ORIGINAL ARTICLE

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

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ABSTRACT

BACKGROUND

Hereditary transthyretin amyloidosis is caused by pathogenic single-nucleotide variants in the gene encoding transthyretin (*TTR*) that induce transthyretin misfolding and systemic deposition of amyloid. Progressive amyloid accumulation leads to multiorgan dysfunction and death. Inotersen, a 2′-*O*-methoxyethyl–modified antisense oligonucleotide, inhibits hepatic production of transthyretin.

METHODS

We conducted an international, randomized, double-blind, placebo-controlled, 15-month, phase 3 trial of inotersen in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy. Patients were randomly assigned, in a 2:1 ratio, to receive weekly subcutaneous injections of inotersen (300 mg) or placebo. The primary end points were the change in the modified Neuropathy Impairment Score+7 (mNIS+7; range, –22.3 to 346.3, with higher scores indicating poorer function; minimal clinically meaningful change, 2 points) and the change in the score on the patient-reported Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire (range, –4 to 136, with higher scores indicating poorer quality of life). A decrease in scores indicated improvement.

RESULTS

A total of 172 patients (112 in the inotersen group and 60 in the placebo group) received at least one dose of a trial regimen, and 139 (81%) completed the intervention period. Both primary efficacy assessments favored inotersen: the difference in the least-squares mean change from baseline to week 66 between the two groups (inotersen minus placebo) was –19.7 points (95% confidence interval [CI], –26.4 to –13.0; P<0.001) for the mNIS+7 and –11.7 points (95% CI, –18.3 to –5.1; P<0.001) for the Norfolk QOL-DN score. These improvements were independent of disease stage, mutation type, or the presence of cardiomyopathy. There were five deaths in the inotersen group and none in the placebo group. The most frequent serious adverse events in the inotersen group were glomerulonephritis (in 3 patients [3%]) and thrombocytopenia (in 3 patients [3%]), with one death associated with one of the cases of grade 4 thrombocytopenia. Thereafter, all patients received enhanced monitoring.

CONCLUSIONS

Inotersen improved the course of neurologic disease and quality of life in patients with hereditary transthyretin amyloidosis. Thrombocytopenia and glomerulonephritis were managed with enhanced monitoring. (Funded by Ionis Pharmaceuticals; NEURO-TTR ClinicalTrials.gov number, NCT01737398.)

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Autosomal dominant mutations in the gene encoding transthyretin (*TTR*) cause a rare systemic disorder known as hereditary transthyretin amyloidosis. The single amino-acid changes that result from these mutations destabilize the tetrameric transthyretin protein complex to cause aggregation of monomers into insoluble, extracellular amyloid deposits.[1] Accumulation of amyloid deposits in multiple organ systems leads to progressive peripheral polyneuropathy, cardiomyopathy, nephropathy, and gastrointestinal dysfunction.[2-5] The average life expectancy, untreated, from symptom onset is 3 to 15 years.[6] The presence of cardiomyopathy is associated with a worse prognosis. Patients typically die from malnutrition and cachexia, renal failure, cardiac disease, and sudden death.[7]

The liver is the primary source of systemic transthyretin protein. Liver transplantation has historically been the standard of care for hereditary transthyretin amyloidosis, but continued deposition of wild-type transthyretin amyloid after transplantation can limit its effectiveness.[8-11] Although some treatments are currently available — such as tafamidis (Vyndaqel) and diflunisal, small molecules that stabilize the circulating tetrameric form of transthyretin and slow disease progression[11-16] — additional treatments could be of value.

Inotersen (formerly IONIS-TTR$_{Rx}$/ISIS 420915) is a 2′-*O*-methoxyethyl–modified antisense oligonucleotide inhibitor of the hepatic production of transthyretin protein. In healthy volunteers, inotersen showed dose-dependent and sustained reductions of circulating transthyretin levels.[17] We conducted a randomized, double-blind, placebo-controlled, phase 3 trial (NEURO-TTR) to determine the efficacy and safety of inotersen treatment in patients with hereditary transthyretin amyloidosis with polyneuropathy in the presence or absence of cardiomyopathy.

METHODS

PATIENTS

The trial was conducted at 24 centers in 10 countries. Adults 18 to 82 years of age who had received a diagnosis of stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy and who had a Neuropathy Impairment Score (NIS) of 10 to 130, a *TTR* mutation determined by genotyping, and documented amyloid deposits determined on biopsy were eligible for this trial. The NIS scale ranges from 0 to 244 points, with a higher score indicating poorer function and a minimal clinically meaningful difference of 2 points.[18] Key exclusion criteria were clinically significant abnormalities in screening laboratory values, a Karnofsky performance status score of 50 or less (on a scale of 0 to 100, with lower scores indicating greater disability), other causes of polyneuropathy besides hereditary transthyretin amyloidosis, previous liver transplantation, and heart failure of New York Heart Association class III or higher. The use of tafamidis or diflunisal during the intervention period was not allowed.

TRIAL OVERSIGHT

The trial protocol, available with the full text of this article at NEJM.org, was approved by institutional review boards or local ethics committees. The trial was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonisation and the principles of the Declaration of Helsinki. All the patients provided written informed consent to participate in the trial. An independent data and safety monitoring committee reviewed unblinded safety data approximately four times per year.

Data were collected by the site investigators, and the sponsor (Ionis Pharmaceuticals) was responsible for data analysis. All the authors had full access to the data. The first draft of the manuscript was written by a contract medical writer and the sponsor, with input from the authors on subsequent drafts. All the authors approved the final version, made the decision to submit the manuscript for publication, vouch for the completeness and accuracy of the data and analyses presented, and affirm that the trial was conducted and reported with fidelity to the protocol and statistical analysis plan, available with the protocol at NEJM.org.

TRIAL DESIGN

After a 6-week screening period, eligible patients were randomly assigned, in a 2:1 ratio, to receive 300 mg of inotersen (equivalent to 284 mg of free acid) or placebo (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Patients were stratified according to the following factors: Val30Met *TTR* mutation (148G→A) versus non-Val30Met *TTR*

mutation, stage 1 versus stage 2 disease, and previous treatment with tafamidis or diflunisal versus no known previous treatment. Patients received three subcutaneous injections during the first week to achieve near steady-state drug levels, followed by a once-weekly subcutaneous injection for the next 64 weeks. A total of 13 of 67 doses (19%) were required to be administered at prespecified clinical visits. All other doses could be administered at home by the patient, a trained family member, or a health professional. All the patients received vitamin A supplements at the recommended daily allowance (approximately 3000 IU) to ensure adequate delivery of dietary vitamin A to tissues in the context of low transthyretin levels. The trial also included a 1-week efficacy-assessment period and a 6-month postintervention evaluation period if a patient was not enrolled in the open-label extension study.

END POINTS AND ASSESSMENTS

The primary end points were the change from baseline to week 66 in the standardized modified Neuropathy Impairment Score+7 (mNIS+7) composite score[18-22] and in the total score on the Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire.[23,24] The mNIS+7 has eight components, with a composite score ranging from −22.3 to 346.3 (the higher the score, the poorer the function). A decrease in score indicates an improvement, and a 2-point change has been defined as the minimal clinically meaningful change detectable.[14,18] The Norfolk QOL-DN is a 35-item questionnaire that comprises five domains, with a total score ranging from −4 to 136 (the higher the score, the poorer the quality of life). Changes in the patient-reported Norfolk QOL-DN score have been shown to be proportional to changes in the NIS.[24] (See Table S1 in the Supplementary Appendix for complete scoring scales according to component of the mNIS+7 and domain of the Norfolk QOL-DN questionnaire.) All mNIS+7 assessors were specially trained and prequalified by a central reader. The NIS component was performed by an independent neurologist who was not aware of the trial-group assignments and not involved in the day-to-day conduct of the trial or care of the patient. Safety assessments included collection of adverse events that occurred from the time of the first dose to the end of the trial (including the postintervention follow-up period), clinical laboratory tests, vital signs, 12-lead electrocardiography, and electroretinography (ERG) examinations to detect early signs of vitamin A deficiency.

STATISTICAL ANALYSIS

The planned sample of 135 patients was calculated under the assumptions of an effect size of 9.6 points and a standard deviation of 14 in the mNIS+7, an effect size of 10.7 and a standard deviation of 18 in the Norfolk QOL-DN score, and a dropout rate of 25%. Using a 2:1 allocation ratio, we estimated that the trial had a power of at least 90% for the mNIS+7 end point and a power of at least 80% for the Norfolk QOL-DN end point, using a two-sided test with an alpha level of 5%.

Efficacy analyses included all randomly assigned patients who received at least one dose of a trial regimen and who had at least one postbaseline efficacy assessment for the mNIS+7 or the Norfolk QOL-DN score. Subgroup analyses were performed on the basis of the three stratification factors and according to the presence or absence of cardiomyopathy, geographic region, and selected demographic characteristics for each of the two end points. The presence of cardiomyopathy was defined by a diagnosis of transthyretin cardiomyopathy at trial entry or by the following criteria: an interventricular wall thickness of 13 mm or more on transthoracic echocardiography at baseline, as ascertained by a central reader, and no known history of persistent hypertension (systolic blood pressure, ≥150 mm Hg) within 12 months before screening. Safety analyses were performed on all randomly assigned patients who received at least one dose of a trial regimen.

The primary end points were analyzed with the use of a ranking strategy, with the mNIS+7 tested first and the Norfolk QOL-DN score tested second. No adjustments were made for multiple testing. The data were analyzed with the use of a mixed-effects model with repeated measures. The mNIS+7 was scored at baseline (two assessments), week 35 (one assessment), and week 66 (two assessments). The two assessments at baseline and week 66 were averaged at the component level. Week 66 was the time point for the primary analysis. Predefined sensitivity analyses included alternative methods for imputing missing data at the visit level. A total of 16 prespecified subgroup analyses are reported. Data are summarized according to trial group with the use of descrip-

tive summary statistics. All statistical tests were conducted with the use of two-sided tests with an alpha level of 5%. Additional details on eligibility criteria, trial regimens, efficacy and safety assessments, and methods of statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS AND FOLLOW-UP

The trial was conducted from March 2013 through November 2017. Of 278 patients who were screened for participation in the trial, 173 were randomly assigned in a 2:1 ratio to receive inotersen or placebo (Fig. 1). A total of 172 patients (112 in the inotersen group and 60 in the placebo group) received at least one dose of a trial regimen. The baseline characteristics were well balanced overall between the two groups (Table 1). The mean age of the trial population was 59 years; 69% of the patients were male, and 92% of the patients were white. Approximately half carried the Val30Met mutation (from a total of 27 mutations). A total of 67% of the patients had stage 1 disease, 58% had previously received tafamidis or diflunisal, and 63% had cardiomyopathy. At the time of trial entry, cardiomyopathy was more prevalent in the inotersen group than in the placebo group, and patients in the inotersen group had a longer duration of disease (since diagnosis of cardiomyopathy) than those in the placebo group.

Of the 172 randomly assigned patients who received at least one dose of a trial regimen, 139 (81%) completed the 15-month intervention period (Fig. 1). A total of 25 (22%) of the patients who received inotersen and 8 (13%) of those who received placebo discontinued the trial regimen. Adverse events were the main reason for discontinuation in the inotersen group (16 patients, 14%), whereas voluntary withdrawal (3 patients, 5%) and disease progression (3 patients, 5%) were the most common reasons for discontinuation in the placebo group. A total of 135 patients were enrolled in the open-label extension study.

PRIMARY EFFICACY END POINTS

Both primary end points, the mNIS+7 and the Norfolk QOL-DN score, achieved significant differences between the inotersen group and the placebo group at week 66 after 15 months of intervention (Fig. 2). The difference in least-squares mean change from baseline to week 66 between the two groups (inotersen minus placebo) was –19.7 points (95% confidence interval [CI], –26.4 to –13.0; P<0.001) for the mNIS+7 and –11.7 points (95% CI, –18.3 to –5.1; P<0.001) for the Norfolk QOL-DN score, favoring inotersen (Table S3 in the Supplementary Appendix). Moreover, significant between-group differences were observed in both end points at the interim week 35 assessment. At week 35, the difference in the least-squares mean change from baseline for the mNIS+7 was –8.7 points (95% CI, –13.5 to –3.9; P<0.001) and for the Norfolk QOL-DN score was –6.1 points (95% CI, –11.8 to –0.5; P=0.03). Prespecified sensitivity analyses showed a robust and beneficial inotersen treatment effect under all assumptions (Table S4 in the Supplementary Appendix).

On average, patients who received inotersen had an increase of 5.8 points (95% CI, 1.6 to 10.0) from baseline in the mNIS+7 (vs. 25.5 points [95% CI, 20.2 to 30.8] with placebo) and of 1.0 points (95% CI, –3.2 to 5.2) in the Norfolk QOL-DN score (vs. 12.7 points [95% CI, 7.4 to 17.9] with placebo) by the end of the intervention period. Further analysis of patients who completed the intervention period showed that 36% of the patients in the inotersen group had an improvement (no increase from baseline) in the mNIS+7 and 50% had an improvement in the Norfolk QOL-DN score (Table S5 in the Supplementary Appendix).

All subgroup analyses that were performed according to stratification factor showed a significant benefit of inotersen as compared with placebo at week 66 in the mNIS+7 (difference in least-squares mean change from baseline: Val30Met mutation, –18.9 [95% CI, –28.1 to –9.6; P<0.001], and non-Val30Met mutation, –21.3 [95% CI, –31.1 to –11.5; P<0.001]; stage 1 disease, –14.2 [95% CI, –22.5 to –5.9; P<0.001], and stage 2 disease, –29.1 [95% CI, –40.2 to –18.0; P<0.001]; previous treatment with tafamidis or diflunisal, –20.0 [95% CI, –29.2 to –10.8; P<0.001], and no previous treatment, –20.8 [95% CI, –30.6 to –11.0; P<0.001]), consistent with the results of the primary analysis. The benefit of inotersen over placebo for the subgroup analyses according to the Norfolk QOL-DN stratification factor was also consistent with the primary analysis (difference in least-squares mean change from baseline: Val30Met mutation, –12.2 [95% CI, –21.6 to –3.0; P=0.01],

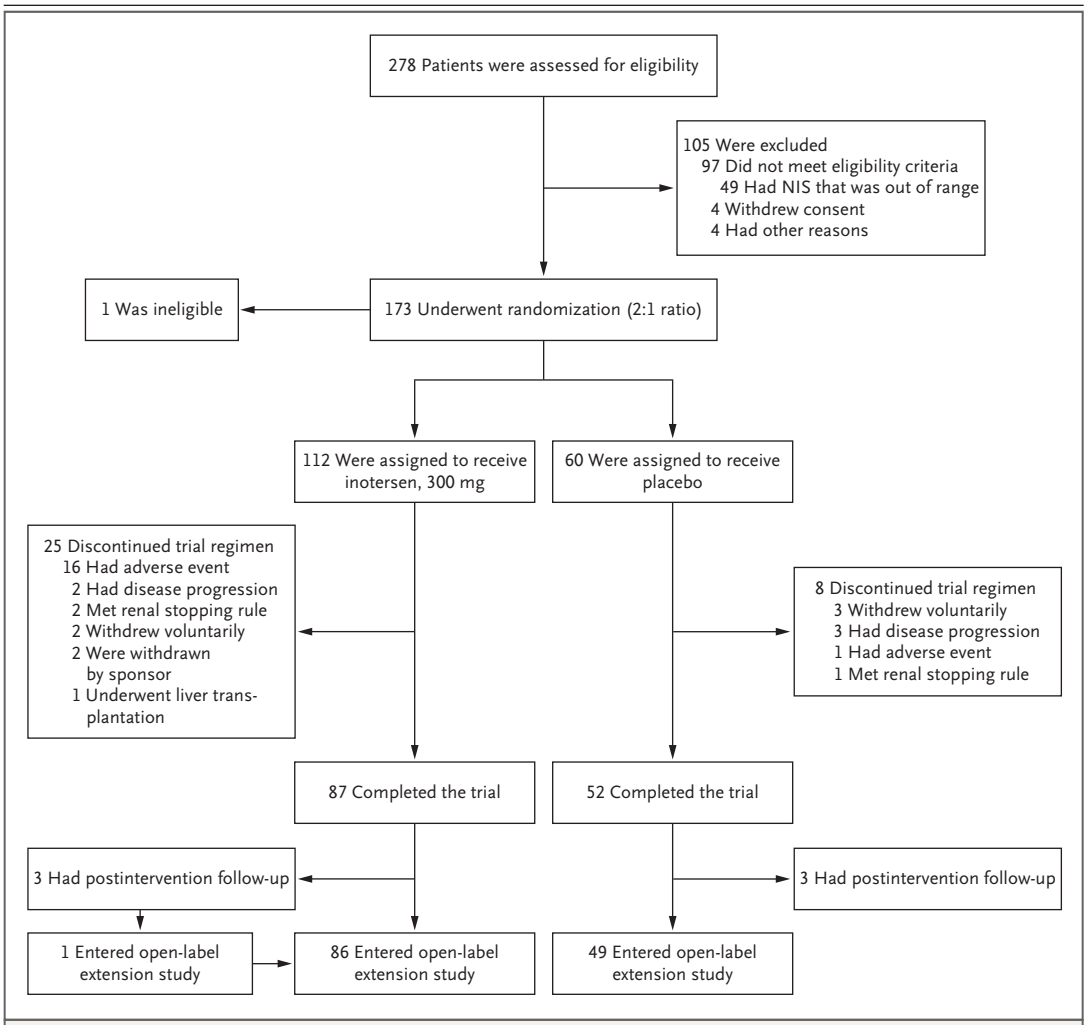

Figure 1. Randomization and Follow-up.

One patient in the inotersen group underwent randomization in error and did not begin the trial regimen. Adverse events leading to discontinuation of inotersen were thrombocytopenia (in 2 patients), abdominal distention, intestinal perforation, nausea, vomiting, pyrexia, hypersensitivity, decreased platelet count, cachexia (in 2 patients), arthralgia, myalgia, chorea, dementia, embolic stroke, intracranial hemorrhage, myelopathy, myoclonus, acute kidney injury, glomerulonephritis, tubulointerstitial nephritis, pruritus, reticular erythematous mucinosis, and deep-vein thrombosis; 6 of 16 patients (38%) discontinued inotersen because of multiple events. Adverse events leading to discontinuation of placebo were pain, increased weight, and arthralgia. Of the 2 patients in the inotersen group who discontinued the trial regimen because they were withdrawn by the sponsor, 1 patient whose data were unblinded for safety monitoring was allowed to enroll in the open-label extension study. NIS denotes Neuropathy Impairment Score.

and non-Val30Met mutation, –11.1 [95% CI, –20.9 to –1.4; P=0.03]; stage 1 disease, –9.9 [95% CI, –18.2 to –1.7; P=0.02], and stage 2 disease, –15.0 [95% CI, –26.2 to –3.9; P=0.008]; previous treatment with tafamidis or diflunisal, –9.0 [95% CI, –18.2 to 0.1; P=0.05], and no previous treatment, –14.7 [95% CI, –24.5 to –4.9; P=0.003]). (For details, see Figs. S2 and S3 in the Supplementary Appendix.)

Consistent benefit for both primary end points in favor of inotersen was also observed at week 66 when analyzed according to the presence of cardiomyopathy (difference in least-squares mean change from baseline: mNIS+7, –17.2 [95% CI, –25.6 to –8.7; P<0.001]; Norfolk QOL-DN score, –9.0 [95% CI, –17.5 to –0.6; P=0.04]) or absence of cardiomyopathy (difference in least-squares mean change from baseline: mNIS+7,

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

Characteristic	Placebo (N=60)	Inotersen (N=112)	Total (N=172)
Age — yr	59.5±14.0	59.0±12.5	59.2±13.0
Male sex — no. (%)	41 (68)	77 (69)	118 (69)
Race — no. (%)†			
White	53 (88)	105 (94)	158 (92)
Black	1 (2)	3 (3)	4 (2)
Asian	3 (5)	1 (<1)	4 (2)
Other or multiple	3 (5)	3 (3)	6 (3)
Geographic region — no. (%)			
Europe	23 (38)	37 (33)	60 (35)
North America	26 (43)	56 (50)	82 (48)
South America or Australasia	11 (18)	19 (17)	30 (17)
BMI‡	24.2±4.9	24.0±4.9	24.1±4.9
Modified BMI§	105.0±22.8	101.1±22.8	102.5±22.8
Val30Met *TTR* mutation — no. (%)¶‖	33 (55)	56 (50)	89 (52)
Disease stage — no. (%)‖**			
1: patient is ambulatory	42 (70)	74 (66)	116 (67)
2: patient is ambulatory with assistance	18 (30)	38 (34)	56 (33)
Previous treatment with tafamidis or diflunisal — no. (%)‖	36 (60)	63 (56)	99 (58)
Duration of disease from diagnosis of hATTR-PN — mo††	39.3±40.3	42.4±51.2	41.3±47.6
Stage 1	45.4±43.1	43.2±47.8	44.0±46.0
Stage 2	24.8±29.0	40.9±57.8	35.8±50.7
Duration of disease from onset of hATTR-PN symptoms — mo††	64.0±52.3	63.9±53.2	63.9±52.7
Stage 1	64.4±53.0	59.4±53.1	61.2±52.9
Stage 2	63.2±52.2	72.6±52.9	69.6±52.4
Presence of cardiomyopathy — no. (%)‡‡	33 (55)	75 (67)	108 (63)
mNIS+7 composite score§§	74.8±39.0	79.2±37.0	77.6±37.6
Norfolk QOL-DN total score¶¶	48.7±26.7	48.2±27.5	48.4±27.2

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The term hATTR-PN denotes hereditary transthyretin amyloidosis with polyneuropathy.
† Race was reported by the patients.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ The modified BMI was defined as BMI×albumin level in grams per deciliter.
¶ See Table S2 in the Supplementary Appendix for a complete listing of *TTR* mutations represented in the trial.
‖ Values are based on data from the electronic case-report form.
** Baseline disease stage and polyneuropathy disability scores were compared and queried as necessary for consistency at the center level in the assessment of ambulatory status.
†† Only year and month were collected for diagnosis of hATTR-PN and onset of hATTR-PN symptoms. The duration from diagnosis of hATTR-PN and onset of hATTR-PN symptoms was calculated relative to the date of informed consent.
‡‡ The presence of cardiomyopathy was defined by a diagnosis of transthyretin cardiomyopathy at trial entry or by the following criteria: an interventricular wall thickness of 13 mm or more on transthoracic echocardiography at baseline, as ascertained by a central reader, or no known history of persistent hypertension (systolic blood pressure, ≥150 mm Hg) within 12 months before screening.
§§ Composite scores on the modified Neuropathy Impairment Score+7 (mNIS+7) scale range from –22.3 to 346.3, with higher scores indicating poorer function.
¶¶ Total scores on the Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire range from –4 to 136, with higher score indicating poorer quality of life.

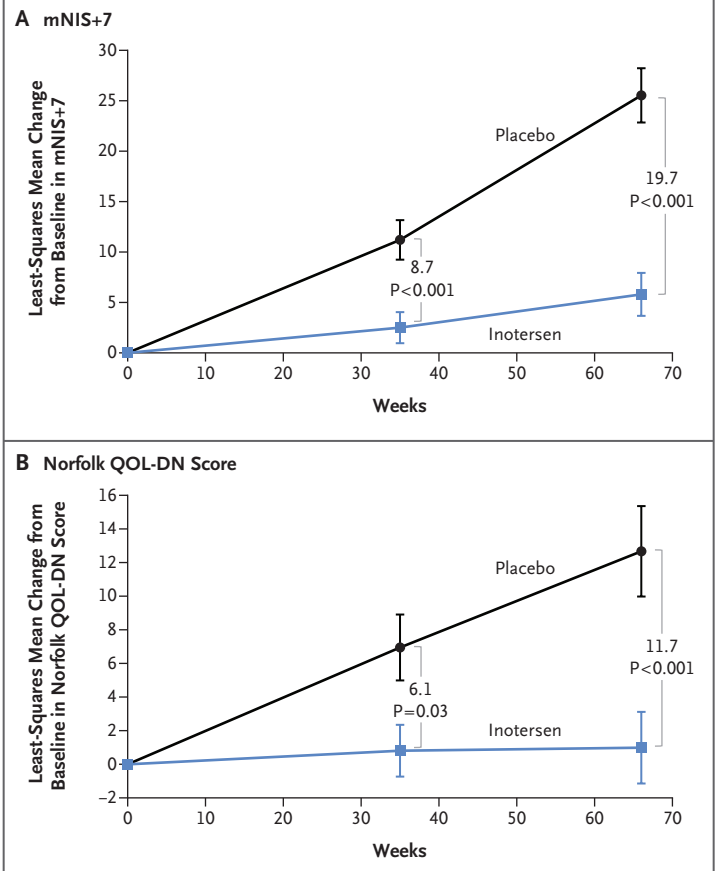

Figure 2. Change from Baseline in Primary End Points.

Brackets indicate the difference in the least-squares mean change from baseline between the inotersen group and the placebo group. Composite scores on the modified Neuropathy Impairment Score+7 (mNIS+7) scale range from −22.3 to 346.3 (the higher the score, the poorer the function), and total scores on the Norfolk Quality of Life–Diabetic Neuropathy (QOL-DN) questionnaire range from −4 to 136 (the higher the score, the poorer the quality of life). A decrease in score indicated an improvement on each scale. A 2-point change in the NIS+7 has been defined as the minimal clinically meaningful change detectable.[14,18] Changes in the patient-reported Norfolk QOL-DN score have been shown to be proportional to changes in the Neuropathy Impairment Score (range, 0 to 244, with a higher score indicating poorer function).[24] I bars indicate standard errors.

−25.2 [95% CI, −36.1 to −14.3; P<0.001]; Norfolk QOL-DN score, −16.4 [95% CI, −27.3 to −5.4; P=0.004]) (Figs. S4 and S5 in the Supplementary Appendix). Global longitudinal strain and other echocardiographic variables, however, did not differ significantly between the inotersen group and the placebo group after 15 months of intervention (Table S6 in the Supplementary Appendix). Further subgroup analyses according to geographic region, age, sex, and patient-reported race showed significant benefit in favor of inotersen in the mNIS+7 at week 66 (Figs. S6 and S7 in the Supplementary Appendix). The least-squares mean difference between the trial groups for body-mass index showed a trend in favor of inotersen to slow weight loss (Table S7 in the Supplementary Appendix).

SECONDARY AND TERTIARY EFFICACY END POINTS

Results from analyses of the mNIS+7 test at the component and subcomponent level, as well as the Norfolk QOL-DN questionnaire according to domain, are shown in Figure S8 in the Supplementary Appendix, along with the results from a second quality-of-life instrument, the 36-Item Short Form Health Survey (Table S8 in the Supplementary Appendix).

PHARMACODYNAMICS

In the inotersen group, reductions in circulating transthyretin reached steady-state levels by week 13 and were sustained through the end of the intervention period (Fig. S9 in the Supplementary Appendix). From week 13 to week 65, decreases in serum transthyretin from baseline levels in the inotersen group reached a median nadir of 79.0% and mean nadir of 74.0%. There was no correlation between the absolute or relative change from baseline in serum transthyretin levels and the change from baseline in the mNIS+7 score in patients who received inotersen (Pearson's r, 0.11, and P=0.33 for absolute change; Pearson's r, 0.06, and P=0.57 for relative change) (Fig. S10 in the Supplementary Appendix). These findings were consistent with a flat drug exposure–response relationship, which was expected at the single-dose level.

SAFETY

There were five deaths during the trial, all in the inotersen group (Table 2). Four of the five deaths were consistent with progression or complication of the underlying disease (two deaths from cachexia and one each from intestinal perforation and congestive heart failure) (Table S9 in the Supplementary Appendix). One patient in the inotersen group had a fatal intracranial hemorrhage in association with a platelet count of less than 10,000 per cubic millimeter that occurred before the introduction of frequent platelet monitoring.

Glomerulonephritis occurred in three patients (3%) in the inotersen group (Table 2). Each of these

three patients carried the Val30Met mutation. Two had shown a decline in the estimated glomerular filtration rate. In all three cases, the renal biopsy showed complex pathologic features, consistent with crescentic glomerulonephritis superimposed on a background of amyloidosis and (in two cases) interstitial fibrosis. One patient was successfully treated with glucocorticoids and cyclophosphamide and regained clinically significant renal function. Another patient did not receive immunosuppressive therapy owing to delayed diagnosis, and permanent hemodialysis was initiated. A third patient was identified as having clinically significant proteinuria after the implementation of more frequent renal monitoring of every 2 to 3 weeks; this patient did not show a decline in renal function. Urinary protein excretion returned to baseline levels after treatment with glucocorticoids.

A higher proportion of patients in the inotersen group (60 of 112, 54%) had a confirmed decrease in the postbaseline platelet count to less than 140,000 per cubic millimeter than in the placebo group (8 of 60, 13%) (Table S10 in the Supplementary Appendix). Decreases in the inotersen group occurred gradually over a period of several weeks, with an onset within the first 13 weeks of dosing and a mean nadir between 3 to 6 months after treatment initiation (Fig. S11 in the Supplementary Appendix). Thrombocytopenia with platelet counts of less than 25,000 per cubic millimeter occurred in 3 patients (3%) who received inotersen. Platelet counts in 2 of these 3 patients returned to baseline or near-baseline levels after discontinuation of the trial regimen and treatment with glucocorticoids. The third patient presented with an intracranial hemorrhage and died before treatment could be initiated. No cases of thrombocytopenia with platelet counts of less than 50,000 per cubic millimeter occurred after the institution of weekly platelet monitoring. Two patients in the inotersen group had a dose reduction to 150 mg weekly because of decreases in platelet counts. There was some evidence of an immune-mediated mechanism in the severe events, as indicated by recovery with glucocorticoid treatment and the presence of antiplatelet IgG in each of the 3 patients. Importantly, further investigation ruled out a heparin-induced thrombocytopenia–type mechanism and effects on platelet production.

Adverse events with both an incidence of at least 10% in either group and an incidence that was at least twice as high in the inotersen group as in the placebo group were nausea, pyrexia, chills, vomiting, anemia, thrombocytopenia, and lowered platelet counts (Table S11 in the Supplementary Appendix). Some events were consistent with known symptoms or complications of the underlying disease, such as nausea, vomiting, and anemia. The incidence of hemorrhages was similar in the two groups.

The mean rate of injection-site reactions was 1.1% of all injections in the inotersen group. A total of 68 events were reported by 36 patients. A total of 97% of the events were mild in severity. There were no severe events, and no patient discontinued inotersen treatment prematurely owing to events at the injection site. The mean percentage of subcutaneous injections that were administered at home was approximately 80% in both trial groups (Table S12 in the Supplementary Appendix).

Other safety variables, including vital signs,

Table 2. Summary of Adverse Events.*

Event	Placebo (N=60)	Inotersen (N=112)
	no. of patients (%)	
Any adverse event	60 (100)	111 (99)
Event related to trial regimen†	23 (38)	87 (78)
Any serious adverse event	13 (22)	36 (32)
Event related to trial regimen†	1 (2)	8 (7)
Glomerulonephritis	0	3 (3)‡
Thrombocytopenia	0	2 (2)
Deep-vein thrombosis	1 (2)	1 (<1)
Intracranial hemorrhage	0	1 (<1)§
Tubulointerstitial nephritis	0	1 (<1)¶
Pulmonary embolism	0	1 (<1)
Embolic stroke	0	1 (<1)
Myelopathy	0	1 (<1)
Death	0	5 (4)

* Shown are adverse events that occurred from the time of the first dose to the end of the trial, including the postintervention follow-up period.
† Shown are patients with events that were considered by the investigator to be related or possibly related to the trial regimen, as well as patients with missing data on the relatedness of the event to the trial regimen.
‡ The event for one patient was originally reported as acute kidney injury but was subsequently diagnosed by biopsy as glomerulonephritis.
§ The patient had a fatal intracranial hemorrhage that was associated with grade 4 thrombocytopenia.
¶ The patient also had glomerulonephritis that was confirmed by biopsy.

body-weight change, corrected QT interval (Fridericia's formula), concomitant medications, suicidal ideation or behavior, and ERG results, were either similar in the two trial groups or were modified favorably during inotersen treatment. There were no clinical manifestations of vitamin A deficiency.

DISCUSSION

In this international, randomized, placebo-controlled trial, inotersen modified the course of neuropathy and improved quality of life in patients with hereditary transthyretin amyloidosis. Both primary end points, the mNIS+7 and the Norfolk QOL-DN score, showed significant benefits with inotersen treatment. These benefits were independent of *TTR* mutation type, disease stage, and cardiomyopathy status at baseline. Subcutaneous injections of inotersen and placebo were administered at home, outside prespecified clinical visits. The clinical response to inotersen treatment was probably due to many factors in addition to the lowering of transthyretin levels, including the individual rate of disease progression, baseline amyloid burden, and the rate of amyloid clearance from tissue. Results from the NEURO-TTR trial are similar to those from a trial of patisiran, also published in this issue of the *Journal*, which used a lipid nanoparticle–encapsulated small interfering RNA to lower production of transthyretin.[25]

The principal safety concerns that were identified for inotersen treatment were thrombocytopenia (three patients had a platelet count of <25,000 per cubic millimeter), the occurrence of glomerulonephritis (three patients), and an imbalance in deaths from any cause (five patients, as compared with none in the placebo group). We cannot be sure whether this imbalance was due to acceleration of the underlying disease in some cases, the play of chance, or some other cause. After the implementation of enhanced monitoring, no additional cases of severe thrombocytopenia occurred, and a single case of glomerulonephritis was identified early without loss of renal function. Integrated analysis of clinical data from patients treated systemically with antisense oligonucleotides from the same 2′-*O*-methoxyethyl–modified chemical class suggests that these severe events may represent a drug–disease interaction.[26-28]

Limitations of the current trial included the exclusion of patients with end-stage disease and insufficient power to measure the effects of inotersen treatment on cardiomyopathy.[29] In addition, patients who were assigned to receive inotersen had more advanced autonomic neuropathy and sensorimotor neuropathy than those assigned to receive placebo, and a greater proportion had cardiomyopathy at trial entry.

In conclusion, weekly subcutaneous injections of inotersen provided benefit to patients with hereditary transthyretin amyloidosis with polyneuropathy, as measured by both clinical assessments and quality-of-life instruments. Implementation of enhanced safety monitoring allowed early detection and management of thrombocytopenia and glomerulonephritis.

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APPENDIX

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