ORIGINAL ARTICLE

Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial

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Background and purpose: Hereditary transthyretin (hATTR) amyloidosis causes progressive polyneuropathy resulting from transthyretin (TTR) amyloid deposition throughout the body, including the peripheral nerves. The efficacy and safety of inotersen, an antisense oligonucleotide inhibitor of TTR protein production, were demonstrated in the pivotal NEURO-TTR study in patients with hATTR polyneuropathy. Here, the long-term efficacy and safety of inotersen are assessed in an ongoing open-label extension (OLE) study.

Methods: Patients who completed NEURO-TTR were eligible to enroll in the OLE (NCT02175004). Efficacy assessments included the modified Neuropathy Impairment Score plus seven neurophysiological tests composite score (mNIS + 7), the Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL-DN) questionnaire total score and the Short-Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Safety and tolerability were also assessed.

Results: Overall, 97% (135/139) of patients who completed NEURO-TTR enrolled in the OLE. Patients who received inotersen for 39 cumulative months in NEURO-TTR and the OLE continued to show benefit; patients who switched from placebo to inotersen in the OLE demonstrated improvement or stabilization of neurological disease progression by mNIS + 7, Norfolk QOL-DN and SF-36 PCS. No new safety concerns were identified. There was no evidence of increased risk for grade 4 thrombocytopenia or severe renal events with increased duration of inotersen exposure.

Conclusion: Inotersen slowed disease progression and reduced deterioration of quality of life in patients with hATTR polyneuropathy. Early treatment with inotersen resulted in greater long-term disease stabilization than delayed initiation. Routine platelet and renal safety monitoring were effective; no new safety signals were observed.

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A complete list of NEURO-TTR open-label extension investigators is provided in Appendix S5.

Introduction

Hereditary transthyretin (hATTR) amyloidosis is a rare autosomal dominant disease that results from the deposition of misfolded transthyretin (TTR) protein

in various organs and tissues, progressing into multiorgan and nervous system degeneration and, eventually, death [1,2]. TTR is a tetrameric protein primarily synthesized in the liver and comprising four single-chain TTR monomers; it functions as a transporter of thyroxine and the retinol/retinol-binding protein complex [3,4]. Mutations in the *TTR* gene destabilize and dissociate the tetrameric complex to monomers that misfold and form amyloid fibrils [3]. More than 140 mutations in the *TTR* gene have been identified, most of which confer pathogenic single amino acid substitutions associated with amyloidosis [4,5].

Clinical manifestations of hATTR amyloidosis are multisystemic, including peripheral neuropathy, cardiomyopathy, autonomic dysfunction, ocular abnormalities and carpal tunnel syndrome [6,7]. hATTR amyloidosis is associated with significant disease burden, impacting multiple aspects of daily life and inducing a rapid decline in quality of life (QOL) [2,8,9]. Patients with hATTR amyloidosis typically live 3–15 years after diagnosis of polyneuropathy [7,10], but survival is shorter (2–5 years) for the ~ 60% of polyneuropathy patients with cardiomyopathy [11–13].

Inotersen is a 2′-*O*-methoxyethyl-modified phosphorothioate antisense oligonucleotide inhibitor of hepatic production of wild-type and mutant TTR protein. Inotersen selectively hybridizes to the *TTR* mRNA, resulting in the degradation of *TTR* mRNA via RNase H1, thereby preventing production of TTR protein [14].

In the pivotal NEURO-TTR trial in adults with stage 1 (ambulatory) or stage 2 (ambulatory with assistance) hATTR amyloidosis with polyneuropathy, inotersen stabilized neuropathy, as measured by the modified Neuropathy Impairment Score plus seven neurophysiological tests composite score (mNIS + 7), and QOL, as measured by the patient-reported Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL-DN) questionnaire total score [12,15]. These results were seen after as few as 8 months of treatment, the first time point at which efficacy was assessed in the 15-month trial, and were independent of disease stage, mutation type or presence of cardiomyopathy [12]. Glomerulonephritis and thrombocytopenia were identified as safety concerns with inotersen treatment in NEURO-TTR. Three patients had a platelet count of $<25 \times 10^3/\mu l$ (Common Terminology Criteria for Adverse Events grade 4 thrombocytopenia) and three patients had acute glomerulonephritis; however, implementation of more frequent blood and urine testing prevented further cases of grade 4 thrombocytopenia or untreatable cases of glomerulonephritis in NEURO-TTR [12].

The efficacy and safety of extended treatment with inotersen for up to 5 years in the open-label extension (OLE) of the NEURO-TTR study are presented.

Methods

This ongoing OLE study (NCT02175004) of the international, randomized, double-blind, placebo-controlled, 15-month pivotal NEURO-TTR trial (NCT01737398) [12] consists of a ≤4-week screening period, a treatment period of up to 260 weeks and a 3-month post-treatment evaluation period. Patients who satisfactorily completed the randomized NEURO-TTR study could enter the OLE to receive 300 mg inotersen once weekly via subcutaneous injection for up to 260 weeks (5 years). This OLE interim analysis was conducted on 31 May 2018.

The trial protocol for the OLE study (Appendix S1; statistical analysis plan provided in Appendix S2) was approved by the relevant institutional review boards or local ethics committees and regulatory authorities. The trial was conducted in accordance with good clinical practice guidelines of the International Conference on Harmonization and the principles of the Declaration of Helsinki. All patients provided written informed consent to participate. Extended methods are provided in Appendix S3.

Results

Study population

Overall, 139 (80%) patients completed the NEURO-TTR study, and 135 (97%) of these patients participated in the OLE [12]. Of the 135 patients who enrolled in the OLE, 85 continued to receive inotersen (inotersen-inotersen) and 50 switched from placebo to inotersen (placebo-inotersen) (Fig. 1). At the time of this interim analysis, 93 (69%) patients were receiving ongoing treatment in the OLE, and 59 (44%) patients had completed week 104 during the treatment period. The primary reasons for early treatment discontinuation are specified in Fig. 1.

Open-label extension baseline demographics and disease characteristics were generally well balanced between the inotersen-inotersen and placebo-inotersen groups (Table 1). However, whilst the mean mNIS + 7 and Norfolk QOL-DN scores were relatively similar at NEURO-TTR and OLE baseline for the inotersen-inotersen group, scores for the placebo-inotersen group indicated more severe disease at OLE baseline due to disease progression on placebo during the NEURO-TTR study (Table 1).

Median treatment exposure for all patients in the OLE was 591 days (range 1–1429 days), and the

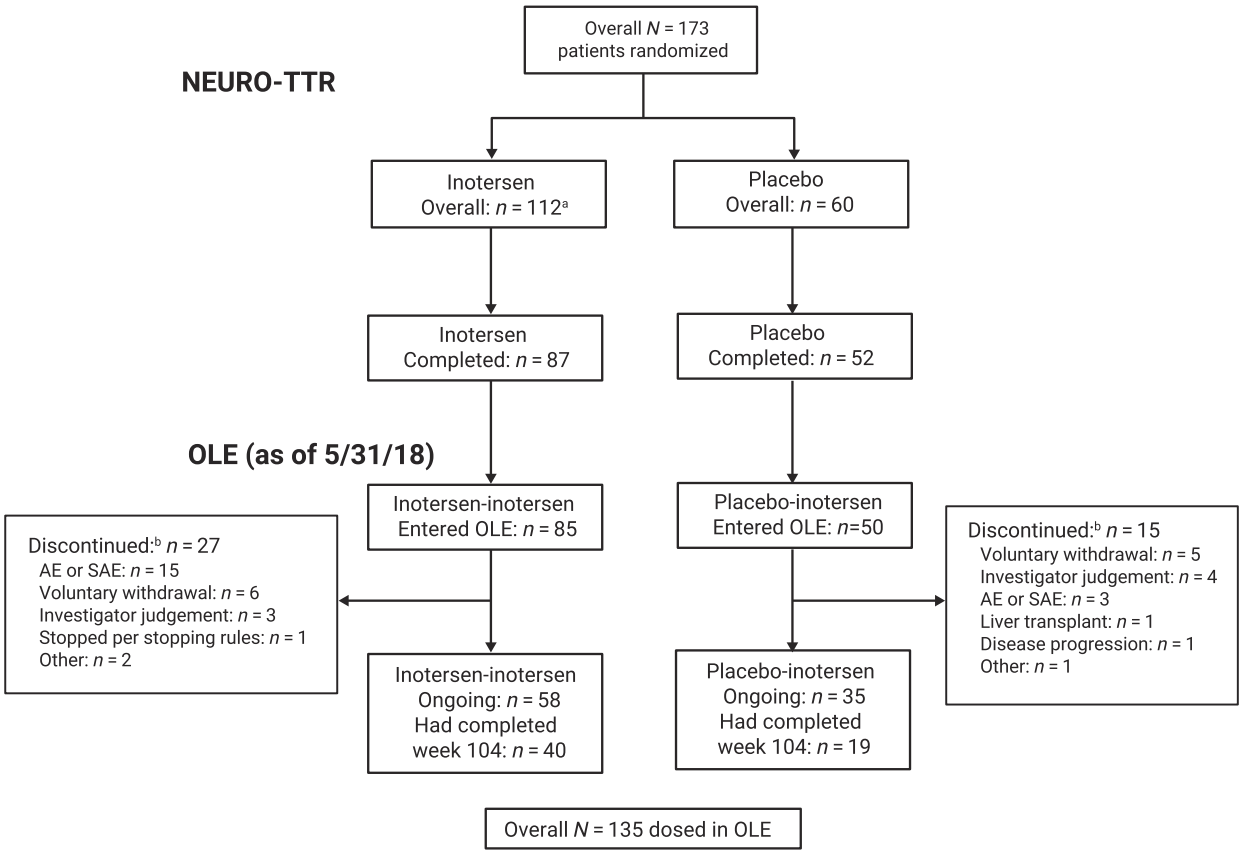


Figure 1 Patient disposition. NEURO-TTR disposition data from Benson *et al.* [12]. AE, adverse event; OLE, open-label extension; SAE, serious adverse event. [a]One patient was randomly assigned in error and did not begin the trial regimen. [b]Primary reason for early treatment discontinuation.

longest combined inotersen exposure of any patient during NEURO-TTR plus the OLE was 1885 days (5.2 years). Further results on treatment exposure, dose pause and concomitant medications are provided in Appendix S4.

Pharmacodynamics

In NEURO-TTR, steady-state serum TTR levels were achieved by week 13 in the inotersen group and sustained through week 65, reaching a median nadir of 79% below baseline between weeks 13 and 65 [12]. In the OLE, these lowered TTR levels were sustained in the inotersen-inotersen group to week 104, reaching a median nadir of 77% relative to the NEURO-TTR baseline (Fig. 2). In the placebo-inotersen group, TTR levels declined substantially by OLE week 7, when the first measurement was taken, and reached steady-state levels by week 13 (Fig. 2). These continued through week 104 in the OLE, reaching a median nadir of 78% relative to the OLE baseline.

Efficacy

In NEURO-TTR, inotersen treatment presented a significant advantage versus placebo in measures of neuropathy impairment (mNIS + 7; Fig. 3a) and neuropathy-related QOL (Norfolk QOL-DN; Fig. 3b). In the OLE, patients who continued treatment with inotersen demonstrated sustained benefit in mNIS + 7 (Fig. 4a), Norfolk QOL-DN (Fig. 4b) and health-related QOL [Short-Form 36 Health Survey, version 2 (SF-36) Physical Component Summary (PCS); Fig. 4c]. Patients who switched from placebo to inotersen in the OLE showed improvement or stabilization in mNIS + 7, Norfolk QOL-DN and SF-36 PCS over time, compared with predicted worsening with placebo (placebo-slope extrapolation; based on disease progression observed in the placebo arm of NEURO-TTR and consistent with natural history [2]; Fig. 4).

Neuropathy impairment (mNIS + 7; Fig. 4a)

For the inotersen-inotersen and placebo-inotersen groups, respectively, mean (SE) change from OLE

Table 1 Baseline demographics and disease characteristics of the OLE safety set

Characteristic	Inotersen-inotersen (n = 85)	Placebo-inotersen (n = 50)
Age at OLE screening, mean (SD), years	60.3 (11.86)	60.5 (14.62)
Male, n (%)	59 (69.4)	35 (70.0)
PND score at OLE baseline[a], n (%)		
I/II	55 (64.7)	28 (56.0)
III/IV	27 (31.8)	21 (42.0)
V	3 (3.5)	1 (2.0)
Val30Met *TTR* mutation[b], n (%)	39 (45.9)	29 (58.0)
Prior TTR stabilizer use[b,c], n (%)	53 (62.4)	27 (54.0)
mNIS + 7 composite score at NEURO-TTR baseline[d], mean (SD)	81.8 (38.0)	74.4 (40.1)
mNIS + 7 composite score at OLE baseline[e], mean (SD)	85.8 (41.1)	98.7 (51.1)
Norfolk QOL-DN total score at NEURO-TTR baseline[f], mean (SD)	49.3 (27.0)	49.0 (26.9)
Norfolk QOL-DN total score at OLE baseline[g], mean (SD)	48.2 (29.2)	60.1 (32.0)
Duration from onset of hATTR amyloidosis PN symptoms to OLE baseline, mean (SD), months	79.7 (49.0)	82.0 (55.8)
Cardiomyopathy[h], n (%)	59 (69.4)	30 (60.0)
Duration from onset of hATTR amyloidosis cardiomyopathy symptoms to OLE baseline, mean (SD)[i], months	57.9 (63.1)	53.1 (30.4)

hATTR, hereditary transthyretin; mNIS + 7, modified Neuropathy Impairment Score plus seven neurophysiological tests composite score; Norfolk QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy questionnaire total score; OLE, open-label extension; PN, polyneuropathy; PND, polyneuropathy disability; TTR, transthyretin; [a]Polyneuropathy disability score is defined as: I, sensory disturbances in limbs without motor impairment; II, difficulty walking without the need of a walking aid; III, one stick or one crutch required for walking; IV, two sticks or two crutches needed; V, wheelchair required or patient confined to bed; [b]based on data entered in the electronic case report form at NEURO-TTR study entry; [c]prior stabilizer use includes tafamidis and/or diflunisal; [d]NEURO-TTR baseline mNIS + 7 based on 81 inotersen-inotersen patients and 50 placebo-inotersen; [e]open-label extension baseline mNIS + 7 based on 80 inotersen-inotersen patients and 49 placebo-inotersen; [f]NEURO-TTR baseline Norfolk QOL-DN based on 80 inotersen-inotersen patients and 50 placebo-inotersen; [g]open-label extension baseline Norfolk QOL-DN based on 78 inotersen-inotersen patients and 49 placebo-inotersen; [h]based on NEURO-TTR study entry; the presence of cardiomyopathy was defined as a diagnosis of hATTR amyloidosis cardiomyopathy at trial entry or by the following criteria: an interventricular wall thickness of 13 mm or more on transthoracic echocardiogram 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; [i]based on 28 inotersen-inotersen patients and 16 placebo-inotersen patients.

baseline to week 104 for mNIS + 7 was 11.18 (3.347) and 5.08 (4.159) points. Relative to the NEURO-TTR baseline, mNIS + 7 improved (<0-point change) in 37%, 30% and 24% of inotersen-inotersen patients

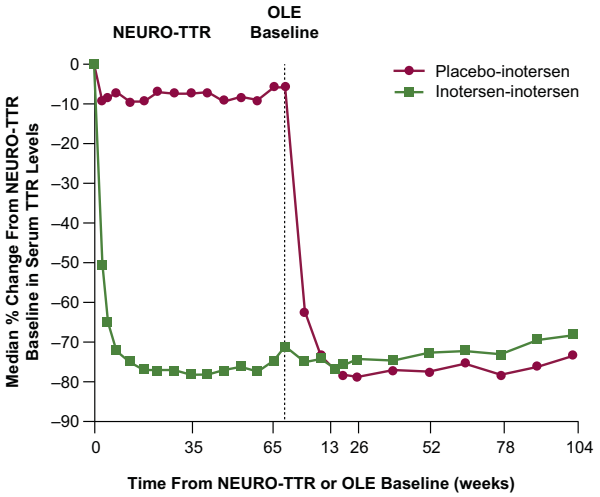


Figure 2 Open-label extension (OLE) median serum transthyretin (TTR) levels relative to the NEURO-TTR baseline. Data shown are for all enrolled patients who received ≥1 dose of inotersen in the OLE and had ≥1 post-baseline efficacy assessment (full analysis set). Median percentage change from the NEURO-TTR baseline is indicated using green squares for the inotersen-inotersen group and red circles for the placebo-inotersen group. The dashed line represents the OLE baseline (OLE week 0).

after 92, 118 and 170 weeks of cumulative treatment during the NEURO-TTR and OLE studies. Of placebo-inotersen patients, 28%, 47% and 47% improved (<0-point change) from OLE baseline at weeks 26, 52 and 104. Compared with the placebo-slope extrapolation, the mean change from NEURO-TTR baseline to OLE week 104 for mNIS + 7 was 40.9 points lower in the inotersen-inotersen group and 23.8 points lower in the placebo-inotersen group (Fig. 4a).

Neuropathy-related QOL (Norfolk QOL-DN; Fig. 4b)
From OLE baseline to week 104, Norfolk QOL-DN mean (SE) change for the inotersen-inotersen group and placebo-inotersen group was 5.22 (3.321) and 2.26 (3.997), respectively. After 92, 118 and 170 weeks of cumulative treatment during NEURO-TTR and the OLE, Norfolk QOL-DN improved (<0-point change) relative to the NEURO-TTR baseline in 51%, 44% and 46% of inotersen-inotersen patients. From the OLE baseline to weeks 26, 52 and 104, Norfolk QOL-DN improved (<0-point change) in 46%, 53% and 42% of patients in the placebo-inotersen group. Relative to the placebo-slope extrapolation, the mean change from NEURO-TTR baseline to OLE week 104 was 22.2 points lower in the inotersen-inotersen group and 10.3 points lower in the placebo-inotersen group (Fig. 4b).

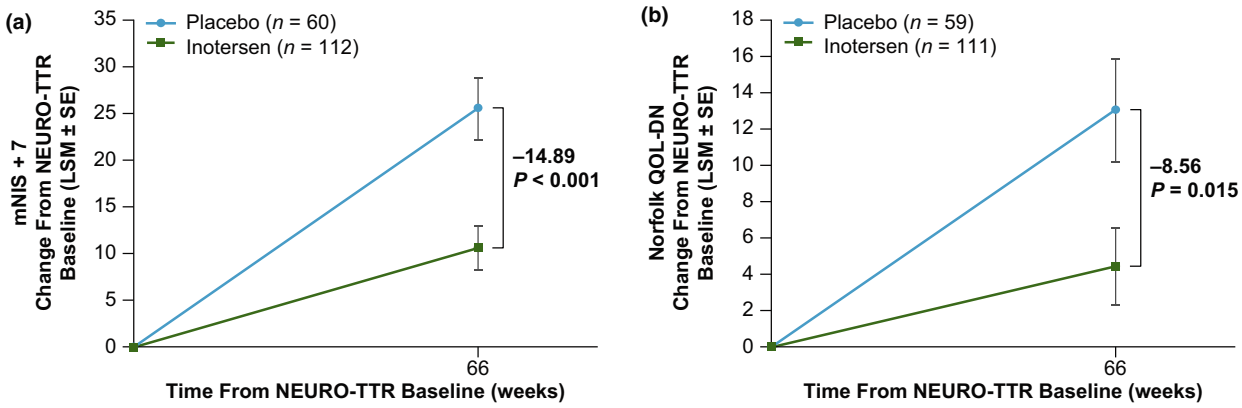


Figure 3 Change from the NEURO-TTR baseline to week 66 in mNIS + 7 and Norfolk QOL-DN for the NEURO-TTR safety set. Least-squares mean (LSM) ± SE change from the NEURO-TTR baseline in (a) the Modified Neuropathy Impairment Score plus seven neurophysiological tests composite score (mNIS + 7) and (b) the Norfolk Quality of Life – Diabetic Neuropathy (QOL-DN) questionnaire total score. Data shown are for all patients who received ≥1 dose of study drug in NEURO-TTR (safety set).

Health-related QOL (SF-36 PCS; Fig. 4c)

In the OLE, inotersen treatment halted worsening of health-related QOL in a significant proportion of both the inotersen-inotersen and placebo-inotersen groups (Fig. 4c). For the inotersen-inotersen and placebo-inotersen groups, respectively, SF-36 PCS mean (SE) change from OLE baseline to week 104 was 0.08 (1.397) and –1.15 (1.367). Relative to the placebo-slope extrapolation, SF-36 PCS scores from NEURO-TTR baseline to OLE week 104 were 8.4 points higher in the inotersen-inotersen group and 3.2 points higher in the placebo-inotersen group (Fig. 4c).

Safety and tolerability

The safety of inotersen in the OLE study is summarized in Table 2. The most common (≥10%) adverse events (AEs) across both treatment groups were nausea, urinary tract infection, vomiting, diarrhea, fatigue, chills, falls, peripheral edema, injection-site pain, thrombocytopenia, syncope, injection-site erythema, headache, muscular weakness, myalgia and dyspnea.

Treatment-emergent AEs (TEAEs) leading to dose pause, dose reduction or study drug discontinuation occurred in 66 (48.9%) patients and included thrombocytopenia in 24 (17.8%) patients, platelet count decreases in four (3.0%) patients, and renal and urinary disorders in five (3.7%) patients. Overall, 19 (14.1%) patients discontinued because of a TEAE: 15 (17.6%) patients in the inotersen-inotersen group and four (8.0%) patients in the placebo-inotersen group.

A total of 47 (34.8%) patients experienced a serious TEAE: 33 (38.8%) patients in the inotersen-inotersen group and 14 (28.0%) patients in the placebo-inotersen group. Few were considered related to inotersen [five patients with five total serious TEAEs: thrombocytopenia (n = 2), nausea (n = 1), chills (n = 1), hypertension (n = 1)].

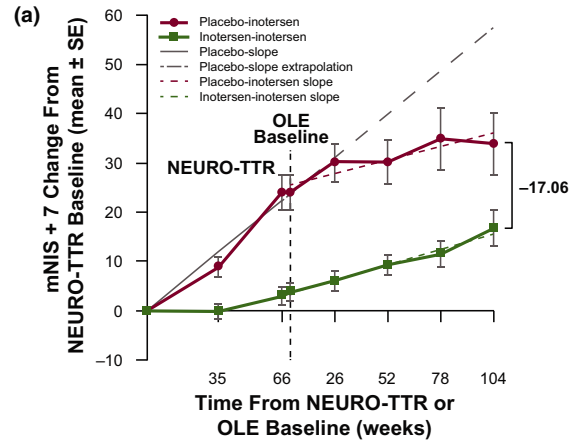
Overall, nine (6.7%) patients died (Table 2; 11 fatal AEs were reported in nine patients (n = 1 for each event): arrhythmia, cardiac arrest, cardiac failure, cardiac failure acute, cardiac failure congestive, autoimmune hepatitis, bacteremia, endocarditis, septic shock, peripheral neuropathy and asphyxia) in the OLE; however, only three of the nine deaths occurred on treatment and none was considered related to treatment.

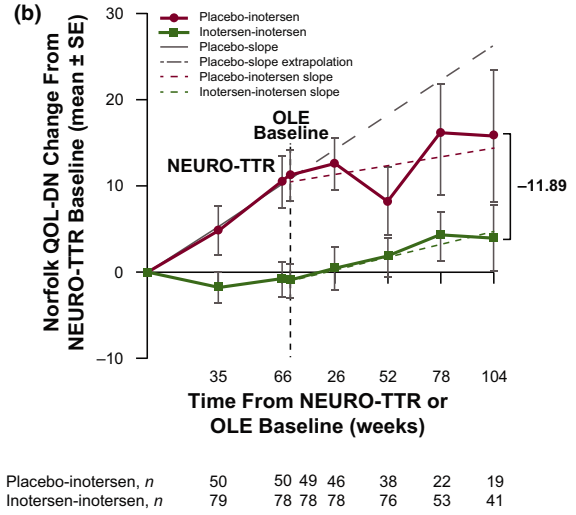
Thrombocytopenia and glomerulonephritis

During the OLE, 29.4% (25/85) of the inotersen-inotersen group and 46.0% (23/50) of the placebo-inotersen group experienced platelet count decreases to $<100 \times 10^3/\mu l$. Maximum platelet count decrease reached grade 1b (≥ 75 to $<100 \times 10^3/\mu l$) in 15 (17.6%) inotersen-inotersen patients versus 18 (36.0%) placebo-inotersen patients, grade 2 (≥ 50 to $<75 \times 10^3/\mu l$) in eight (9.4%) inotersen-inotersen patients versus five (10.0%) placebo-inotersen patients, or grade 3 (≥ 25 to $<50 \times 10^3/\mu l$) in two (2.4%) inotersen-inotersen patients versus no placebo-inotersen patients. There were no cases of grade 4 platelet count decrease ($<25 \times 10^3/\mu l$) or acute glomerulonephritis in the OLE.

Discussion

In the OLE of the NEURO-TTR study, long-term exposure to inotersen resulted in continued efficacy after 2 years with no additional safety concerns or signs of increased toxicity for up to 5 years' cumulative inotersen exposure. Throughout the OLE, the





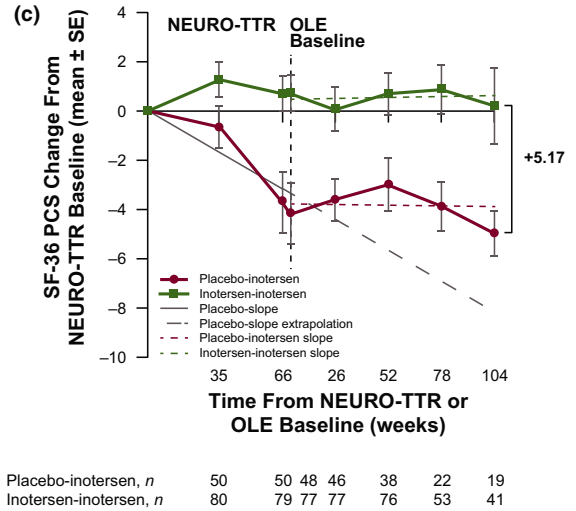


Figure 4 Mean change from the NEURO-TTR baseline to open-label extension (OLE) week 104 in efficacy measures. Mean (± SE) change from the NEURO-TTR baseline in (a) the Modified Neuropathy Impairment Score plus seven neurophysiological tests composite score (mNIS + 7); (b) the Norfolk Quality of Life – Diabetic Neuropathy (QOL-DN) questionnaire total score; (c) the 36-item Short-Form Health Survey, version 2 (SF-36) Physical Component Summary (PCS) score. Data shown are for all enrolled patients who received ≥1 dose of inotersen in the OLE and had ≥1 post-baseline efficacy assessment (full analysis set). Green squares indicate results for the inotersen-inotersen group and red circles indicate results for the placebo-inotersen group. The vertical dashed line represents the OLE baseline (OLE week 0). Sample sizes for each time point and treatment group are indicated under the figure.

placebo-inotersen group exhibited greater neurological worsening from the NEURO-TTR baseline than the inotersen-inotersen group, and earlier initiation of inotersen resulted in better outcomes in measures of neuropathy progression, neuropathy-related QOL and health-related QOL. However, initiation of inotersen in patients previously given placebo resulted in disease stabilization, suggesting that intervention later in disease can still elicit a significant drug response.

Table 2 Summary of open-label extension (OLE) treatment-emergent adverse events (TEAEs)[a]

Event, *n* (%)	Inotersen-inotersen (*n* = 85)	Placebo-inotersen (*n* = 50)	Total (*N* = 135)
Any TEAEs	80 (94.1)	49 (98.0)	129 (95.6)
Mild TEAE(s)[b]	13 (15.3)	12 (24.0)	25 (18.5)
Moderate TEAE(s)[b]	33 (38.8)	27 (54.0)	60 (44.4)
Severe TEAE(s)[b]	34 (40.0)	10 (20.0)	44 (32.6)
TEAEs related to study treatment	53 (62.4)	37 (74.0)	90 (66.7)
TEAEs leading to discontinuation	15 (17.6)	4 (8.0)	19 (14.1)
TEAEs leading to dose reduction	10 (11.8)	3 (6.0)	13 (9.6)
TEAEs leading to dose interruption/delay	22 (25.9)	31 (62.0)	53 (39.3)
Serious TEAEs	33 (38.8)	14 (28.0)	47 (34.8)
Serious TEAEs related to study treatment	4 (4.7)	1 (2.0)	5 (3.7)
Fatal TEAEs	9 (10.6)	0	9 (6.7)
Fatal TEAEs related to study treatment	0	0	0

[a]Shown are adverse events that occurred from the time of the first dose in the OLE to the patient's last contact date in the OLE study as of 31 May 2018; [b]each patient is counted once by maximum severity of any TEAE.

Transthyretin reduction in the OLE was consistent with results of the phase 1 and NEURO-TTR trials [12,14]. Reductions in TTR levels were seen early in patients who switched from placebo to inotersen in the OLE, in the absence of a loading dose, with steady-state levels reached by week 13 and sustained through week 104. Reduced TTR levels may decrease amyloid deposition, decrease injury of nerve fibers by TTR oligomers or facilitate increased axonal regrowth [4]. Although circulating vitamin A levels were low (as expected since TTR is the carrier protein for retinol-binding protein), there was no difference between inotersen and placebo in the incidence of the AE of special interest, 'Ocular AEs related to vitamin A deficiency' in the NEURO-TTR study [12,16].

The limitations of this study include its interim nature; thus, the sample size of patients at later time points was limited [44 (33%) patients receiving ongoing treatment in the OLE study had not yet completed week 104 as of 31 May 2018], which could affect efficacy results at later time points. No statistical analyses were performed and thus the results are only qualitative. Another potential limitation of this study is its open-label design with no placebo control, which could influence patient responses to QOL assessments and, to a much lesser extent, mNIS + 7 assessments.

The long-term safety of inotersen is promising, with no additional safety concerns or increased toxicity observed after exposure of up to 5 years. The effectiveness of regular, routine platelet and renal monitoring to manage the risk of severe thrombocytopenia and glomerulonephritis was established during the pivotal NEURO-TTR trial [12] and is reinforced by the results of long-term treatment in the OLE study.

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Disclosures of conflicts of interest

Thomas Brannagan: Advisory boards for Akcea Therapeutics, Pfizer and Alnylam Pharmaceuticals; study investigator for Ionis Pharmaceuticals Inc. and Alnylam Pharmaceuticals; speaker for Alnylam Pharmaceuticals; received honoraria for speaking for Akcea Therapeutics. Annabel K. Wang: Study investigator, consultant and speaker for Ionis Pharmaceuticals Inc. Teresa Coelho: Financial support to attend scientific meetings from Pfizer, Alnylam and Biogen. Márcia Waddington Cruz: Consulting and travel honoraria from NHI, Prothena, FoldRx, Ionis, Pfizer, Alnylam, PTC; principal investigator for Ionis Pharmaceuticals Inc. Michael J. Polydefkis: Honoraria from Pfizer and Alnylam Pharmaceuticals Inc. Peter J. Dyck: Training and consulting honoraria from Ionis Pharmaceuticals Inc. and Alnylam Pharmaceuticals. Violaine Plante-Bordeneuve: Consulting honoraria from Alnylam Pharmaceuticals, Ionis and Pfizer and travel honoraria from Ionis. John L. Berk: Honoraria from Ionis Pharmaceuticals Inc. and Alnylam Pharmaceuticals; study investigator for Ionis Pharmaceuticals Inc., Alnylam Pharmaceuticals and Pfizer. Fabio Barroso: Honoraria for conducting clinical research from Ionis Pharmaceuticals. Giampaolo Merlini: Advisory committee for Pfizer and Janssen. Isabel Conceição: Consultancy for Alnylam and Pfizer; honoraria from Alnylam, Pfizer and Sanofi; speakers bureau for Alnylam, Pfizer and Sanofi. Steven G. Hughes: Consultant for Ionis Pharmaceuticals and Akcea Therapeutics. Jesse Kwoh and Shiangtung Jung: Employed by Ionis Pharmaceuticals. Spencer Guthrie: (formerly) Employed by Akcea Therapeutics. Michael Pollock: Employed by Akcea Therapeutics. Merrill D. Benson: Study investigator for Ionis Pharmaceuticals Inc. Morie Gertz: Consulting honoraria from Ionis, AbbVie, Alnylam, Amgen, Annexon, Appellis, Celgene, Janssen, Medscape, Physicians Education Resource, Prothena, Research to Practice, Teva and Spectrum, and grants from Spectrum.

Data availability statement

The data availability statement is not provided in the paper as the original version of the paper was submitted prior to the journal's adoption of Expects data policy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. NEURO-TTR open-label extension study protocol.

Appendix S2. Statistical analysis plan.

Appendix S3. Extended methods.

Appendix S4. Supplementary results: treatment exposure, dose pause and concomitant medications.

Appendix S5. List of NEURO-TTR open-label extension investigators.

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