The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

ABSTRACT

BACKGROUND

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

METHODS

In this phase 3 trial, we randomly assigned patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive intravenous patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks. The primary end point was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7; range, 0 to 304, with higher scores indicating more impairment) at 18 months. Other assessments included the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (range, −4 to 136, with higher scores indicating worse quality of life), 10-m walk test (with gait speed measured in meters per second), and modified body-mass index (modified BMI, defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter; lower values indicated worse nutritional status).

RESULTS

A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group). The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group; the least-squares mean (±SE) change from baseline was −6.0±1.7 versus 28.0±2.6 (difference, −34.0 points; P<0.001) at 18 months. The mean (±SD) baseline Norfolk QOL-DN score was 59.6±28.2 in the patisiran group and 55.5±24.3 in the placebo group; the least-squares mean (±SE) change from baseline was −6.7±1.8 versus 14.4±2.7 (difference, −21.1 points; P<0.001) at 18 months. Patisiran also showed an effect on gait speed and modified BMI. At 18 months, the least-squares mean change from baseline in gait speed was 0.08±0.02 m per second with patisiran versus −0.24±0.04 m per second with placebo (difference, 0.31 m per second; P<0.001), and the least-squares mean change from baseline in the modified BMI was −3.7±9.6 versus −119.4±14.5 (difference, 115.7; P<0.001). Approximately 20% of the patients who received patisiran and 10% of those who received placebo had mild or moderate infusion-related reactions; the overall incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In this trial, patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis. (Funded by Alnylam Pharmaceuticals; APOLLO ClinicalTrials.gov number, NCT01960348.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Adams at the Department of Neurology, CHU Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre CEDEX, France, or at david.adams@aphp.fr.

N Engl J Med 2018;379:11-21.
DOI: 10.1056/NEJMoa1716153

Hereditary transthyretin amyloidosis is an autosomal dominant, multisystemic, progressive, life-threatening disease caused by mutations in the gene encoding transthyretin (*TTR*).[1] The liver is the primary source of circulating tetrameric transthyretin protein. In hereditary transthyretin amyloidosis, both mutant and wild-type transthyretin deposit as amyloid in peripheral nerves and the heart, kidney, and gastrointestinal tract,[1,2] resulting in polyneuropathy and cardiomyopathy.[1,3] Neuropathic changes result in profound sensorimotor disturbances, with deterioration in activities of daily living and ambulation.[4] Autonomic nerve involvement causes hypotension, diarrhea, impotence, and bladder disturbances.[4] Cardiac manifestations include heart failure, arrhythmias, orthostatic hypotension, or sudden death due to severe conduction disorders.[5] Hereditary transthyretin amyloidosis is inexorably progressive, with survival of 2 to 15 years after the onset of neuropathy[6-8] but only 2 to 5 years among patients presenting with cardiomyopathy.[9,10]

Current treatment options for hereditary transthyretin amyloidosis are limited and include orthotopic liver transplantation and transthyretin tetramer stabilizers (tafamidis or diflunisal). However, many patients who are treated with these approaches continue to have disease progression.[4,10-16]

RNA interference (RNAi) is an endogenous mechanism for controlling gene expression. It results in the cleavage of target messenger RNA (mRNA) by small interfering RNAs bound to the RNA-induced silencing complex. Patisiran, a hepatically directed investigational RNAi therapeutic agent (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), harnesses this process to reduce the production of mutant and wild-type transthyretin by targeting the 3′ untranslated region of transthyretin mRNA.[17] Previously, dose-dependent reduction of circulating transthyretin levels has been observed with patisiran administration in healthy volunteers and in patients with hereditary transthyretin amyloidosis.[17,18] In addition, patisiran has shown the potential to halt the disease or improve disease control in a phase 2, open-label extension study involving patients with hereditary transthyretin amyloidosis.[19] Here we present efficacy and safety data from the APOLLO trial, a randomized, placebo-controlled, phase 3 trial involving patients with hereditary transthyretin amyloidosis with polyneuropathy.

Methods

Trial Oversight

We carried out a multicenter, international, randomized, double-blind, placebo-controlled, phase 3 trial of patisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy. The protocol, including the statistical analysis plan, was developed by the sponsor, Alnylam Pharmaceuticals, and is available at NEJM.org. The trial was approved by central and local institutional review boards or ethics committees and conducted according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and the World Health Organization Declaration of Helsinki. All the participants provided written informed consent.

All the investigators gathered the data. The first author and sponsor-employed authors analyzed the data, and all the authors vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol. The first author and sponsor-employed authors prepared the first draft with editorial assistance provided by Adelphi Communications, under contract with Alnylam Pharmaceuticals. All the authors made the decision to submit the manuscript for publication. All the authors, their institutions, and the sponsor were required to maintain data confidentiality during the trial.

Trial Participants

Key eligibility criteria included an age of 18 to 85 years; a documented pathogenic variant in *TTR*; a diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, with a Neuropathy Impairment Score (NIS) of 5 to 130 (range, 0 to 244, with higher scores indicating more impairment) and a polyneuropathy disability score of IIIb or lower (with higher scores indicating more-impaired walking ability); and adequate liver and renal function. Patients with previous liver transplantation or who were planning to undergo liver transplantation during the trial period, or who had a New York Heart Association class of III or IV, were excluded. Full eligibility criteria are provided in the protocol.

Trial Design and Regimens

Patients were enrolled at 44 sites across 19 countries. Patients were randomly assigned (in a 2:1 ratio) to receive patisiran (0.3 mg per kilogram of body weight) or placebo intravenously over a

period of approximately 80 minutes, once every 3 weeks for 18 months.[20] Randomization was stratified according to NIS (5 to 49 vs. 50 to 130), early onset of disease (age <50 years) in the presence of the V30M variant versus all other pathogenic variants (including late-onset disease in the presence of the V30M variant), and previous use of a transthyretin stabilizer (yes vs. no). Patients received premedication to minimize the risk of infusion-related reactions, with details provided by Adams et al.[20] Patients completing the 18-month efficacy assessments were eligible to participate in an open-label extension study (ClinicalTrials.gov number, NCT02510261).

END-POINT MEASURES AND SAFETY ASSESSMENTS

The primary end point was the change from baseline to 18 months in the modified Neuropathy Impairment Score+7 (mNIS+7),[21,22] a composite measure of neuropathy that assesses motor, sensory, and autonomic neuropathy (range, 0 to 304, with higher scores indicating more impairment). Further details on mNIS+7, including standardization of assessments and investigator training, have been reported.[20]

Secondary end points, in hierarchical order for statistical testing, were quality of life (score on the Norfolk Quality of Life–Diabetic Neuropathy [Norfolk QOL-DN] questionnaire; range, −4 to 136, with higher scores indicating worse quality of life), motor strength (NIS-weakness; range, 0 to 192, with higher scores indicating more impairment), disability (score on the Rasch-built Overall Disability Scale [R-ODS]; range, 0 to 48, with lower scores indicating more disability), gait speed (10-m walk test, with speed measured in meters per second), nutritional status (modified body-mass index [BMI], defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter; lower values indicated worse nutritional status), and patient-reported autonomic symptoms (Composite Autonomic Symptom Score 31; range, 0 to 100, with higher scores indicating more autonomic symptoms), which have been described by Adams et al.[20] All efficacy end points were assessed at baseline and at 9 and 18 months, except modified BMI (at baseline and at weeks 12, 27, 51, 66, and 78).

Exploratory end points included pharmacodynamic biomarkers (transthyretin and vitamin A) and measures of cardiac structure and function (echocardiography and measurement of N-terminal pro–brain natriuretic peptide [NT-proBNP]) (see the Supplementary Appendix), as well as assessment of neuropathy stage with the use of the polyneuropathy disability score (with higher scores indicating more impaired walking ability). Safety was monitored throughout the trial as specified in the protocol (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The primary population for efficacy and safety analyses was the modified intention-to-treat population (all randomly assigned patients who received ≥1 dose of patisiran or placebo). Selected analyses were also performed in a predefined cardiac subpopulation (baseline left ventricular wall thickness ≥13 mm in the absence of a history of aortic valve disease or hypertension), to enable specific assessment of patisiran on cardiac manifestations.

Assuming a mean (±SD) increase in the mNIS+7 of 24±16 points at 18 months in the placebo group, we calculated that a sample of 154 patients would provide 90% power for a t-test to detect an 8.95-point (37.3%) mean difference between the two trial groups at a two-sided alpha level of 0.05. The planned sample was estimated at 200 patients to account for discontinuation.

Efficacy end points were assessed with the use of a mixed model for repeated measures (see the Supplementary Appendix). Secondary end points were analyzed in a prespecified hierarchical order to control the overall type I error (order as described above).

RESULTS

TRIAL POPULATION

From December 2013 through January 2016, a total of 225 patients were randomly assigned in a 2:1 ratio to receive patisiran (148 patients) or placebo (77) (Fig. 1). The two groups were generally balanced with respect to baseline demographic and clinical characteristics (Table 1). The V30M mutation was present in 38% of the patients in the patisiran group and 52% of those in the placebo group, with the remaining patients having 1 of 38 other pathogenic variants (Table S1 in the Supplementary Appendix). Overall, 126 patients (56%) were included in the predefined cardiac subpopulation, with a higher percentage in the patisiran group (61%, as compared

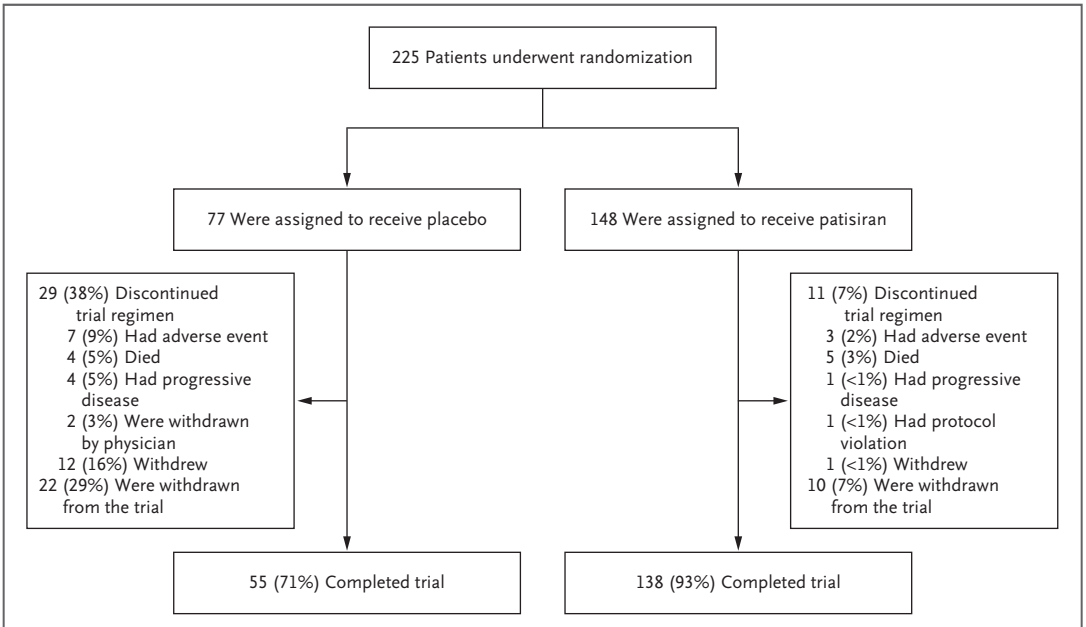

Figure 1. Randomization and Follow-up.

Patients were assigned in a 2:1 ratio to the patisiran group or the placebo group. Shown is the modified intention-to-treat population, which includes all the patients who underwent randomization and received at least one dose of patisiran or placebo. Patients who discontinued the trial regimen permanently stopped the regimen before the last scheduled dose (week 78 visit). Patients who discontinued the trial regimen owing to progressive disease had a modified Neuropathy Impairment Score+7 (range, 0 to 304, with higher scores indicating more impairment) that increased by at least 24 points from baseline (on the basis of an average of two measurements) and a worsening in the stage of familial amyloidotic polyneuropathy relative to baseline at 9 months.

with 47% in the placebo group). Overall, 138 patients in the patisiran group (93%) and 55 in the placebo group (71%) completed the trial (Fig. 1).

PHARMACODYNAMICS

In the patisiran group, the reduction in serum transthyretin levels was rapid and sustained over a period of 18 months (Fig. 2A). The median reduction in the serum transthyretin level during the 18 months was 81% (range, −38 to 95) and was similar across age, sex, or genotype.

EFFICACY

Primary End Point

The change from baseline in the mNIS+7 was significantly lower with patisiran than with placebo at 18 months, indicating a benefit with respect to polyneuropathy. The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group. At 18 months, the least-squares mean (±SE) change in mNIS+7 from baseline was −6.0±1.7 with patisiran, as compared with 28.0±2.6 with placebo (least-squares mean difference, −34.0 points; 95% confidence interval [CI], −39.9 to −28.1; P<0.001) (Fig. 2B). The effect of patisiran on mNIS+7 was seen as early as 9 months.

The response to treatment was observed broadly across the patisiran group, with 74% of the patients having a less than 10-point increase from baseline in the mNIS+7 at 18 months, as compared with 14% of the patients in the placebo group. The treatment effect was significant for all subgroups and components of the mNIS+7 (Figs. S2 and S3 in the Supplementary Appendix) and was consistent across all trial sites. A correlation was observed between the degree of the reduction in transthyretin levels from baseline and the change in the mNIS+7 at 18 months (Fig. 3).

At 18 months, 56% of the patients who received patisiran had an improvement (decrease from baseline at 18 months) in the mNIS+7, as compared with 4% of the patients who received placebo (Fig. 2D). In patients who received pati-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N=77)	Patisiran (N=148)	Total (N=225)
Median age (range) — yr	63 (34–80)	62 (24–83)	62 (24–83)
Male sex — no. (%)	58 (75)	109 (74)	167 (74)
Race — no. (%)†			
Asian	25 (32)	27 (18)	52 (23)
Black	1 (1)	4 (3)	5 (2)
White	50 (65)	113 (76)	163 (72)
Other	0	1 (<1)	1 (<1)
>1 Race	0	2 (1)	2 (<1)
Missing data	1 (1)	1 (<1)	2 (<1)
Geographic region — no. (%)‡			
North America	10 (13)	37 (25)	47 (21)
Western Europe	36 (47)	62 (42)	98 (44)
Rest of world	31 (40)	49 (33)	80 (36)
Median time since diagnosis of hereditary transthyretin amyloidosis (range) — yr	1.4 (0.0–16.5)	1.3 (0.0–21.0)	1.4 (0.0–21.0)
TTR genotype — no. (%)			
V30M	40 (52)	56 (38)	96 (43)
With onset of disease before 50 yr of age	10 (13)	13 (9)	23 (10)
Non-V30M§	37 (48)	92 (62)	129 (57)
Previous use of tetramer stabilizer — no. (%)	41 (53)	78 (53)	119 (53)
FAP stage — no. (%)			
1: unimpaired ambulation	37 (48)	67 (45)	104 (46)
2: assistance with ambulation	39 (51)	81 (55)	120 (53)
3: wheelchair-bound or bedridden	1 (1)	0	1 (<1)
Polyneuropathy disability score — no. (%)			
I: preserved walking, sensory disturbances	20 (26)	36 (24)	56 (25)
II: impaired walking without need for a stick or crutches	23 (30)	43 (29)	66 (29)
IIIA: walking with one stick or crutch	22 (29)	41 (28)	63 (28)
IIIB: walking with two sticks or crutches	11 (14)	28 (19)	39 (17)
IV: confined to wheelchair or bedridden	1 (1)	0	1 (<1)
New York Heart Association class — no. (%)			
I	40 (52)	70 (47)	110 (49)
II	36 (47)	77 (52)	113 (50)
Missing data	1 (1)	1 (<1)	2 (<1)

* Differences in baseline demographic and clinical characteristics between the patisiran and placebo groups were tested with the use of t-tests for continuous variables (age and log-transformed years since diagnosis of hereditary transthyretin amyloidosis) and Fisher's exact tests for categorical variables (sex, race, geographic region, V30M or non-V30M *TTR* genotype, previous use or nonuse of tetramer stabilizer, and New York Heart Association class). A significant difference between the groups ($P<0.05$) was found for *TTR* genotype only. FAP denotes familial amyloidotic polyneuropathy.

† Race was reported by the patients.

‡ North America included Canada and the United States. Western Europe included France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. The rest of world included Argentina, Brazil, Bulgaria, Cyprus, Japan, Mexico, South Korea, Taiwan, and Turkey.

§ The non-V30M *TTR* genotype represents 38 different *TTR* mutations, which are listed in Table S1 in the Supplementary Appendix.

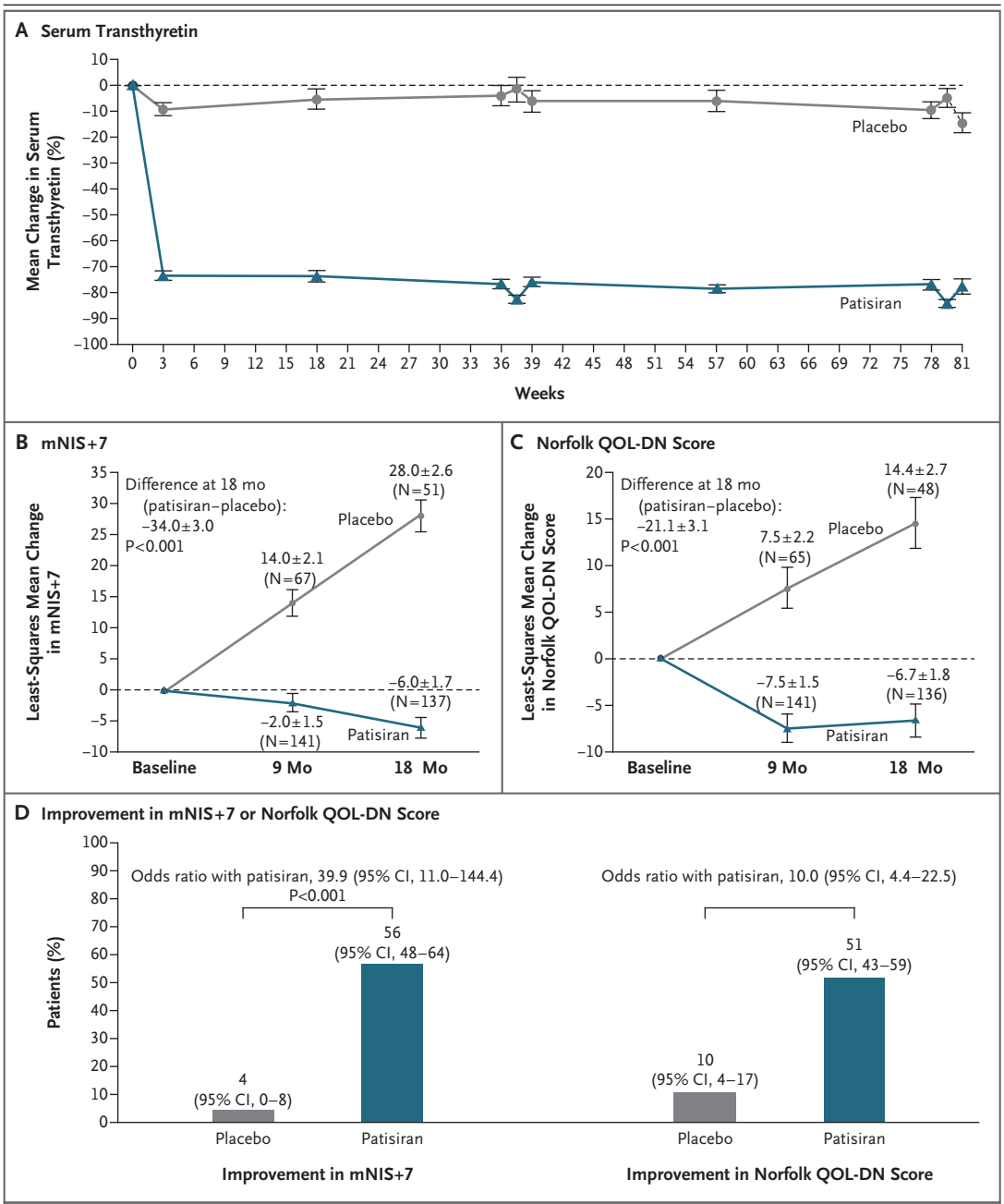

Figure 2. Comparisons of Changes between the Patisiran Group and the Placebo Group over Time.

Panel A shows the percentage change in serum transthyretin levels from baseline over time in the patisiran group and the placebo group. The nadirs in transthyretin reduction at 9 and 18 months correspond to the predose and postdose assessments. Panel B shows the least-squares mean change in the modified Neuropathy Impairment Score+7 (mNIS+7). At baseline, the mean mNIS+7 was 80.9 (range, 8.0 to 165.0) in the patisiran group and 74.6 (range, 11.0 to 153.5) in the placebo group. Panel C shows the least-squares mean change in Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) scores (range, –4 to 136; with higher scores indicating worse quality of life). At baseline, the mean Norfolk QOL-DN score was 59.6 (range, 5.0 to 119.0) in the patisiran group and 55.5 (range, 8.0 to 111.0) in the placebo group. In Panels A through C, I bars indicate standard errors. Panel D shows the percentage of patients with an improvement (decrease from baseline) in the mNIS+7 or the Norfolk QOL-DN score from baseline after 18 months. A post hoc analysis was used to calculate the odds ratio for improvement in the Norfolk QOL-DN score.

siran and did not have an improvement in the mNIS+7 (54 of 137 patients with available data), the median change from baseline in the mNIS+7 at 18 months was lower than that observed in all 51 patients who received placebo and had available data (9.9-point increase and 26.5-point increase, respectively).

Secondary End Points

The change from baseline in the Norfolk QOL-DN score was significantly lower with patisiran than with placebo at 18 months, indicating better quality of life with patisiran. At baseline, the mean (±SD) Norfolk QOL-DN score was 59.6±28.2 in the patisiran group and 55.5±24.3 in the placebo group. At 18 months, the least-squares mean (±SE) change in the Norfolk QOL-DN score from baseline was −6.7±1.8 with patisiran, as compared with 14.4±2.7 with placebo (least-squares mean difference, −21.1 points; 95% CI, −27.2 to −15.0; P<0.001) (Fig. 2C). Consistent effects in favor of patisiran were noted in Norfolk QOL-DN scores across all subgroups (Fig. S4 in the Supplementary Appendix). At 18 months, 51% of the patients who received patisiran had an improvement (decrease from baseline at 18 months) in the Norfolk QOL-DN score, as compared with 10% of those who received placebo (Fig. 2D).

Significant between-group differences in favor of patisiran treatment were observed for all other secondary end points (Table 2). Improvement relative to baseline was also seen in gait speed in the 10-m walk test (53% of the patients who received patisiran vs. 13% of those who received placebo) and motor strength (40% vs. 1%), as determined by the NIS-weakness test at 18 months. For all secondary end points, between-group differences in favor of patisiran were evident at the first efficacy assessment time point (3 months for modified BMI and 9 months for all others).

Select Exploratory End Points

Measures of neuropathy stage also favored patisiran, with the polyneuropathy disability score stable (96 patients [65%]) or improved (12 patients [8%]) from baseline in 108 of 148 patients (73%); in the placebo group, stabilization occurred in 23 of 77 patients (30%) and none had improvement at 18 months. Among patients whose polyneuropathy disability score worsened at 18 months, worsening by more than one level was observed in 5 of 30 patients (17%) in the patisiran group, as compared with 16 of 32 (50%) in the placebo group.

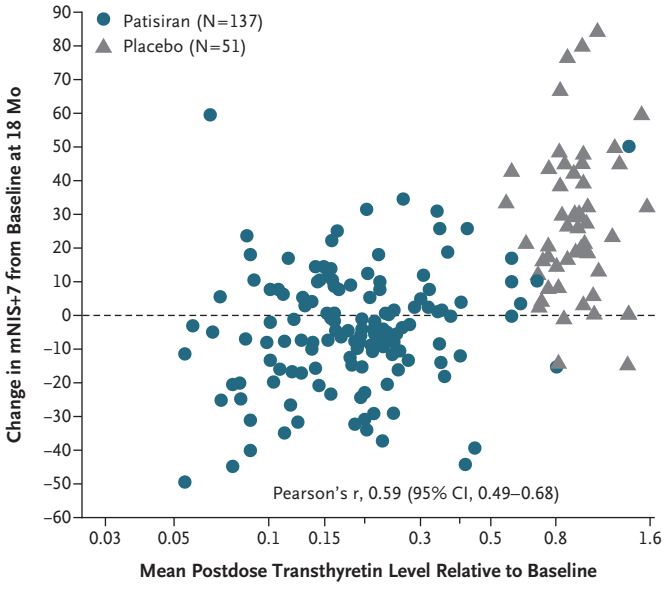

Figure 3. Correlation of Reduction in Transthyretin Levels with Change in mNIS+7 from Baseline at 18 Months.

The analysis included 188 patients with nonmissing mNIS+7 assessments at month 18.

In the cardiac subpopulation, the geometric mean baseline level of NT-proBNP, a measure of cardiac stress that is an independent predictor of death in patients with transthyretin cardiac amyloidosis, was 726.9 pg per milliliter (coefficient of variation, 220.3%) in the patisiran group and 711.1 pg per milliliter (coefficient of variation, 190.8%) in the placebo group. At 18 months, the adjusted geometric mean ratio to baseline was 0.89 with patisiran and 1.97 with placebo (ratio, 0.45; P<0.001), representing a 55% difference in favor of patisiran. Patisiran treatment was also associated with better cardiac structure and function than placebo, including significant differences in mean left ventricular wall thickness (P=0.02) and longitudinal strain (P=0.02) at 18 months (Table 2).

SAFETY

Overall, 97% of the patients in each trial group reported adverse events (Table 3), most of which were mild or moderate in severity. The frequency of severe adverse events (28% in the patisiran group and 36% in the placebo group) and seri-

Table 2. Secondary and Exploratory End Points.

End Point	Placebo	Patisiran	Least-Squares Mean Difference (Patisiran – Placebo)	P Value
Secondary end points in the modified ITT population*				
No. of patients	77	148		
Neuropathy Impairment Score–weakness†				
Mean (±SD) baseline score	29.0±23.0	32.7±25.2		
Least-squares mean (±SE) change from baseline at 18 mo	17.9±2.0	0.1±1.3	–17.9±2.3	<0.001
Score on the Rasch-built Overall Disability Scale‡				
Mean (±SD) baseline score	29.8±10.8	29.7±11.5		
Least-squares mean (±SE) change from baseline at 18 mo	–8.9±0.9	0.0±0.6	9.0±1.0	<0.001
10-m walk test — m/sec§				
Mean (±SD) baseline value	0.79±0.32	0.80±0.40		
Least-squares mean (±SE) change from baseline at 18 mo	–0.24±0.04	0.08±0.02	0.31±0.04	<0.001
Modified BMI¶				
Mean (±SD) baseline value	989.9±214.2	969.7±210.5		
Least-squares mean (±SE) change from baseline at 18 mo	–119.4±14.5	–3.7±9.6	115.7±16.9	<0.001
Composite Autonomic Symptom Score 31‖				
Mean (±SD) baseline score	30.3±16.4	30.6±17.6		
Least-squares mean (±SE) change from baseline at 18 mo	2.2±1.9	–5.3±1.3	–7.5±2.2	<0.001
Exploratory end points in the cardiac subpopulation**				
No. of patients	36	90		
Left ventricular wall thickness — mm				
Mean (±SD) baseline value	16.4±2.1	16.8±2.6		
Least-squares mean (±SE) change from baseline at 18 mo	–0.1±0.3	–1.0±0.2	–0.9±0.4	0.02
Left ventricular longitudinal strain — %				
Mean (±SD) baseline value	–15.66±3.51	–15.13±3.41		
Least-squares mean (±SE) change from baseline at 18 mo	1.46±0.48	0.08±0.28	–1.37±0.56	0.02
NT-proBNP††				
Baseline value				
Geometric mean — pg/ml	711.1	726.9		
Coefficient of variation — %	190.8	220.3		
Ratio to baseline at 18 mo‡‡	1.97	0.89	0.45§§	<0.001

* The modified intention-to-treat (ITT) population included all the patients who underwent randomization and received at least one dose of patisiran or placebo.

† Scores on the weakness component of the Neuropathy Impairment Score range from 0 to 192, with higher scores indicating more impairment. The number of patients who were assessed at 18 months was 51 in the placebo group and 137 in the patisiran group.

‡ Scores on the Rasch-built Overall Disability Scale range from 0 to 48, with lower scores indicating more disability. The number of patients who were assessed at 18 months was 54 in the placebo group and 138 in the patisiran group.

§ A lower value indicates a slower gait speed. The number of patients who were assessed at 18 months was 55 in the placebo group and 138 in the patisiran group.

¶ The modified body-mass index (BMI) was the BMI (weight in kilograms divided by square of height in meters) × albumin level in grams per liter. The number of patients who were assessed at 18 months was 52 in the placebo group and 133 in the patisiran group.

‖ Values for the Composite Autonomic Symptom Score 31 range from 0 to 100, with higher scores indicating more autonomic symptoms. The number of patients who were assessed at 18 months was 53 in the placebo group and 136 in the patisiran group.

** The cardiac subpopulation included patients with a baseline left ventricular wall thickness of 13 mm or more in the absence of a history of aortic valve disease or hypertension.

†† N-terminal pro–brain natriuretic peptide (NT-proBNP) is a measure of cardiac stress that is an independent predictor of death in patients with transthyretin cardiac amyloidosis.

‡‡ Shown is the adjusted geometric mean ratio to baseline at month 18.

§§ Shown is the ratio of adjusted geometric mean ratio to baseline at month 18 between the two trial groups (patisiran:placebo).

ous adverse events (36% and 40%, respectively) was similar in the two groups (Table 3, and Table S2 in the Supplementary Appendix). Adverse events leading to discontinuation of the trial regimen occurred more frequently with placebo (14%) than with patisiran (5%); adverse events that led to discontinuation of the trial regimen in two or more patients were cardiac failure (two patients [1%] in the patisiran group) and acute kidney injury (two patients [3%] in the placebo group). Death occurred in seven patients (5%) in the patisiran group and in six patients (8%) in the placebo group. The causes of death were primarily cardiovascular in nature and consistent with those expected in patients with hereditary transthyretin amyloidosis (Table S4 in the Supplementary Appendix). The incidence of cardiac adverse events (28% in the patisiran group and 36% in the placebo group), cardiac serious adverse events (14% and 13%, respectively), and cardiac failure (9% and 10%, respectively) was similar in the two groups. The incidence of cardiac arrhythmias was lower with patisiran (19%) than with placebo (29%).

Common adverse events that occurred more frequently with patisiran than with placebo included peripheral edema (30% vs. 22%) and infusion-related reactions (19% vs. 9%) (Table 3, and Table S3 in the Supplementary Appendix). These were all mild or moderate in severity. One patient withdrew owing to a moderate infusion-related reaction of flushing. Symptoms of infusion-related reactions that were reported in at least 3% of patients in either group were back pain, flushing, abdominal pain, and nausea (Table S3 in the Supplementary Appendix); there were no reported severe or serious infusion-related reactions, and the frequency of infusion-related reactions decreased over time. No clinically relevant changes in laboratory values related to patisiran, including platelet counts and indicators of liver or kidney function, were observed during the trial. Of the 187 patients eligible to participate in an open-label extension study, 186 (99%) were enrolled.

Table 3. Safety and Side Effects.

Event	Placebo (N=77)	Patisiran (N=148)
	no. of patients (%)	
Any adverse event	75 (97)	143 (97)
Adverse events occurring in ≥10% of patients in either group		
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	44 (30)
Fall	22 (29)	25 (17)
Nausea	16 (21)	22 (15)
Infusion-related reaction	7 (9)	28 (19)
Constipation	13 (17)	22 (15)
Urinary tract infection	14 (18)	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	11 (14)	5 (3)
Anemia	8 (10)	3 (2)
Syncope	8 (10)	3 (2)
Adverse event leading to discontinuation of the trial regimen	11 (14)	7 (5)
Adverse event leading to withdrawal from the trial	9 (12)	7 (5)
Death	6 (8)	7 (5)
Any serious adverse event	31 (40)	54 (36)
Any severe adverse event	28 (36)	42 (28)

DISCUSSION

Current treatment options for hereditary transthyretin amyloidosis are limited; however, our data indicate that the lowering of transthyretin levels may be an effective therapeutic approach. We found that patisiran, an RNAi therapeutic, significantly improved neuropathy in patients with hereditary transthyretin amyloidosis. The effects extended across the sensorimotor and autonomic domains and were consistent across patient subgroups. In addition, patisiran treatment resulted in significant improvements in quality of life, walking, nutritional status, and activities of daily living. The broad patient population recruited to the APOLLO phase 3 trial is characteristic of the wide disease spectrum expected in clinical practice. Our results are corroborated by a trial of

inotersen, also published in this issue of the *Journal*, which used an antisense oligonucleotide approach to transthyretin lowering and showed the slowing of neuropathy progression in patients with hereditary transthyretin amyloidosis.[23]

Hereditary transthyretin amyloidosis has a rapidly progressive course, highlighted by the worsening condition seen in patients who received placebo during the trial, a finding consistent with those of other reports.[6,24,25] Across trial end points, patients in the placebo group had evidence of increasing sensorimotor and autonomic impairment, leading to worsening symptoms and decreased functional ability. Disease progression was also evident from the higher rate of discontinuation of the trial regimen in the placebo group (38%, as compared with 7% in the patisiran group), as well as the high incidence of adverse events likely to be associated with worsening disease (e.g., falls, urinary tract infections, and syncope) in the placebo group.

In contrast, disease progression was halted or reversed with patisiran treatment across all primary and secondary end points. In addition, the polyneuropathy disability score improved in 8% of the patients in the patisiran group at 18 months, whereas no patients in the placebo group had improvement. This included transition from assisted to unassisted walking, a notable milestone for patients with hereditary transthyretin amyloidosis, which is consistent with the effect of patisiran on gait speed.

There was also evidence that patisiran improved cardiac manifestations of hereditary transthyretin amyloidosis, as indicated by echocardiographic measures of cardiac structure and function and a reduction in NT-proBNP levels. It is possible that the increased gait speed in patients who received patisiran may have resulted from favorable effects on both the neuropathic and cardiac aspects of the disease.

The principal safety finding was mild-to-moderate infusion-related reactions, the incidence of which decreased over time. The number of deaths in the overall population, and in the cardiac subgroup, was similar in the patisiran group and the placebo group. There were no safety signals regarding thrombocytopenia or renal dysfunction with patisiran, although these events have been observed with other oligonucleotide therapies.[26] In conclusion, the APOLLO phase 3 trial showed that patisiran provided benefit to patients with hereditary transthyretin amyloidosis by treating a broad range of symptoms.

Supported by Alnylam Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the patients and their families who were involved in the trial; the additional APOLLO trial investigators, who are listed in the Supplementary Appendix; W.J. Litchy (Mayo Clinic), Brian Bettencourt (formerly at Alnylam Pharmaceuticals), and Matt White (Alnylam Pharmaceuticals) for their contributions; and the staff at Adelphi Communications and Angela M. Partisano (Alnylam Pharmaceuticals) for editorial assistance with an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: David Adams, M.D., Ph.D., Alejandra Gonzalez-Duarte, M.D., William D. O'Riordan, M.D., Chih-Chao Yang, M.D., Mitsuharu Ueda, M.D., Ph.D., Arnt V. Kristen, M.D., Ivailo Tournev, M.D., Hartmut H. Schmidt, M.D., Teresa Coelho, M.D., John L. Berk, M.D., Kon-Ping Lin, M.D., Giuseppe Vita, M.D., Shahram Attarian, M.D., Ph.D., Violaine Planté-Bordeneuve, M.D., Ph.D., Michelle M. Mezei, M.D.C.M., Josep M. Campistol, M.D., Juan Buades, M.D., Ph.D., Thomas H. Brannagan III, M.D., Byoung J. Kim, M.D., Jeeyoung Oh, M.D., Ph.D., Yesim Parman, M.D., Yoshiki Sekijima, M.D., Ph.D., Philip N. Hawkins, F.Med.Sci., Scott D. Solomon, M.D., Michael Polydefkis, M.D., M.H.S., Peter J. Dyck, M.D., Pritesh J. Gandhi, Pharm.D., Sunita Goyal, M.D., Jihong Chen, Ph.D., Andrew L. Strahs, Ph.D., Saraswathy V. Nochur, Ph.D., Marianne T. Sweetser, M.D., Ph.D., Pushkal P. Garg, M.D., Akshay K. Vaishnaw, M.D., Ph.D., Jared A. Gollob, M.D., and Ole B. Suhr, M.D., Ph.D.

The authors' affiliations are as follows: Assistance Publique–Hôpitaux de Paris (APHP), National Reference Center for Familial Amyloidotic Polyneuropathy, Centre Hospitalier Universitaire (CHU) Bicêtre, INSERM Unité 1195, Université Paris-Sud, Le Kremlin-Bicêtre (D.A.), the Department of Neuromuscular Disorders and ALS, Hôpital de la Timone, Marseille (S.A.), and the Department of Neurology, Amyloid Network, CHU Henri Mondor–APHP, Créteil (V.P.-B.) — all in France; the National Institute of Medical Sciences and Nutrition–Salvador Zubiran, Mexico City (A.G.-D.); the Department of Clinical Research, eStudySite, San Diego, CA (W.D.O.); the Department of Neurology, National Taiwan University Hospital (C.-C.Y.), and the Department of Neurology, Taipei Veterans General Hospital (K.-P.L.), Taipei, Taiwan; Kumamoto University Hospital, Kumamoto (M.U.), and the Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto (Y.S.) — both in Japan; the Department of Cardiology, University of Heidelberg, Heidelberg (A.V.K.), and Medizinische Klinik B für Gastroenterologie und Hepatologie, Universitätsklinikum Münster, Münster (H.H.S.) — both in Germany; University Multiprofile Hospital for Active Treatment, Sofia, Bulgaria (I.T.); Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal (T.C.); the Amyloidosis Center, Department of Medicine, Boston Medical Center (J.L.B.), and Harvard Medical School (S.D.S.), Boston; the Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy (G.V.); the Departments of Neurology and Medicine, Vancouver General Hospital, Vancouver, BC, Canada (M.M.M.); the Department of Nephrology, Hospital Clinic, Barcelona (J.M.C.), and the Balearic Islands Health Research Institute and Hospital Son Llatzer, Palma de Mallorca (J.B.) — all in Spain; the Department of Neurology, Columbia University, College of Physicians

and Surgeons, New York (T.H.B.); Samsung Medical Center, Sungkyunkwan University School of Medicine (B.J.K.), and the the Department of Neurology, Konkuk University Medical Center (J.O.), Seoul, South Korea; the Department of Neurology, Istanbul University, Istanbul, Turkey (Y.P.); the Division of Medicine, University College London, London (P.N.H.); Johns Hopkins Bayview Medical Center, Baltimore (M.P.); the Department of Neurology, Mayo Clinic, Rochester, MN (P.J.D.); Alnylam Pharmaceuticals, Cambridge, MA (P.J.G., S.G., J.C., A.L.S., S.V.N., M.T.S., P.P.G., A.K.V., J.A.G.); and the Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (O.B.S.).

REFERENCES

1. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med 2015; 47:625-38.
2. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012;126:1286-300.
3. Conceição I, González-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst 2016;21:5-9.
4. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013;8:31.
5. Dungu JN, Anderson LJ, Whelan CJ, Hawkins PN. Cardiac transthyretin amyloidosis. Heart 2012;98:1546-54.
6. Adams D, Coelho T, Obici L, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology 2015;85:675-82.
7. Koike H, Tanaka F, Hashimoto R, et al. Natural history of transthyretin Val-30Met familial amyloid polyneuropathy: analysis of late-onset cases from non-endemic areas. J Neurol Neurosurg Psychiatry 2012;83:152-8.
8. Mariani LL, Lozeron P, Théaudin M, et al. Genotype-phenotype correlation and course of transthyretin familial amyloid polyneuropathies in France. Ann Neurol 2015;78:901-16.
9. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J 2012; 164(2):222-228.e1.
10. Castaño A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. Heart Fail Rev 2015;20:163-78.
11. Liepnieks JJ, Zhang LQ, Benson MD. Progression of transthyretin amyloid neuropathy after liver transplantation. Neurology 2010;75:324-7.
12. Adams D, Buades J, Suhr O, Obici L, Coelho T. Preliminary assessment of neuropathy progression in patients with hereditary ATTR amyloidosis after orthotopic liver transplantation (OLT). Orphanet J Rare Dis 2015;10:Suppl 1. abstract.
13. Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol 2013;260: 2802-14.
14. Cortese A, Vita G, Luigetti M, et al. Monitoring effectiveness and safety of Tafamidis in transthyretin amyloidosis in Italy: a longitudinal multicenter study in a non-endemic area. J Neurol 2016;263:916-24.
15. Planté-Bordeneuve V, Gorram F, Salhi H, et al. Long-term treatment of transthyretin familial amyloid polyneuropathy with Tafamidis: a clinical and neurophysiological study. J Neurol 2017;264:268-76.
16. Lozeron P, Théaudin M, Mincheva Z, Ducot B, Lacroix C, Adams D. Effect on disability and safety of Tafamidis in late onset of Met30 transthyretin familial amyloid polyneuropathy. Eur J Neurol 2013;20:1539-45.
17. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013;369:819-29.
18. Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. Orphanet J Rare Dis 2015;10:109.
19. Partisano AM, Berk JL, Adams D, et al. Long-term, open-label clinical experience with patisiran, an investigational RNAi therapeutic for patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy. Orphanet J Rare Dis 2017;12:Suppl 1:165. abstract.
20. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol 2017;17:181.
21. Suanprasert N, Berk JL, Benson MD, et al. Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials. J Neurol Sci 2014;344:121-8.
22. Dyck PJ, Kincaid JC, Dyck PJB, et al. Assessing mNIS+7$_{\text{Ionis}}$ and international neurologists' proficiency in a familial amyloidotic polyneuropathy trial. Muscle Nerve 2017;56:901-11.
23. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22-31.
24. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology 2012;79:785-92.
25. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA 2013;310:2658-67.
26. Sepp-Lorenzino L, Ruddy M. Challenges and opportunities for local and systemic delivery of siRNA and antisense oligonucleotides. Clin Pharmacol Ther 2008;84:628-32.