the earliest disease stage possible. This strategy is also supported by the observation that patients from the phase 2 OLE, who had less advanced disease at patisiran initiation and were treated for the longest time, did not experience disease progression across a number of measures.

Consistent with patisiran's treatment hypothesis, reduction in serum TTR levels with patisiran treatment was maintained at Global OLE 12 months for the APOLLO-patisiran and phase 2 OLE patisiran groups and was also observed in the APOLLO-placebo group after initiation of patisiran treatment.

The patisiran safety profile remained consistent with previous studies.[6,14,17] During the Global OLE, IRRs were more frequently reported in the APOLLO-placebo group compared with the

APOLLO-patisiran and phase 2 OLE patisiran groups which was expected, as IRRs tend to decrease in frequency with subsequent infusions.

In the Global OLE, deaths occurred most frequently in the APOLLO-placebo group, which had the greatest disease burden at Global OLE enrolment and could be considered at an advanced stage of the disease (eg, higher PND scores, higher NYHA class scores, worse mNIS+7 scores, worse Norfolk QOL-DN scores, and higher NT-proBNP levels). As more severe disease is associated with mortality, this higher death rate is expected despite the positive effects of patisiran in preventing further progression. The mortality rate was lowest in the phase 2 OLE patisiran group, which included patients with the least advanced disease at baseline, further supporting the need for early treatment. None of the deaths reported were considered to be treatment related.

The exposure-adjusted mortality rate observed at interim analysis across all patisiran-treated patients from APOLLO, phase 2 OLE, and Global OLE (4·8 deaths/100 PY) was at the lower end of the expected range based on disease progression of ATTR amyloidosis estimated from natural history studies and placebo data from clinical trials (range 7–29 deaths/100 PY), especially for those who started patisiran treatment early in the disease course.[9,12,18-20] This corroborates findings from APOLLO, which demonstrated lower exposure-adjusted mortality rates with patisiran versus placebo. Despite accounting for non-V30M genotype and elevated NT-proBNP, known risk factors for mortality, the point estimates of the exposure-adjusted mortality rate were lower in the patisiran group compared with the placebo group in the APOLLO study.[16,21-23] These data, when coupled with the favourable safety data reported with inclisiran (over 2700 PY of exposure in patients with cardiovascular disease) and the FDA approval of givosiran, continue to support the safety and potential of RNAi therapeutics.[24,25]

The Global OLE encompasses a large number of patients with a broad spectrum of disease from many countries in order to assess the efficacy and safety of long-term patisiran treatment in patients with ATTRv amyloidosis with polyneuropathy. However, this report is an interim analysis

and is potentially limited by the need to evaluate whether the clinical benefits are maintained to the end of the study. The population for this study was self-selected from previous patisiran studies and therefore open to selection bias. However, it should be noted that potential bias was minimised by the very high retention rate of eligible patients (211/212 [99·5%]). Other limitations include the unblinded nature of an open-label study (which could potentially influence patient responses to assessments), fewer patients in the APOLLO-placebo group compared with the APOLLO-patisiran group (due to the 2:1 randomisation in APOLLO), and the lack of a placebo group to compare data against. Additionally, the results are descriptive and no inferential analyses were performed.

The overall findings of the 12-month interim data from the Global OLE study underscore the importance of patisiran treatment early in the disease course to halt or reverse the progression of polyneuropathy, dysautonomia, disability, malnutrition, and QOL impairment. Delay in treatment may negatively impact outcomes, including survival, and therefore the data here along with future and ongoing real-world studies in this disease aim to further emphasise the role of early diagnosis and treatment.

Research in context

Evidence before this study

We searched PubMed, www.clinicaltrials.gov, and abstracts presented at international congresses (International Society of Amyloidosis, European Meetings on transthyretin-mediated amyloidosis for Doctors and Patients, International Congress on Neuromuscular Diseases, and Peripheral Nerve Society from 1 July 2015 to 30 June 2020 to identify publications describing the burden of hereditary transthyretin (ATTRv) amyloidosis, and clinical data for treatments investigated for this disease. The following search terms were used: ‘ATTRv amyloidosis’, ‘hATTR amyloidosis’, ‘familial amyloid

polyneuropathy', 'familial amyloid cardiomyopathy', 'FAP', and 'FAC'. Publications describing individual case studies or preclinical investigations of pharmacotherapies were excluded. The existing evidence indicates that ATTRv amyloidosis is a progressively debilitating disease, associated with multisystem involvement, for which only a limited number of therapies are approved or available. Of these therapies, patisiran is an RNA interference (RNAi) therapeutic that has been shown to reduce levels of the disease-causing transthyretin (TTR) protein. Patisiran demonstrated a positive benefit-risk profile in a previous 18-month phase 3 study (APOLLO; NCT01960348) in patients with ATTRv amyloidosis with polyneuropathy.

Added value of this study

To our knowledge, this 12-month interim analysis of an open-label extension (OLE) study reports the longest duration of treatment with an RNAi therapeutic, patisiran, in patients with ATTRv amyloidosis with polyneuropathy. The data reported here show that treatment with patisiran led to improvement or sustained stability in measures of polyneuropathy (modified Neuropathy Impairment Score +7), quality of life (Norfolk QOL-Diabetic Neuropathy questionnaire), autonomic function (Composite Autonomic Symptom Score 31), disability (Rasch-built Overall Disability Scale), and nutritional status (modified body mass index) compared with their treatment-naïve baseline values. Overall, these findings indicate that halting or reversing progression of polyneuropathy is achievable and can be maintained in patients with ATTRv amyloidosis with polyneuropathy.

The study also showed the acceptable safety profile of long-term patisiran treatment in patients with ATTRv amyloidosis with polyneuropathy. The overall mortality rate on patisiran is at the lower end of the expected range based on disease natural history data.

Implications of all the available evidence

The 12-month interim data show that efficacy and safety of patisiran is consistent with results previously reported in the phase 2 OLE and APOLLO studies. The long-term benefits beyond this interim report require further follow-up.

Contributors

MTSw performed the literature search. DA, TC, MTSw, and MTW contributed to the conception and design of the study. EA, EB, MTSw, and MTW helped to analyse the data. IMC, JJW, and MW-C assisted with data collection. EA, JDG, and MSS assisted with figures and writing. JV contributed to data analysis and writing. DA, SA-D, SA, JLB, THB, TC, AD, AG-D, AVK, TK, IALL, EM, MMM, VP-B, MP, DQ, HHS, MTSw, MU, MTW, EB, and JW all contributed to data collection, figures, and writing. JJW was also responsible for medical monitoring of the clinical trial. All authors helped to interpret the data and critically revise the publication, are accountable for the accuracy and integrity of the publication and provided final approval to submit for publication.

Declaration of interests

DA reports consultancy fees and institutional grants from Alnylam Pharmaceuticals and Pfizer Inc. and symposium honoraria from Pfizer Inc. outside the submitted work. SA-D reports personal fees from Alnylam Pharmaceuticals outside the submitted work. SA reports grants from Alnylam Pharmaceuticals and Pfizer Inc. outside the submitted work. JLB acknowledges study investigator and coordination time and hospital services compensation from Alnylam Pharmaceuticals for the work under consideration; personal fees for a visiting Professor presentation from Alnylam Pharmaceuticals, advisory committee from Akcea Therapeutics, study investigator and coordinator compensation from Pfizer Inc. and scientific advisory board fees from Intellia Therapeutics and Corino Therapeutics outside the submitted work. THB reports grants and personal fees from Alnylam Pharmaceuticals during the conduct of the study; grants and personal fees from Ionis Pharmaceuticals and personal fees from Akcea Therapeutics and Pfizer Inc. outside the submitted

work. TC reports financial support to attend scientific meetings from Pfizer Inc. and personal fees from Alnylam Pharmaceuticals and Akcea Therapeutics outside the submitted work. IMC reports primary investigator fees from Alnylam Pharmaceuticals during the conduct of the study and consultancy fees from Pfizer Inc and Ionis Pharmaceuticals and primary investigator fees from Ionis Pharmaceuticals outside the submitted work. AD acknowledges research funding from Pfizer Inc., Celgene Corporation, Alnylam Pharmaceuticals, Takeda Pharmaceuticals, Akcea Therapeutics, and Prothena Corporation, advisory board fees from Caelum Biosciences, and institutional funding for advisory board participation from Intellia Therapeutics outside the submitted work. JDG reports institutional grants from Alnylam Pharmaceuticals during the conduct of the study and honoraria for an expert advisory board from Alnylam Pharmaceuticals outside the submitted work. AG-D reports consultancy fees from Alnylam Pharmaceuticals and Pfizer Inc. outside the submitted work. AVK reports honoraria, fees for lectures and speakers' bureaus. IALL acknowledges personal fees, non-financial support, and other support outside the submitted work. EM reports honorarium paid to her institution (Mayo Clinic) from Alnylam Pharmaceuticals for symposium speaking. MMM reports pending honorarium for poster presentation and principal investigator fees from Alnylam Pharmaceuticals during the conduct of the study; speaker and advisory board fees from Alnylam Pharmaceuticals, Akcea Therapeutics, and Pfizer Inc., and non-financial support from Alnylam Pharmaceuticals outside the submitted work. VP-B reports principal investigator and advisory board fees from Alnylam Pharmaceuticals and principal investigator and symposium speaker fees from Ionis/Akcea Therapeutics, during the conduct of the study. MP acknowledges consultancy and principal investigator fees from Alnylam Pharmaceuticals in relation to this work and consultancy and principal investigator fees from Alnylam Pharmaceuticals and Ionis Pharmaceuticals, and consultancy fees from Eidos and Pfizer Inc. outside the submitted work. DQ reports grants, personal fees and non-financial support from Alnylam Pharmaceuticals; grants and non-financial support from Pfizer and Cytokinetics; and grants from Ionis, Momenta, and Argenx during the conduct of the study. MSS reports consultancy fees and symposium and advisory board participation honoraria

from Alnylam Pharmaceuticals and Pfizer Inc. outside the submitted work. MU acknowledges personal fees and non-financial support for advisory board participation, travel, and speaking from Alnylam Pharmaceuticals and Pfizer Inc. outside the submitted work. MW-C reports honorarium from NHI, Prothena Corporation, FoldRx, Ionis Pharmaceuticals, Pfizer Inc., Alnylam Pharmaceuticals, PTC, and Genzyme for travel expenses related to presentations at medical meetings, for acting as a principal investigator in clinical trials, and as a consultant. JW reports advisory board and lecture fees from Alnylam Pharmaceuticals, Pfizer Inc., and Akcea Therapeutics outside the submitted work. TK and HHS have nothing to disclose. EA, MTSw, JV, and MTW are employees of Alnylam Pharmaceuticals; in addition, EA, MTSw, JV, and MTW have stock options and EA, MTSw, JV, and MTW have stocks. EB and JJW are former employees of Alnylam Pharmaceuticals and had stock options.

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Data sharing

The datasets generated and analysed during the current study are not publicly available.

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Figure legends

Figure 1: **Patient disposition**

AE=adverse event. OLE=open-label extension.

Figure 2: **Integrated changes in: mNIS+7 from (A) APOLLO and (B) the phase 2 OLE and the Global OLE; (C) Norfolk-QOL-DN from APOLLO and the Global OLE; COMPASS-31 from (D) APOLLO and (E) the phase 2 OLE and the Global OLE; mBMI from (F) APOLLO and (G) the phase 2 OLE and the Global OLE; and in R-ODS from (H) APOLLO and (I) the phase 2 OLE and the Global OLE**

For APOLLO patients initiating alternative ATTRv amyloidosis treatment, mNIS+7 and Norfolk QOL-DN assessments after alternative treatment are treated as missing. Norfolk QOL-DN was not administered in the phase 2 OLE and therefore change over time was not evaluated. ATTRv=hereditary transthyretin. CI=confidence interval. COMPASS-31=Composite Autonomic Symptom Score 31. mBMI=modified body-index. mNIS+7=modified Neuropathy Impairment Score +7. Norfolk QOL-DN=Norfolk Quality of Life-Diabetic Neuropathy questionnaire. OLE=open-label extension. R-ODS=Rasch-built Overall Disability Scale. [*]APOLLO-placebo: received placebo in APOLLO and started patisiran for the first time in the Global OLE. [†]APOLLO-patisiran: received patisiran for 18 months in APOLLO and continued to receive patisiran in the Global OLE. [‡]Phase 2 OLE patisiran: received patisiran for 24 months and continued to receive patisiran in the Global OLE.

Figure 1

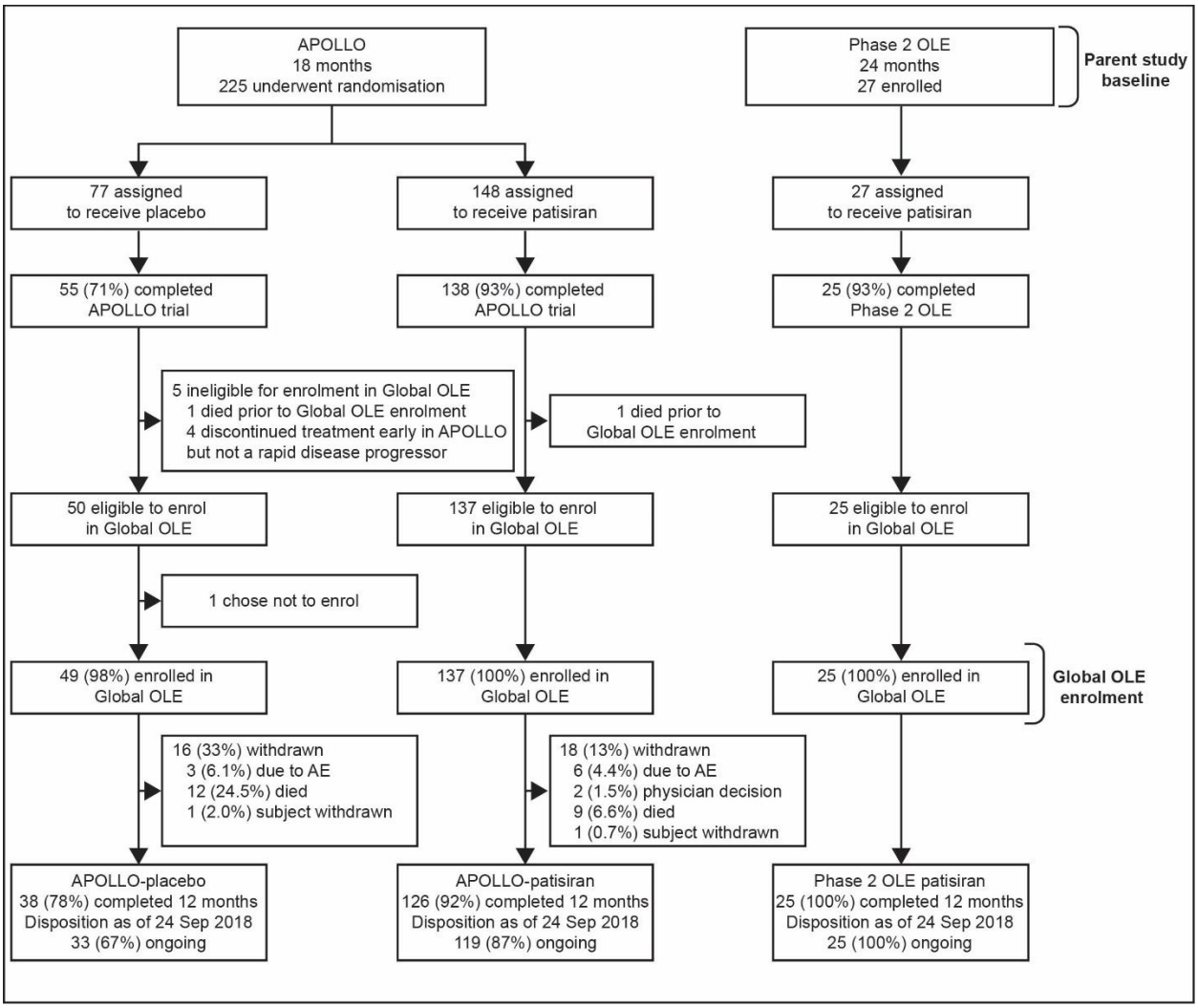
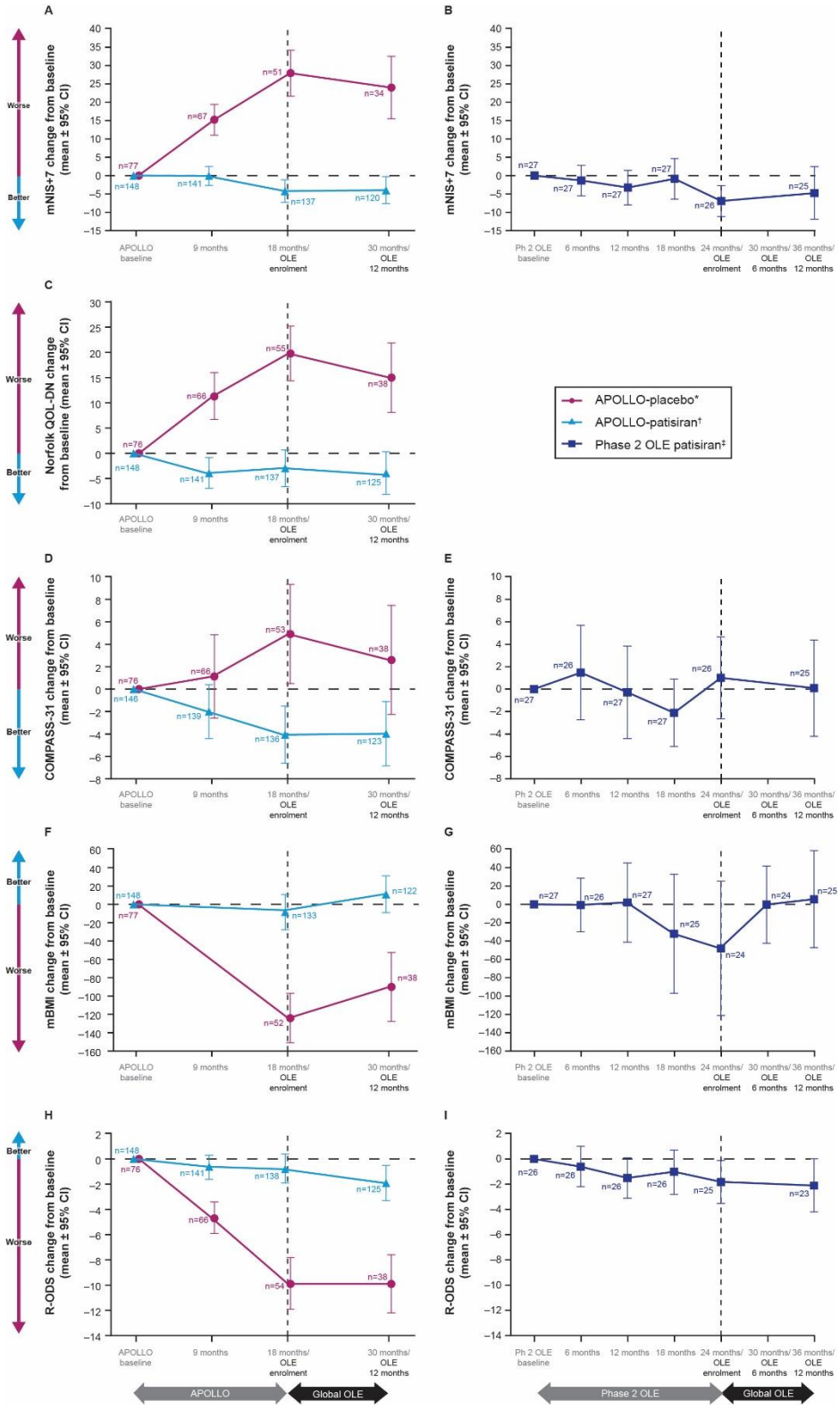

APOLLO
18 months
225 underwent randomisation
Phase 2 OLE
24 months
27 enrolled
Parent study baseline
77 assigned to receive placebo
148 assigned to receive patisiran
27 assigned to receive patisiran
55 (71%) completed APOLLO trial
138 (93%) completed APOLLO trial
25 (93%) completed Phase 2 OLE
5 ineligible for enrolment in Global OLE
1 died prior to Global OLE enrolment
4 discontinued treatment early in APOLLO but not a rapid disease progressor
1 died prior to Global OLE enrolment
50 eligible to enrol in Global OLE
137 eligible to enrol in Global OLE
25 eligible to enrol in Global OLE
1 chose not to enrol
49 (98%) enrolled in Global OLE
137 (100%) enrolled in Global OLE
25 (100%) enrolled in Global OLE
Global OLE enrolment
16 (33%) withdrawn
3 (6.1%) due to AE
12 (24.5%) died
1 (2.0%) subject withdrawn
18 (13%) withdrawn
6 (4.4%) due to AE
2 (1.5%) physician decision
9 (6.6%) died
1 (0.7%) subject withdrawn
APOLLO-placebo
38 (78%) completed 12 months
Disposition as of 24 Sep 2018
33 (67%) ongoing
APOLLO-patisiran
126 (92%) completed 12 months
Disposition as of 24 Sep 2018
119 (87%) ongoing
Phase 2 OLE patisiran
25 (100%) completed 12 months
Disposition as of 24 Sep 2018
25 (100%) ongoing

Figure 2


A
B
C
D
E
F
G
H
I
Worse
Better
mNIS+7 change from baseline (mean ± 95% CI)
Norfolk QOL-DN change from baseline (mean ± 95% CI)
COMPASS-31 change from baseline (mean ± 95% CI)
mBMI change from baseline (mean ± 95% CI)
R-ODS change from baseline (mean ± 95% CI)
APOLLO baseline
9 months
18 months/ OLE enrolment
30 months/ OLE 12 months
Ph 2 OLE baseline
6 months
12 months
18 months
24 months/ OLE enrolment
30 months/ OLE 6 months
36 months/ OLE 12 months
APOLLO-placebo*
APOLLO-patisiran†
Phase 2 OLE patisiran‡
APOLLO
Global OLE
Phase 2 OLE

Parameter	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)	Global OLE total (n=211)
Age, years, mean (SD)	63·5 (11·0)	61·0 (12·1)	58·5 (15·1)	61·3 (12·3)
Sex, n (%)				
Male	37/49 (76)	102/137 (74)	17/25 (68)	156/211 (74)
Female	12/49 (24)	35/137 (26)	8/25 (32)	55/211 (26)
Ethnicity, n (%)*				
Asian	14/49 (29)	23/137 (17)	0/25 (0)	37/211 (18)
Black	0/49 (0)	4/137 (3)	0/25 (0)	4/211 (2)
White	34/49 (69)	107/137 (78)	25 (100)	166/211 (79)
Other	0/49 (0)	1/137 (1)	0/25 (0)	1/211 (<1)
>1 race	0/49 (0)	2/137 (1)	0/25 (0)	2/211 (1)
Missing	1/49 (2)	0/137 (0)	0/25 (0)	1/211 (<1)
Region†, n (%)				
North America	5/49 (10)	34/137 (25)	1/25 (4)	40/211 (19)

Western Europe	26/49 (53)	61/137 (45)	23/25 (92)	110/211 (52)
Rest of world	18/49 (37)	42/137 (31)	1/25 (4)	61/211 (29)
Time since ATTRv amyloidosis diagnosis, years, median (IQR)				
To entry into Global OLE	2·8 (2·0, 5·4)	3·0 (2·1, 4·2)	4·8 (4·0, 5·6)	3·4 (2·2, 5·0)
To time of first patisiran dose[‡]	2·9 (2·1, 5·5)	1·4 (0·6, 2·7)	2·7 (1·9, 3·5)	2·1 (1·0, 3·5)
Genotype, n (%)				
V30M	24/49 (49)	56/137 (41)	18/25 (72)	98/211 (46)
Non-V30M	25/49 (51)	81/137 (59)	7/25 (28)	113/211 (54)
Concurrent TTR tetramer stabiliser use[§], n (%)	2/49 (4)	0/137 (0)	13/25 (52)	15/211 (7)
PND score, n (%)				
0: no symptoms	0/49 (0)	1/137 (1)	0/25 (0)	1/211 (<1)
I: preserved walking, sensory disturbances	7/49 (14)	32/137 (23)	10/25 (40)	49/211 (23)
II: impaired walking but can walk without stick/crutch	9/49 (18)	36/137 (26)	13/25 (52)	58/211 (27)
IIIA/B: walk with 1 or 2 sticks/crutches	25/49 (51)	60/137 (44)	2/25 (8)	87/211 (41)
IV: confined to wheelchair or bedridden	8/49 (16)	8/137 (6)	0/25 (0)	16/211 (8)
NIS score, median (IQR)[‖]	81 (46, 116)	61 (27, 92)	23 (14, 54)	62(27, 93)

mNIS+7 score, median (IQR)[**]	94 (76, 136)	71 (39, 105)	40 (26, 57)	76 (40, 108)
Norfolk QOL-DN total score, median (IQR) [††]	78 (54, 91)	55 (30, 84)	N/A[‡‡]	60 (35, 85)
R-ODS, median (IQR)[§§]	18 (10, 30)	31 (20, 41)	39 (30, 45)	29 (18, 40)
10-MWT (m/s), median (IQR)	0·6 (0·2, 0·8)	0·9 (0·5, 1·2)	1·3 (1·0, 1·5)	0·8 (0·5, 1·2)
COMPASS-31, median (IQR)[‖‖]	36 (19, 45)	23 (11, 37)	11 (6, 24)	24 (11, 40)
mBMI[***], median (IQR)	864 (721, 1007)	982 (841, 1104)	974 (916, 1095)	964 (813, 1094)
NYHA classification, n (%)				
I: no symptoms	**22/49 (45)**	**67/137 (49)**	**19/25 (76)**	108/211 (51)
II: symptoms with ordinary physical activity	**21/49 (43)**	**59/137 (43)**	**4/25 (16)**	84/211 (40)
III: symptoms with less than ordinary physical activity	4/49 (8)	9/137 (7)	2/25 (8)	15/211 (7)
IV: symptoms at rest	2/49 (4)	2/137 (1)	0/25 (0)	4/211 (2)
NT-proBNP, pg/mL, median (IQR)	868 (257, 2269)	375 (132, 1147)	166 (32, 307)	376 (132, 1378)

***Table 1*: Patient demographics and disease characteristics at Global OLE enrolment**

Bold text highlights specific baseline difference between groups. 10-MWT=10-metre walk test. ATTRv=hereditary transthyretin. COMPASS-31=Composite Autonomic Symptom Score-31. FAP=familial amyloid polyneuropathy. mBMI=modified body mass index. IQR=interquartile range. mNIS+7=modified Neuropathy Impairment Score+7. NIS=Neuropathy Impairment Score. Norfolk QOL-DN=Norfolk Quality of Life-Diabetic Neuropathy questionnaire. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. NYHA=New York Heart Association. OLE=open-label extension. PND=polyneuropathy disability. R-ODS=Rasch-built Overall Disability Scale. SD=standard deviation. TTR=transthyretin. *Race

was reported by patients. † North America: USA, Canada; Western Europe: Germany, Spain, France, United Kingdom, Italy, Netherlands, Portugal, Sweden; Rest of world: Eastern Europe: Bulgaria, Cyprus, Turkey; Asia: Japan, Korea, Taiwan; Central and South America: Mexico, Argentina, Brazil. ‡First dose of patisiran in the parent study (APOLLO-patisiran and phase 2 OLE groups), or in the Global OLE study (APOLLO-placebo group). §Use of tafamidis or diflunisal for at least 2 weeks within the first month following first dose in the Global OLE. ||Range 0–244: maximum impairment, 244. **Range 0–304: maximum impairment, 304. ††Range –4 to 136: lowest QOL, 136. ‡‡Norfolk QOL-DN was not collected in the phase 2 OLE study. §§Range 0–48: highest disability, 0. ||||Range 0–100: maximum impairment, 100. ***mBMI (kg/m^2) × albumin (g/L).

	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)	Global OLE total (n=211)
Months of patisiran exposure in Global OLE: mean (SD) [range]	17·2 (8·8) [1·3–33·8]	19·8 (7·0) [1·3–39·0]	30·5 (2·1) [23·0–34·5]	20·5 (8·0) [1·3–39·0]
Cumulative number of doses given	1167	3784	1054	6005
Death*, n(%)	13/49 (27)	10/137 (7)†	0/25 (0)	23/211 (11)
AEs, n (%)				
AE	48/49 (98)	131/137 (96)	25/25 (100)	204/211 (97)
Severe AE	23/49 (47)	35/137 (26)	3/25 (12)	61/211 (29)
Serious AE	28/49 (57)	48/137 (35)	6/25 (24)	82/211 (39)
AE leading to study withdrawal	15/49 (31)	11/137 (8)	0/25 (0)	26/211 (12)
Common AEs ≥10% of patients, n(%)				
Diarrhoea	18/49 (37)	21/137 (15)	2/25 (8)	41/211 (19)
Peripheral oedema	12/49 (24)	20/137 (15)	4/25 (16)	36/211 (17)
Urinary tract infection	12/49 (24)	19/137 (14)	3/25 (12)	34/211 (16)
Fall	7/49 (14)	20/137 (15)	1/25 (4)	28/211 (13)
Nasopharyngitis	6/49 (12)	17/137 (12)	5/25 (20)	28/211 (13)
Cough	7/49 (14)	14/137 (10)	4/25 (16)	25/211 (12)
Infusion-related reaction	13/49 (27)	10/137 (7)	2/25 (8)	25/211 (12)

***Table 2*: Safety and exposure of patisiran during the Global OLE**

AE=adverse event. OLE=open-label extension. SD=standard deviation. *All deaths summarised, including deaths due to AEs that are not treatment emergent. †In this group, 1 additional patient with breast cancer died 6·5 months after withdrawing from the study.

Number of patients (%)*/number of events†	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)	Global OLE total (n=211)
At least 1 SAE	28/49 (57)/76	48/137(35)/88	6/25 (24)/8	82/211 (39)/172
Cerebrovascular accident	1/49 (2)/1	3/137 (2)/3	1/25 (4)/1	5/211 (2)/5
Cardiac arrest	4/49 (8)/5	0/137 (0)	0/25 (0)	4/211 (2)/5
Syncope	2/49 (4)/2	2/137 (1)/2	0/25 (0)	4/211 (2)/4
Acute myocardial infarction	1/49 (2)/1	2/137 (1)/2	0/25 (0)	3/211 (1)/3
Asthenia	1/49 (2)/1	2/137 (1)/2	0/25 (0)	3/211 (1)/3
Cardiac failure	1/49 (2)/1	1/137 (1)/3	1/25 (4)/1	3/211 (1)/5
Cardiac failure congestive	1/49 (2)/1	2/137 (1)/2	0/25 (0)	3/211 (1)/3
Cellulitis	1/49 (2)/2	2/137 (1)/2	0/25 (0)	3/211 (1)/4
Conduction disorder	0/49 (0)	3/137 (2)/3	0/25 (0)	3/211 (1)/3
Hip fracture	2/49 (4)/2	1/137 (1)/1	0/25 (0)	3/211 (1)/3
Pneumonia	2/49 (4)/2	1/137 (1)/1	0/25 (0)	3/211 (1)/3
Urinary tract infection	3/49 (6)/3	0/137 (0)	0/25 (0)	3/211 (1)/3

Table 3: **Serious adverse events occurring in ≥1% of patients in the Global OLE**

OLE=open-label extension. SAE=serious adverse event. *If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term. †The total number of events for all patients; a patient can be counted more than once if the patient has multiple events.

Appendix

Table of Contents

Methods

The current study protocol is available from:
https://www.alnylam.com/OLE-Study-Protocol-Amendment.pdf

The APOLLO study protocol is available from:
https://www.nejm.org/doi/suppl/10.1056/NEJMoa1716153/suppl_file/nejmoa1716153_protocol.pdf

Procedures

All patients received premedication comprising 10 mg of dexamethasone intravenously (IV) or equivalent corticosteroid, acetaminophen/paracetamol orally, and H1/H2 blockers IV.

Outcomes

Deaths were adjudicated as cardiovascular (CV), non-cardiovascular (non-CV), or unknown.

Statistical analysis

Patisiran exposure was calculated as cumulative exposure across the trials based on the patient's first and most recent dose. Descriptive statistics for clinical laboratory tests, vital signs, and efficacy parameters were presented as actual values and changes from baseline (calculated within patient). The integrated exposure-adjusted mortality rate was conducted post hoc and calculated as total number of deaths per total patient-years (PY) of exposure ×100; deaths occurring between first patisiran dose and 90 days after the last dose were included in the calculation. The total patient-year exposure time was calculated as the sum of each patient's time using a minimum of the exposure time in years or follow-up time in years (applying a data cut-off of 24 September 2018). A post hoc analysis of exposure-adjusted mortality between the treatment groups in APOLLO was performed by evaluating mortality in subgroups of patients with the non-V30M genotype and/or elevated serum NT-proBNP at APOLLO baseline (>3000 pg/mL; indicative of cardiac involvement).

Appendix Table 1: Global OLE study sites*

Country	Site name
Argentina	Instituto FLENI
Bulgaria	UMHAT Aleksandrovska Sofia - Clinic of Neurology Diseases
Brazil	Hospital Universitario Clementino Fraga Filho-UFRJ
	Hospital das Clinicas da USP de Ribeirao Preto
Canada	Vancouver Coastal Health Research Institute, University of British Columbia
Cyprus	Cyprus Institute of Neurology and Genetics (CING)
Germany	Heidelberg University Hospital
	Universitaetsklinikum Muenster
Spain	Hospital Clinic Barcelona
	Hospital Son Llatzer
	Hospital Juan Ramon Jimenez
	Hospital Clinico San Carlos
France	CHU Bicetre and CHU X.Bichat
	Centre de Référence des Maladies Neuromusculaires et de la SLA
	Univ. Lille, Inserm, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, F-59000 Lille
	CHU Henri Mondor – Assistance Publique Hopitaux de Paris, Creteil
United Kingdom	University College London (UCL) - Medical School
Italy	Fondazione IRCCS Policlinico San Matteo
	Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma. Università Cattolica del Sacro Cuore, Roma
	A.O.U. Policlinico "G. Martino"
Japan	Kumamoto University Hospital
	Shinshu University Hospital
South Korea	Samsung Medical Center
	Konkuk University Hospital
Mexico	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, (INCMNSZ)
Netherlands	Groningen UMC
Portugal	Centro Hospitalar Universitário do Porto, E.P.E – Unidade Corino de Andrade
	Department of Neurosciences and Mental Health, Hospital de Santa Maria-CHULN, and Faculty of Medicine, Lisbon University
Sweden	Umeå University Hospital
Turkey	Istanbul University, Istanbul Faculty of Medicine, Department of Neurology
Taiwan	National Taiwan University Hospital
	Taipei Veterans General Hospital
United States	The Amyloidosis Center, Boston University School of Medicine
	Mayo Clinic - Rochester
	Columbia University Medical Center
	University of Colorado
	eStudySite
	Johns Hopkins Medicine - Department of Neurology
	Washington University School of Medicine
	Northwestern University
	Barbara Ann Karmanos Cancer Institute
	Mount Sinai Medical Center
	Duke University Medical Center (DUMC)

*Sites listed include those that enrolled patients as of 24 September 2018.

Appendix Table 2: Global OLE outcome measure ranges

Outcome measure	Range of scoring system
Neurologic impairment assessed using NIS	0–244: maximum impairment, 244
Motor function assessed by NIS-W	0–192: maximum impairment, 192
Neurologic impairment assessed using mNIS +7	0–304: maximum impairment, 304
Neurologic impairment assessed using NIS+7	0–270: maximum impairment, 270
Quality of life using Norfolk QOL-DN	−4 to 136: lowest QOL, 136
Autonomic function assessed using COMPASS-31	0–100: maximum impairment, 100
Disability reported by patients using R-ODS	0–48: highest disability, 0
Ambulation assessed by PND score	0–IV: maximum impairment, IV
Ambulation assessed by FAP stage	0–3: maximum impairment, 3

COMPASS-31=Composite Autonomic Symptom Score-31. EQ-5D=EuroQOL questionnaire. FAP=familial amyloid polyneuropathy. mNIS+7=modified Neuropathy Impairment Score+7. NIS=Neuropathy Impairment Score. NIS+7=Neuropathy Impairment Score+7. NIS-W=NIS-Weakness. Norfolk QOL-DN=Norfolk Quality of Life-Diabetic Neuropathy questionnaire. OLE=open-label extension. PND=polyneuropathy disability. R-ODS=Rasch-built Overall Disability Scale.

Appendix Table 3: All Global OLE outcome measures

Outcome measure
Neurologic impairment assessed using NIS
Neurologic impairment assessed using mNIS +7
Neurologic impairment assessed using NIS+7
Quality of life using Norfolk QOL-DN
Quality of life using EQ-5D
Autonomic function assessed using COMPASS-31
Serum TTR lowering
Nutritional status using mBMI
Disability reported by patients using R-ODS
Motor function assessed by NIS-W
Motor function assessed by timed 10-MWT
Motor function assessed by grip strength test
Ambulation assessed by PND score
Ambulation assessed by FAP stage
Nerve fibre density assessed by IENFD and SGNFD
Serum vitamin A
Serum NT-proBNP
Serum troponin I
Magnetic resonance neurography (Germany and France only)
Cardiac structure and function assessed by echocardiograms
Burden of disease and healthcare utilisation using a patient-reported pharmacoeconomics questionnaire

10-MWT=10-metre walk test. COMPASS-31=Composite Autonomic Symptom Score-31. EQ-5D=EuroQOL questionnaire. FAP=familial amyloid polyneuropathy. IENFD=intraepidermal nerve fibre density. mBMI=modified body mass index. mNIS+7=modified Neuropathy Impairment Score+7. NIS=Neuropathy Impairment Score. NIS+7= Neuropathy Impairment Score+7. NIS-W=NIS-Weakness. Norfolk QOL-DN=Norfolk Quality of Life-Diabetic Neuropathy questionnaire. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. OLE=open-label extension. PND=polyneuropathy disability. R-ODS=Rasch-built Overall Disability Scale. SGNFD=sweat gland nerve fibre density. TTR=transthyretin.

Appendix Table 4: Description of patient deaths during the Global OLE*

Treatment arm	Age†/ Gender	Genotype	NT-proBNP at Global OLE enrolment (pg/mL)	PND at Global OLE enrolment	AEs leading to death	Relationship to study drug
APOLLO-placebo	38/M	V30M	106	IIIB	Hip fracture	Unrelated
APOLLO-placebo	59/M	F64L	6905	II	Arrhythmia	Unrelated
APOLLO-placebo	60/M	E89Q	3784	II	Dehydration	Unrelated
APOLLO-placebo	74/M	V30M	15101	IV	Pancreatitis	Unrelated
APOLLO-placebo	66/M	S77Y	3160	II	Hypovolaemic shock	Unrelated
APOLLO-placebo	72/M	V30M	3052	IV	Cardiac arrest	Unrelated
APOLLO-placebo	66/M	T60A	868	IIIB	Amyloidosis	Unrelated
APOLLO-placebo	74/M	V30M	2169	IIIB	Cardiac arrest	Unrelated
APOLLO-placebo	69/F	I84T	1333	II	Acute respiratory distress syndrome, haemorrhagic shock	Unrelated
APOLLO-placebo	53/F	S50R	436	IIIB	Septic shock	Unrelated
APOLLO-placebo	77/M	A97S	2501	IIIB	Acute myocardial infarction	Unrelated
APOLLO-placebo	74/F	A97S	1790	IV	Cardiogenic shock	Unrelated
APOLLO-placebo	68/M	E89Q	1583	IV	Cardiac arrest	Unrelated
APOLLO-patisiran	81/M	V30M	3218	IIIA	Cerebrovascular accident	Unrelated
APOLLO-patisiran	77/F	T60A	1542	IIIB	Death (cause unknown)	Unrelated
APOLLO-patisiran	76/M	V30M	1144	IIIA	Acute myocardial infarction, Atrial flutter, Acute kidney injury	Unrelated
APOLLO-patisiran	72/M	T60A	10282	II	Chronic kidney disease	Unrelated
APOLLO-patisiran	70/M	T60A	3844	IV	Familial amyloidosis	Unrelated
APOLLO-patisiran	70/M	L58H	376	II	Acute myocardial infarction	Unrelated
APOLLO-patisiran	66/M	T60A	6145	IV	Amyloidosis	Unrelated
APOLLO-patisiran	52/M	S50R	2811	IIIA	Neurogenic shock	Unrelated
APOLLO-patisiran	41/M	S50R	4932	IV	Electrolyte imbalance, Acute respiratory failure	Unrelated
APOLLO-patisiran	70/F	A97S	2218	IIIB	Cardiopulmonary failure	Unrelated

AE=adverse event. F=female. M=male. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. OLE=open-label extension. PND=polyneuropathy disability. *Includes deaths occurring within 90 days of last dose of patisiran. †Patient age at death. Investigators could report >1 adverse event as leading to death for a patient.

Appendix Table 5: Change from parent study baseline and Global OLE enrolment to Global OLE 12 months in PND and FAP

Assessment, n (%)	From parent study baseline			From Global OLE enrolment		
	APOLLO-placebo (n=77)	APOLLO-patisiran (n=148)	Phase 2 OLE patisiran (n=27)	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)
PND score						
Improved	0/77 (0·0)	12/148 (8)	1/27 (4)	6/49 (12)	9/137 (7)	1/25 (4)
No change	17/77 (22)	77/148 (52)	16/27 (59)	27/49 (55)	97/137 (71)	20/25 (80)
Worsened	21/77 (27)	37/148 (25)	8/27 (30)	5/49 (10)	20/137 (15)	4/25 (16)
Missing	39/77 (51)	22/148 (15)	2/27 (7)	11/49 (22)	11/137 (8)	0/25 (0)
FAP stage						
Improved	1/77 (1)	6/148 (4)	0/27 (0)	2/49 (4)	4/137 (3)	0/25 (0)
No change	22/77 (29)	100/148 (68)	21/27 (78)	32/49 (65)	115/137 (84)	24/25 (96)
Worsened	15/77 (19)	20/148 (14)	4/27 (15)	4/49 (8)	7/137 (5)	1/25 (4)
Missing	39/77 (51)	22/148 (15)	2/27 (7)	11/49 (22)	11/137 (8)	0/25 (0)

FAP=familial amyloid polyneuropathy. OLE=open-label extension. PND=polyneuropathy disability.

Appendix Table 6: Change in select clinical assessments from parent study baseline and Global OLE enrolment to Global OLE 12 months

Mean (SD)	APOLLO-placebo (n=49)*	APOLLO-patisiran (n=137)*	Phase 2 OLE patisiran (n=25)*
10-MWT, ms^{-1}			
Parent study baseline	0·79 (0·32)	0·80 (0·40)	1·14 (0·43)
Global OLE enrolment	0·54 (0·39)	0·85 (0·49)	1·26 (0·41)
Global OLE 12 months†	0·60 (0·42)	0·90 (0·48)	1·21 (0·42)
Change from parent study baseline	–0·21 (0·35)	0·06 (0·26)	0·04 (0·26)
Change from Global OLE enrolment	0·05 (0·22)	–0·01 (0·20)	–0·06 (0·19)
Grip strength, kg			
Parent study baseline	17·80 (10·67)	18·40 (13·57)	25·81 (11·86)
Global OLE enrolment	10·23 (9·05)	18·03 (12·65)	27·86 (13·13)
Global OLE 12 months†	11·01 (9·43)	18·69 (14·20)	27·57 (13·41)
Change from parent study baseline	–8·76 (7·42)	–0·89 (9·19)	2·03 (5·83)
Change from Global OLE enrolment	0·14 (2·84)	–0·25 (6·81)	–0·28 (4·04)
NT-proBNP‡, pg/mL			
Parent study baseline	531·29 (86·66)	531·04 (59·62)	508·13 (185·23)
Global OLE enrolment	837·39 (171·19)	396·84 (47·77)	113·35 (33·92)
Global OLE 12 months§	654·32 (149·75)	405·44 (51·41)	120·47 (39·58)
Fold change relative to Global OLE enrolment (geometric mean fold change, 95% CI)	1·07 (0·86–1·32)	1·17 (1·06–1·29)	1·06 (0·85–1·33)
Fold change relative to parent baseline (geometric mean fold change, 95% CI)	2·01 (1·61–2·52)	0·97 (0·87–1·08)	0·93 (0·61–1·44)

10-MWT=10-metre walk test. CI=confidence interval. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. OLE=open-label extension. SD=standard deviation. *Patients in parent study: APOLLO-placebo, n=77; APOLLO-patisiran, n=148; phase 2 OLE, n=27. †n=38, 124 and 25 for patients in APOLLO-placebo, APOLLO-patisiran, and phase 2 OLE, respectively. ‡Geometric mean NT-proBNP (pg/mL) and standard error of the mean. §n=38, 119, and 25 for patients in APOLLO-placebo, APOLLO-patisiran, and phase 2 OLE, respectively.

Appendix Table 7: Summary of IRR events in the Global OLE

Number of patients (%)*/number of events†	APOLLO-placebo (n=49)	APOLLO-patisiran (n=137)	Phase 2 OLE patisiran (n=25)	Global OLE total (n=211)
Number of patients with at least 1 IRR	13/49 (27)	10/137 (7)	2/25 (8)	25/211 (12)
Total number of IRRs	77	81	16	174
Number of patients with IRR symptoms and number of symptoms				
Nausea	1/49 (2)/2	1/137 (1)/1	0/25 (0)	2/211 (1)/3
Injection site swelling	2/49 (4)/2	0/137 (0)	0/25 (0)	2/211 (1)/2
Back pain	2/49 (4)/25	2/137 (1)/26	1/25 (4)/1	5/211 (2)/52
Neck pain	2/49 (4)/2	0/137 (0)	0/25 (0)	2/211 (1)/2
Dizziness	0/49 (0)	1/137 (1)/1	1/25 (4)/15	2/211 (1)/16
Headache	0/49 (0)	1/137 (1)/4	1/25 (4)/1	2/211 (1)/5
Apathy	1/49 (2)/1	1/137 (1)/1	0/25 (0)	2/211 (1)/2
Erythema	1/49 (2)/1	1/137 (1)/1	0/25 (0)	2/211 (1)/2
Pruritus	0/49 (0)	2/137 (1)/2	0/25 (0)	2/211 (1)/2
Rash	2/49 (4)/3	1/137 (1)/1	0/25 (0)	3/211 (1)/4
Flushing	2/49 (4)/18	2/137 (1)/41	1/25 (4)/1	5/211 (2)/60
Hypertension	2/49 (4)/2	1/137 (1)/1	0/25 (0)	3/211 (1)/3
Number of patients with IRR leading to infusion, interruption and number of interruptions	4/49 (8)/7	0/137 (0)	1/25 (4)/1	5/211 (2)/8
Number of patients with IRR leading to treatment discontinuation	0/49 (0)	0/137 (0)	0/25 (0)	0/211 (0)

IRR=infusion-related reaction. OLE=open-label extension. *If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term. †The total number of events for all patients; a patient can be counted more than once if the patient has multiple events.

Appendix Table 8: Integrated exposure-adjusted mortality rates across the patisiran development programme in patients with ATTRv amyloidosis with polyneuropathy

	APOLLO-placebo (n=49)	APOLLO-patisiran (n=148)	Phase 2 OLE patisiran (n=27)	All patisiran-treated patients* (n=224)
Total patient-years exposure	68·6	442·2	118·6	629·4
Deaths†, n (%)	13/49 (27)	15/148 (10)	2/27 (7)	30/224 (13)
Overall exposure-adjusted mortality rate, deaths per 100 patient-years (95% CI)	18·9 (10·4–31·2)	3·4 (2·0–5·4)	1·7 (0·3–5·2)	4·8 (3·3–6·7)
Cardiac deaths,†‡ n (%)	6/49 (12)	11/148 (7)	1/27 (4)	18/224 (8)
Exposure-adjusted cardiac mortality rate, deaths per 100 patient-years (95% CI)	8·7 (3·5–17·7)	2·5 (1·3–4·3)	0·8 (0·05–3·7)	2·9 (1·7–4·4)

ATTRv=hereditary transthyretin; CI=confidence interval. OLE=open-label extension. *The integrated safety population encompasses all patients exposed to patisiran. Data are recorded from first patisiran dose in either the APOLLO, Phase 2 OLE, or Global OLE studies until Global OLE 12 months. †Includes all deaths reported within 3 months after the last dose of patisiran. ‡Cardiac deaths were considered a subset of deaths adjudicated as being cardiovascular-related, excluding the subcategory of fatal stroke. Post hoc analysis of exposure-adjusted mortality rate is calculated as: (total number of deaths/total patient-years of exposure)×100. For each patient, exposure in years is defined as: (last dose date of study drug – first dose date of study drug+91)/365·25. The total patient-years of exposure time is calculated as the sum of each patient's time using the minimum of the exposure time in years or the follow-up time in years (applying the 24 September 2018 cut-off to data from the Global OLE study).

Appendix Table 9: Patisiran Global OLE study group by study site

Study site	Role	Name
A.O.U. Policlinico "G. Martino", Italy	Primary Investigator	Giuseppe Vita
	Investigators	Vincenzo Rizzo
		Massimo Russo
		Anna Mazzeo
		Luca Gentile
The Amyloidosis Center, Boston University School of Medicine, United States	Primary Investigator	John L Berk
	Study Coordinators	Caitlin Brueckner
		Victoria Lazzari
	Investigator	Janice Wiesman
Bassett Medical Center, United States	Primary Investigator	Douglas DeLong
	Study Coordinator	Jennifer Victory
	Investigators	James Dalton
		John May
	Clinical research nurse	Catherine Gilmore
Centre de Référence des Maladies Neuromusculaires et de la SLA, France	Primary Investigator	Shahram Attarian
	Study Coordinator	Saran Diallo
	Investigators	Emilien Delmont
		Jean Pouget
		Annie Verschueren
		Aude-Marie Grapperon
		Emmanuelle Campana-Salort
Department of Neurosciences and Mental Health, Hospital de Santa Maria-CHULN, and Faculty of Medicine, Lisbon University, Portugal	Primary Investigator	Isabel M Conceição
	Study Coordinator	Ana Lopes
		Filipa Lamas
	Investigators	Carlos Neves
		Jose Castro
		Pedro Pereira
		Isabel Castro
		Ana Franco
		Miguel Oliveira Santos
		Conceição de Azevedo Coutinho
		Catarina Falcao de Campos
Centro Hospitalar Universitário do Porto, E.P.E – Unidade Corino de Andrade, Portugal	Primary Investigator	Teresa Coelho
	Investigators	Antonio Hipólito Reis
		Nuno Correia
		Javier M Perez
		Ana Martins da Silva
		Cristina Alves
		Marcio Cardoso
		Katia Valdrez
		Julia R Monte
		Bernardete Pessoa
		Nadia Guimaraes
		Monica Freitas
		Joana Ramalho
		Natalia Ferreira
Chikamori Hospital, Japan	Primary Investigator	Daisuke Kuzume
Univ. Lille, Inserm, CHU Lille, U1172 - LilNCog - Lille Neuroscience & Cognition, F-59000 Lille, France	Primary Investigator	Celine Tard
	Study Coordinators	Nawal Waucquier
		Isabelle Rougeaux
		Sylvie Brice
		Emmanuelle Kasprzyk
		Elise Elrezzi
		Sayah Meguig
	Investigators	Eric Hachulla
		Clement Gauvain

		Maria-Claire Migaud-Chervy
		Dominique Deplanque
		Elsa Jozefowicz
		Loic Lebellec
CHU Bicetre and CHU X.Bichat, France	Primary Investigator	David Adams
	Study Coordinators	Line Balaya-Gouraya
		Nathalie Jehan Lacour
		Halima Bournane
		Nathalie Martin
		Mongia Elabed
		Niamey Sacko
		Yasmine Boubrit
		Amina Gaouar
		Fetra Rakotondratafika
	Investigators	Marie Théaudin-Saliou
		Cécile Cauquil-Michon
		Celine Labeyrie
		Adeline Not
		Abdallah Al-Salameh
		Anne-Lise Lecoq
		Maeva Stephant
		Andoni Echaniz-Laguna
		Laurent Becquemont
		Guillemette Beaudonnet
		Vincent Algalarrondo
		Ludivine Eliahou
		Michel S Slama
CHU de Fort de France, Martinique (France)	Primary Investigator	Aissatou Signate
	Investigators	Emeline Berthelot
		Jocelyn Inamo
CHU Henri Mondor – Assistance Publique Hopitaux de Paris, Creteil, France	Primary Investigator	Violaine Planté-Bordeneuve
	Study Coordinators	Laetitia Vervoitte
		Cecile Focseneanu
	Investigators	Thierry Gendre
		Raphaele Arrouasse
		Samar S. Ayache
		Laura Ernande
		Philippe Le Corvoisier
		Hayet Salhi
CHU La Reunion, France	Primary Investigator	Ariane Choumert
	Study Coordinator	Vincent Ehinger
		Julie Ruiz
	Investigators	Cyril Charlin
		Thomas Megelin
Columbia University Medical Center, United States	Primary Investigator	Thomas H Brannagan III
	Study Coordinators	Raisy Fayerman
		Arreum Kim
		Allan Paras
		Leidy J Gonzalez
	Investigators	Steven Tsang
		Fernanda Wajnsztajn
		Jeffrey Shije
		Christina Ulane
		Inna Kleyman
		Louis Weimer
		Comana Cioroiu
Cyprus Institute of Neurology and Genetics (CING), Cyprus	Primary Investigator	Sakis Lambrianides
	Study Coordinator	Rana Abu-Manneh
	Investigators	Eleni Zamba-Papanicolaou

		Petros Agathangelou
		Eleni Leonidou
Ehime University Hospital, Japan	Primary Investigator	Satoshi Tada
	Study Coordinator	Akemi Fujita
	Investigators	Masahiro Nagai
		Rina Ando
		Yuko Hosokawa
		Yuki Yamanishi
eStudySite, United States	Primary Investigator	J Scott Overcash
	Study Coordinators	Elena Giardino
		Leslie Boyer
		Lien Dang
		An Le
		Tyler Nguyen
		Lien Giang
		Peter Sellers
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		Nghi Truong
		Maita Vinas
		Nicole Hrkman
		Sarah Miller
		David Nguyen
		Ashley Smith
		Helen Pu
		Steve Li
		Thao Vuong
		Holly Dioso
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		Michael Waters
		Derya J Coskun
		Karla A Zepeda
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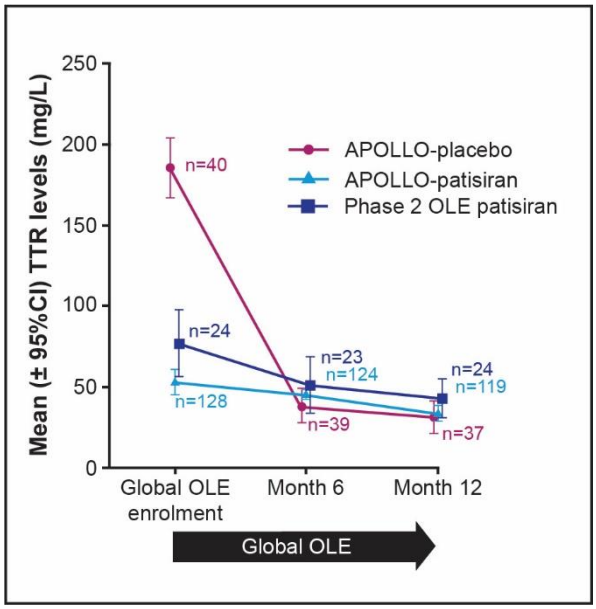
		Thi Hoa (Therese) Do

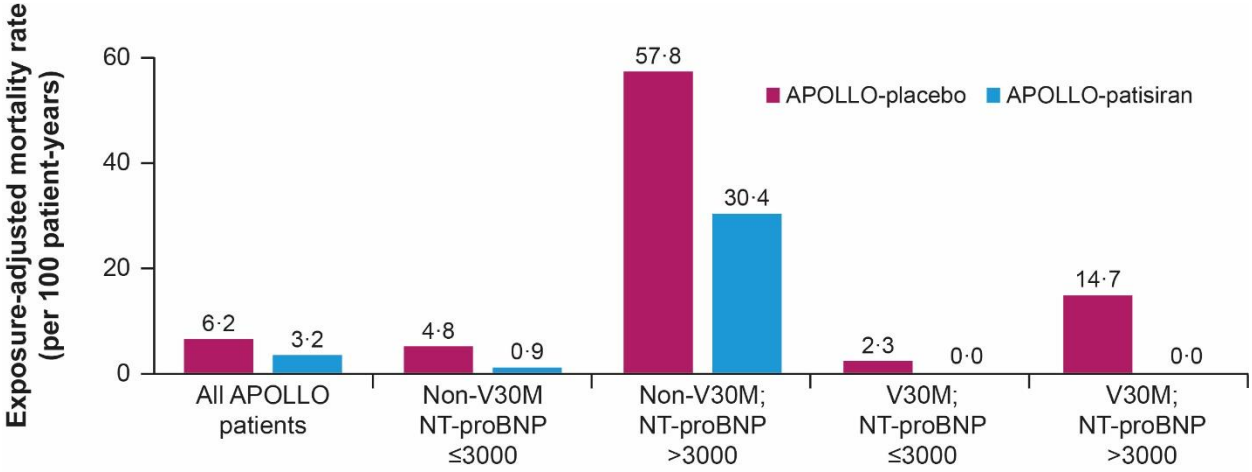
Appendix Figure 1: Serum TTR levels (mg/L) up to Global OLE 12 months*



*Patients were excluded from the pharmacodynamic analysis if more than 45 days had elapsed between the last dose of patisiran in the parent study and the first dose of patisiran in the Global OLE study.

CI=confidence interval. OLE=open-label extension. TTR=transthyretin.

Appendix Figure 2: Post hoc analysis of exposure-adjusted mortality rates by genotype and baseline NT-proBNP levels in APOLLO



NT-proBNP units (pg/mL). NT-proBNP=N-terminal prohormone of B-type natriuretic peptide.