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Assessing mNIS+7$_{Ionis}$ and International Neurologists' Proficiency in a FAP Trial

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Abstract

Introduction—Polyneuropathy signs (Neuropathy Impairment Score, NIS), neurophysiologic tests (m+7_{Ionis}), disability, and health scores were assessed in baseline evaluations of 100 patients entered into an oligonucleotide familial amyloidotic polyneuropathy (FAP) trial.

Methods—We assessed: 1) Proficiency of grading neurologic signs and correlation with neurophysiologic tests, and 2) clinometric performance of mNIS+7_{Ionis} and its subscores and correlation with disability and health scores.

Results—The modified Neuropathy Impairment Score + 7 neurophysiologic tests (mNIS+7_{Ionis}) sensitively detected, characterized and broadly scaled diverse polyneuropathy impairments. Polyneuropathy signs (NIS and subscores) correlated with neurophysiology tests, disability, and health scores. Smart Somatotopic Quantitative Sensation Testing of Heat as Pain 5 provided a needed measure of small fiber involvement not adequately assessed by other tests.

Discussion—Specially trained neurologists accurately assessed neuropathy signs as compared to referenced neurophysiologic tests. The score, mNIS+7_{Ionis}, broadly detected, characterized, and scaled polyneuropathy abnormality in FAP, which correlated with disability and health scores.

Keywords

oligonucleotide trials; familial amyloid polyneuropathy (FAP); polyneuropathy signs; neurophysiologic tests; peripheral neuropathy; disability; proficiency

INTRODUCTION

Transthyretin amyloidosis (ATTR) is a fatal dominantly inherited disease due to >100 point mutations of transthyretin (TTR), a transport protein of thyroxine and retinol – binding protein mainly synthesized by the liver.[2-12] Typically, the disease manifests in early or later adult life as a symmetric length-dependent sensorimotor-autonomic polyneuropathy, also

called familial amyloidotic polyneuropathy (FAP).[11,13-18] The polyneuropathy may be overshadowed by cardiomyopathy or other organ involvement.[12,19]

Recently, ATTR has received increasing attention, because it is fatal, may be more common than usually recognized[10,15] and has become treatable.[14,20] Although still not adequately evaluated, orthotopic liver transplantation, resulting in marked reduction of circulating mutant TTR, appears to slow disease progression.[21-23] Stabilization of circulating tetrameric protein TTR using Vyndaqel® or Diflunisal slows FAP progression.[14,20] Oligonucleotide therapies directed at TTR messenger RNA have been shown to markedly reduce both mutant and wild plasma TTR levels and are in phase 3 clinical trials.[24,25]

In a previous retrospective review of Mayo Clinic, Rochester, MN, USA patients with FAP, we assessed the clinometric properties of NIS+7 (a composite score of polyneuropathy signs and neurophysiologic tests) to quantitate the overall kind and severity of polyneuropathy impairment in FAP.[17] The score broadly characterized and quantified muscle weakness, muscle stretch reflex decrease, sensation loss of feet and hands, and neurophysiologic test abnormalities. From analysis of the data, 3 modifications of NIS+7 were recommended to more broadly and adequately represent the diversity and severity of polyneuropathy impairments: 1) assess sensation loss of both large and small fiber modalities somatotopically using validated approaches and suitable reference values; 2) assess only amplitudes of attributes of nerve conduction and include attributes of an upper limb nerve, e.g., the ulnar nerve; and 3) assess sudomotor decrease at distributed body sites.

In a recently published multinational study, rapid progression of FAP was demonstrated using the Neuropathy Impairment Score (NIS), and its severity was correlated with functional scales of locomotion.[18]

The ongoing Phase 3 FAP clinical trials with TTR lowering agents (IONIS-TTR_{Rx} and patisiran)[24,25] use modifications of NIS+7 scores that have incorporated the first 2 of the 3 recommended modifications suggested above. The modified NIS+7 scores differ slightly, and herein the score utilized in the IONIS-TTR_{Rx} trial (NEURO-TTR) is referred to as $mNIS+7_{Ionis}$.

This study assessed the clinometric performance of polyneuropathy signs (NIS) and neurophysiologic tests ($m + 7_{Ionis}$) in evaluation at baseline of the first 100 FAP patients entered into the NEURO-TTR trial. The following questions were addressed: 1) do NIS and its subscores and modified+7 neurophysiologic tests adequately detect, characterize, and scale polyneuropathy abnormalities and their severity in FAP; 2) can international neurologists, given special training and agreeing to grade abnormality specifically, accurately grade abnormality of polyneuropathy signs as inferred from correlations with abnormality of neurophysiologic tests; 3) do clinical signs and neurophysiologic test scores correlate with disability and health scores; and 4) are correlations of $mNIS+7_{Ionis}$ as strong, or stronger, than are components of $mNIS+7_{Ionis}$ with disability and health scores in FAP?

MATERIALS AND METHODS

Brief description of Ionis-TTR$_{RX}$ Phase 3 Trial of FAP

This report is restricted to an evaluation of the baseline polyneuropathy assessments in duplicate of neuropathy signs (NIS), unmodified (+ 7) and modified neurophysiologic tests (m+7$_{Ionis}$), and functional health and disability scores [amyloid gait score here called polyneuropathy disability score (PND), Dyck/Rankin and Inflammatory Neuropathy Cause and Treatment (INCAT) from Neuropathy Symptoms and Change (NSC)] and health scores (Norfolk-DN QOL, NSC, and SF-36) of the first 100 FAP patients enrolled into the NEURO-TTR trial (Ionis Pharmaceuticals, Inc. NCT01737398). All study subjects were required to sign written consent forms reviewed by the Institutional Review Boards of participating medical centers. IONIS-TTR$_{Rx}$ is a second-generation 2′-*O*-(2-methoxyethyl) modified antisense oligonucleotide drug targeted to TTR. The binding of IONIS-TTR$_{Rx}$ to the TTR messenger RNA results in degradation of the RNA and thereby reduces the production of TTR protein. Patients had to meet the following entry criteria at screening: an NIS ≥ 10 - ≤ 130, demonstrated tissue deposition of amyloid, a TTR mutation by genotyping, and age 18 to 82 years. In addition, patients were excluded if they had a prior history of liver transplantation, diabetes mellitus, or the presence of other causes of polyneuropathy and were not allowed to receive transthyretin stabilizing drugs during the study.

Description of Polyneuropathy Endpoints

The NIS has been described extensively and used in previously published therapeutic trials in chronic inflammatory demyelinating polyradiculoneuropathy,[26,27] polyneuropathy associated with monoclonal gammopathies of undetermined significance,[28] and diabetic sensorimotor polyneuropathies [29,30]. The NIS comprises scores of muscle weakness (NIS-W, 0-192), decrease of muscle stretch reflexes (NIS-R, 0-20), and abnormality of 4 sensory modalities of sensation loss in the toes and fingers (NIS-S, 0-32) – the total NIS score may vary from 0 to 244. The NIS components (clinical assessments) are the same in NIS+7 as in modification of NIS+7 (mNIS+7$_{Ionis}$).

The NIS+7 and mNIS+7$_{Ionis}$ differ in the neurophysiologic tests in the +7. The +7 tests in the NIS+7 include 5 attributes of nerve conduction [fibular nerve compound muscle action potential (CMAP) amplitude, motor nerve conduction velocity (MNCV) and motor nerve distal latency (MNDL), tibial nerve MNDL, and sural nerve sensory nerve action potential (SNAP) amplitude], vibratory detection threshold of the great toe using CASE IVc, (WR Medical Electronics, Maplewood, MN, USA), and heart rate decrease with deep breathing (HR$_{db}$) also assessed by equipment from WR Medical Electronics, Inc. Each of the +7 tests is expressed as a normal deviate (nd) from percentiles derived from reference values obtained in a study of healthy subjects from Olmsted County, MN, USA.[31].

To provide a more accurate and representative assessment of the kind and distribution of sensation loss in the mNIS+7$_{Ionis}$, the vibration detection threshold of the great toe was replaced by Smart Somatotopic Quantitative Sensation Testing (S ST QSTing) of touch-pressure (TP) and heat as pain 5 (HP5) (of 1-10 severity) of the body surface area.[14,17] As

directed by the algorithm, up to 10 distributed unilateral anatomical sites are tested. Healthy subject reference values are available for all 10 assessed sites and for both touch-pressure and heat as pain 5 sensation (reference data unpublished). The automated algorithm of testing of S ST QSTing assumes that sensation loss in FAP is symmetric and length dependent. For a patient with only distal sensation loss of lower and upper limbs, only 4 distal sites of 1 side of the body require testing. For a patient with generalized sensation loss, a variable number of sites (up to 10) may need to be tested. The S ST QSTing score ranges from 0-80 depending on the severity and distribution of sensation loss. In addition, the mNIS $+7_{Ionis}$ uses different attributes of nerve conduction than were used in NIS+7, including an upper limb nerve. The attributes in mNIS+7_{Ionis} include CMAPs of ulnar, fibular, and tibial nerves and SNAPs of ulnar and sural nerves. This change was made to employ measures of amplitude over measures of conduction velocity or distal latency. Attributes of nerve conduction are expressed as normal deviates from percentiles as described for mNIS+7_{Ionis}. The heart rate decrease with deep breathing (HR_{db}) remains unchanged in mNIS+7_{Ionis} from that used in NIS+7.[32,33]

Approaches Used to Accurately Assess Clinical Signs and Neurophysiologic Tests

Because mNIS+7_{Ionis} uses assessment of clinical neuropathy signs and neurophysiologic tests, emphasis was placed on choice of investigators, training, proficiency, and adequate handling of their clinical measurements. Neurologists chosen for the trial had to be faculty neurologists who planned to evaluate the same patient over the duration of the trial.[34] They were trained neurologists or clinical neurophysiologists, typically on the teaching staff of a Neurology department in a medical school. To obtain uniformity of grading, all received special training and certification by members of the Mayo Clinic Peripheral Neuropathy Research Laboratory (MC PNRL). Healthy subjects and patients with FAP were used in training. In assessment of neuropathy signs, specificity was emphasized over sensitivity based on results of recently published Cl vs NPhys trials results.[34-36] As much as was possible at each clinical trial site, separate personnel performed the different neuropathy assessments, i.e., neurologic examinations, nerve conduction studies, smart somatotopic quantitative sensation testing, and autonomic testing. Study site personnel did not summate test scores; this was done later at the MC PNRL. Several additional strategies were used to make independent assessments. The duplicate neuropathic assessments had to be separated by at least 24 hours. The tracings of attributes of nerve conduction were carefully reviewed in the MC PNRL by one of the authors (WJL) to evaluate the adequacy of test performance. The conversion of nerve conduction measurements to percentiles and normal deviates was done later by programmed calculations in the MC PNRL. The performance of S ST QSTing and HR_{db} was directed by smart algorithms and reference values.

After special training and certification, and prior to onset of the trial, examiners submitted test results of all neuropathy evaluations of a healthy subject aged < 50 years and another ≥ 50 years. This was done to ensure adequate performance of the tests and approval of test performance by the MC PNRL personnel. In assessment of polyneuropathy signs, neurologists were asked to grade as abnormal only unequivocal abnormality related to FAP and taking age, gender, and anthropomorphic variables into account.[34,35] Standard paper/electronic forms were used for entry of neuropathic signs, symptoms, and neurophysiologic

tests.[1,36] Examiners were asked to use a scribe to record neuropathy signs as they were elicited to avoid transcription error.[27] Signs and neurophysiologic test results were transmitted electronically to the MC PNRL.

Neurophysiologic tests were done by trained and certified clinical neurophysiologists or their technologists, both of whom had received specially prepared syllabi and special training. For assessment of S ST QSTing, automated and highly standardized equipment (prototypes developed at Mayo Clinic, Rochester, MN and fabricated to industry standards at WR Medical Electronics, Maplewood, MN, USA) was made available to every clinical site. The S ST QSTing algorithms of testing and estimated thresholds were developed by one of the authors (PJD) and programmed for use for QSTing by WR Medical Electronics. It uses highly standardized and automated stimuli, algorithms of testing, and finding threshold and reference values, and its accuracy and proficiency has been demonstrated.[33]

Neuropathic Symptoms, Disability, and Health Scores

Three health and disability scores were used to evaluate overall functional disability: the PND, Dyck/Rankin score, and the INCAT from the NSC score. The INCAT from NSC score assesses disability due to weakness of distal and proximal muscles of upper and lower limbs and scores abnormality from 1 to 10. Also assessed were 2 health scores, Norfolk QOL-DN and the SF-36.

Analysis Plan

At a conceptual level, abnormality of clinical signs, symptoms, and neurophysiologic tests were set at a fifth or first percentile level and as corrected for age, gender, and anthropomorphic variables. In this study, such reference values were available from a healthy subject cohort drawn from the Olmsted County, MN, USA population with subjects excluded based on neurologic evaluation and review of their medical records.[31,37] Individuals with diabetes, metabolic diseases, or polyneuropathy were excluded. Highly standardized approaches were used to evaluate attributes of nerve conduction, quantitative sensation, and autonomic tests.[31,37] These neuropathic test results were assessed for the influence of age, gender, and anthropomorphic variables. Results were expressed as measured values, percentiles, and normal deviates.

Data were analyzed using standard statistical techniques with a primary intention to quantitate neuropathy signs and neurophysiologic test abnormalities and to describe associations between the various FAP measurements including NIS (pts), Σ5 NCs (nds), S ST QSTing (pts), S ST QSTing of TP (pts), S ST QSTing of HP5 (pts), HR_{db} (nds), and dysfunction, disability, and health scores. Test/re-test reproducibility results were assessed for a significant degree of agreement using the Krippendorff alpha.

The accuracy of individual clinical signs was assessed by Spearman correlations with a comparable neurophysiologic test, with the 2 evaluations determine independently. Eleven such comparisons were possible. In the 11 available comparisons, the neurophysiologic tests were judged to be the gold standard evaluation, because they were more objective, standard, quantitated, and referenced as compared with the neuropathic signs clinically evaluated. For

a broader exploration of the correlations among assessed neuropathy signs (NIS) or their subscores (NIS-W, -R, or –S), they were compared to composite disability or health scores.

In several tables, Spearman rank correlation coefficients (r) and *P*-values (*P*) were combined into 6 strata to provide simplified expressions of strength and significance of correlations.

Multiple comparisons were conducted, so a Bonferroni correction was applied to the *P*-values as needed in Table 1. When adjusted *P*-values are reported, they are clearly noted. Statistical analysis was conducted using the SAS System version 9.3 (Cary, NC).

RESULTS

Demographic and baseline characteristics

The patients were recruited from 16 medical centers from 6 countries: USA (65), Portugal (14), France (13), England (5), Italy (2), and Brazil (1). Seventy-six were women, and 24 were men. Their median age was 65, range 27 – 81 years. Non-USA patients (n=35) had a higher frequency of Val30met mutations (66%) than did USA patients (25%).

The test/re-test reproducibility of signs (NIS), symptoms (NSC), attributes of nerve conduction (i.e., Σ5NC, S ST QSTs of TP or HP5), and HR_{db} are given in Table 1. Note the high reproducibility values for neuropathic signs (NIS), nerve conductions (Σ5NCs) and HR_{db}. The reproducibility value for S ST QSTing is somewhat lower, especially for touch-pressure sensation. Because all of the duplicate evaluations were performed within a day or within a few days of each other and by the same examiners, the adequacy of test/re-test reproducibility can be questioned. By contrast, the $m+7_{Ionis}$ neurophysiologic test reproducibility results should not have been influenced (or to a lesser degree) by patient or examiner recall of preceding evaluations or test results, because these tests are less subjective.

Characterization of FAP Impairments Using $mNIS+7_{Ionis}$ and Detection, Scaling and Ceiling Effects

The composite score $mNIS+7_{Ionis}$ and its subscores broadly characterized and quantitated distributed muscle weakness, muscle stretch reflex decrease, and large and small fiber sensation loss. As seen in Figure 1, autonomic impairments were probably not adequately assessed by HR_{db}, because this test could not be performed in about one-third of patients due to cardiac arrhythmia or electronic pacing. Many subscores had some values at 0 in keeping with inclusion of mild FAP patients or those with limited types of dysfunction. In the S ST QSTing test, a score of 0 was observed for HP5 in 22 patients, and 5 patients did not have an abnormality of nerve conduction. Score values at ceiling might constitute a greater problem than do scores at zero, since such values prevent recognition of worsening in subsequent evaluations. Values of scores at ceiling included NIS—reflexes (n = 8), S ST QSTing of HP5 (n= 1), and HR_{db} (n=7).

Correlation of Individual Polyneuropathy Signs with a Closely Matched Neurophysiologic Test Assessing Accuracy of Assessment of Clinical Polyneuropathy Signs

Considering the 37 individual neuropathy signs assessed in NIS, there were 11 for which a closely matched individual neurophysiologic test was available for comparison. For these 11 pairs of evaluations, the neurophysiologic test served as the gold standard assessment, because it was a highly standardized, quantitated, and referenced assessment. As shown in Table 2, 9 of the 11 clinical signs correlated strongly with their closely matched neurophysiologic test, i.e., high values of correlation coefficients and significance. To illustrate, weakness of toe or ankle dorsiflexion correlated closely with fibular nerve compound muscle action potential (CMAP) amplitudes. Seven additional signs correlated closely with comparable neurophysiologic tests. However, significant correlations were not found between clinical testing of touch-pressure or pin prick sensation and quantitative sensation tests of hands.

Correlation of Composite Measure of Polyneuropathy Signs (NIS) with Neurophysiological Tests (m+7$_{Ionis}$)

As shown in Table 3, strong correlations were observed between assessments of clinically assessed neuropathic signs (NIS) or symptoms (NSC) and neurophysiologic tests. The correlation of polyneuropathy signs (NIS) with m+7$_{Ionis}$ neurophysiologic tests performed as well or better than did any subscores of signs with neurophysiologic tests. Polyneuropathy signs (NIS) and symptoms (NSC) correlated more strongly with the modified attributes of nerve conduction using only motor and sensory amplitudes (the attributes used in mNIS +7$_{Ionis}$) than with those used in NIS+7 attributes (used for study of diabetic polyneuropathy) (data not shown). Clinical measures of polyneuropathy signs or symptoms correlated strongly with somatotopic assessment of touch-pressure but not with somatotopic assessment of HP5; the latter is a measure of small sensory fiber dysfunction. Similarly, scored signs (NIS) and symptoms (NSC) did not correlate with HR$_{db}$. By contrast, the autonomic sub-score of NSC correlated at a low level of significance with measured HP5 (S ST QSTing of HP5) and with HR$_{db}$.

Correlation of Neuropathy Signs and Neurophysiologic Tests with Disability and Health Scores

The data are shown in Table 4. Considering the correlation between signs and neurophysiologic tests, the strongest correlations occurred between mNIS+7$_{Ionis}$ and disability and health scores. Almost as strong correlations were obtained for NIS total or from the weakness (NIS-W) subscore and disability and health scores. The correlation between reflexes (NIS-R) and disability and health scores was not as strong. The correlations between symptom scores (NSC) provided confirmatory information. Symptoms of weakness (NSC weakness) and sensory loss (NSC sensation) correlated strongly with disability and health scores. Scores of positive neuropathic sensory symptoms, pain, and autonomic scores correlated at lower levels of significance with disability and health scores. Somatotopic evaluation of touch-pressure but not of heat as pain sensation correlated with all disability and health scores.

In Figure 2, we show the distribution of mNIS+7_{Ionis} score values of FAP patients staged by the PND. Scored values are significantly different among the three stages.

DISCUSSION

Previously published cohort studies of FAP[2,6,7,11,15,16,18] found considerable variability in age of onset, clinical manifestations, and course of this polyneuropathy. To illustrate, the somatotopic distribution and severity of muscle weakness, muscle stretch reflex decrease, the balance of large to small fiber sensation loss, and autonomic deficits varied considerably among patients. This variability of clinical expression, the rarity of FAP, and the desire to include a representative cohort of FAP impairments were important considerations in the choice to use a composite neuropathy score as an outcome measure in the NEURO-TTR trial. mNIS+7_{Ionis} was designed to somatotopically quantitate muscle weakness and large and small fiber sensory loss. Autonomic dysfunction, however, was not assessed somatotopically and, as shown here, HR_{db} is not an adequate outcome measure of small fiber involvement in FAP.

Neurophysiologic test results (m+7) were added to a score of clinical signs (NIS) for 2 reasons: 1) for m+7_{Ionis} tests to serve as reference standards against which accuracy of assessment of clinical signs could be compared, and 2) to aid in comprehensive scoring of FAP impairments. We reasoned that use of such composite scoring would not prevent it from demonstrating a meaningful beneficial effect, assuming that an efficacious treatment would benefit all kinds and severities of FAP impairments.

In our analysis of the first 100 FAP patients from 6 different countries entered into the NEURO-TTR trial, we found that a broad range of polyneuropathy functional impairments and severities had been recruited. Typically, the composite score mNIS+7_{Ionis} and its component scores detected and broadly scaled these abnormalities with sufficient room to recognize expected worsening. From a review of the distribution of the kind and severities of polyneuropathy signs and neurophysiologic test abnormalities, it appeared that the goal of recruiting a broad range of severities of FAP severities is being achieved in this trial. Component scores of mNIS+7_{Ionis} without abnormality at baseline evaluations (mean of 2 evaluations) were: NIS-R (n=7), S ST QSTing of HP5 (n=22), and several other endpoints (Figure 1). None of the recruited patients had mNIS+7_{Ionis} scores at ceiling. However, ceiling scores were observed for some subscores: NIS reflexes (n=8), S ST QSTing of HP5 (n=1), and HR_{db} (n=7). Overall, we judged that mNIS+7_{Ionis} broadly detected and scaled polyneuropathy abnormality over a broad range of different expressions and severities.

Availability of highly standardized neurophysiologic tests, reference values of nerve conduction, and quantitative sensation tests in the mNIS+7_{Ionis} composite score allowed us to test for the accuracy of closely matched clinical signs. Most clinical signs had been accurately assessed by international neurologists. This conclusion was supported by the significant correlation of composite scores of clinical signs with neurophysiologic tests. It is direct evidence that neurologists, given special training and certification, had accurately assessed polyneuropathy signs.

From our correlation studies of polyneuropathy signs as compared to neurophysiologic tests, we also observed that correlations were much stronger for some composite scores of nerve conduction than for others. Thus, those chosen for $m+7_{Ionis}$ performed much better than those in +7 (the latter chosen for study of diabetic polyneuropathy and emphasizing attributes of nerve conduction velocity and distal latencies). We also note that the strong correlations between assessed neuropathy signs and neurophysiologic tests came from assessments made at 16 medical centers located in 6 different countries, providing evidence that $mNIS+7_{Ionis}$ can be assessed accurately and proficiently at multiple medical centers and in different countries. However, we judge that the good clinometric performance of neurologists and neurophysiologists observed here came from performance related to insights gained from previously conducted Clinical vs Neurophysiologic Trials (Cl vs NPhys)[33-35,38,39]. The choice of expert neurologists and clinical neurophysiologists, special training sessions to grade abnormality specifically using appropriate reference values, and quality control at a central reading and quality assurance center probably contributed to the observed accuracy of polyneuropathy measurements.

How broadly applicable is $mNIS+7_{Ionis}$ for therapeutic trials in other countries or other neuropathies? From our results it appears that rigorous trials are possible in multiple countries assuming that the approaches found to be useful in this trial are utilized. However, whether $mNIS+7_{Ionis}$ would find usefulness in trials of other polyneuropathies cannot be inferred from the results of this trial.

Another question, not directly addressed in this trial, is whether $mNIS+7_{Ionis}$ can be scored or utilized without the involvement of MC PNRL personnel. We assume that it can, knowing that normative reference values of attributes of nerve conduction are widely available and that reference values of quantitative sensation and autonomic tests will increasingly be published or made available to users by neurophysiologic instrument makers.

This study has demonstrated that accurate grading of clinical neuromuscular impairments can be performed to the degree that it correlates with neurophysiologic tests and other health outcomes in FAP. The clinical approaches to accurate grading of polyneuropathy signs was inferred from results of Cl vs NPhys Trials 1 and 2.[34,35] In Cl vs NPhys trial 1,[34] 12 international neuromuscular experts evaluated and recorded the polyneuropathy signs of 24 patients with diabetes and with and without polyneuropathy. The appearances and voices of patients were masked. Each patient was examined on a second occasion. In this trial , the experts markedly over-reported polyneuropathy signs and the diagnosis of polyneuropathy as compared to independently assessed, referenced, and sensitive nerve conduction abnormality. In addition, their judgment of abnormality of polyneuropathy signs and diagnosis of polyneuropathy were excessively variable among themselves. When the same trial was repeated approximately 1 year later,[35] but on this occasion employing a consensus process emphasizing more specific use of “unequivocal abnormality” of signs for the diagnosis of polyneuropathy, an improvement in accuracy and proficiency resulted. Therefore, for the conduct of the NEURO-TTR trial of FAP and as discussed in Materials and Methods, a series of steps were taken to encourage neurologists to grade abnormality of polyneuropathy signs using specific criteria, comparison to healthy subjects, and to be objective and specific in their assessments. In their judgment of neuropathic abnormality,

neurologists were asked not to include signs attributable to old age, previous or concurrent disease, or injury other than FAP. In addition, all of the evaluations underwent surveillance at the central MC PNRL to encourage compliance with these standards.

The availability of m+7$_{Ionis}$ neurophysiologic test results in the mNIS+7$_{Ionis}$ score provided a built-in standard by which the accuracy of clinical signs could be judged. It was reassuring that most clinical signs for which a comparable neurophysiologic test had also been measured were found to be strongly correlated. Furthermore, it was reassuring that severity of polyneuropathy signs or symptoms assessed more broadly also correlated with neurophysiologic tests.

It is an important finding of this study that the entire score NIS (and even mNIS+7$_{Ionis}$) performed as well or better than any of its subscores. This fact provides evidence that we have not included subscores that dilute the correlation of the overall scores. We also assessed whether the different symptom or disability scores performed as well or better than NIS or of one of its subscores in correlation with neurophysiologic tests. They did not, with 2 exceptions, i.e., S ST QSTing of HP5 and HR$_{db}$. Whereas NIS and its subscores did not correlate with somatotopic assessment of HP5 or with HR$_{db}$, the autonomic subscores of NSC did.

The question of whether small fiber sensory (S ST QSTing of HP) or autonomic (HR$_{db}$) dysfunction measures should be included in mNIS+7$_{Ionis}$ needs to be considered, be because S ST QSTing of HP5 did not correlate with most other polyneuropathy measures in mNIS +7$_{Ionis}$. Also, test/retest reproducibility was not as high as it was for some other neuropathy measurements. Nevertheless, we judge that S ST QSTing of HP5 should be included in mNIS+7$_{Ionis}$, because selective small fiber sensory loss would not be adequately assessed and this abnormality occurs to a marked degree in a subset of FAP patients.

The strong correlations of mNIS+7$_{Ionis}$ or its subscores with disability and health scores was helpful in demonstrating that the entire score provided as strong or stronger correlations with disability or health scores than did their component subscores. However, we observed that some of the component subscores, e.g., NIS, NIS-W, NSC-W and others, performed very well also.

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Abbreviations

ATTR	Transthyretin amyloidosis
CMAP	Compound muscle action potential
Disability Scores	Amyloid gait stage, Dyck/Rankin and INCAT from NSC

FAP	Familial amyloidotic polyneuropathy
Health Scores	Norfolk-DN-QOL, NSC and SF-36
HP5	Heat as pain 5 (of 1-10 severity) as tested by CASE IVc, WR Medical Electronics; Maplewood, MN
HR_{db}	Heart rate decrease with deep breathing
INCAT	Inflammatory neuropathy cause and treatment
MC PNRL	Mayo Clinic Peripheral Nerve Research Lab
MNCV	Motor nerve conduction velocity
MNDL	Motor nerve distal latency
NC	Nerve conduction
ND	Normal deviate
NIS	Neuropathy Impairment Score
NIS-W	NIS of weakness
NIS-R	NIS of muscle stretch reflexes
NIS-S	NIS of clinical sensation of toes and fingers
NSC	Neuropathy Symptoms and Change Score
$mNIS+7_{Ionis}$	Modified NIS + 7 score (neurophysiologic tests used in Ionis-TTR_{RX} clinical trial in FAP)
PND	Polyneuropathy disability score, also called amyloid gait stage
S ST QSTing	SMART Somatotopic Quantitative Sensation Testing using CASE IVc, WR Medical Electronics, Maplewood, MN, USA
SNAP	Sensory nerve action potential
TP	Touch pressure sensation
TTR	transthyretin

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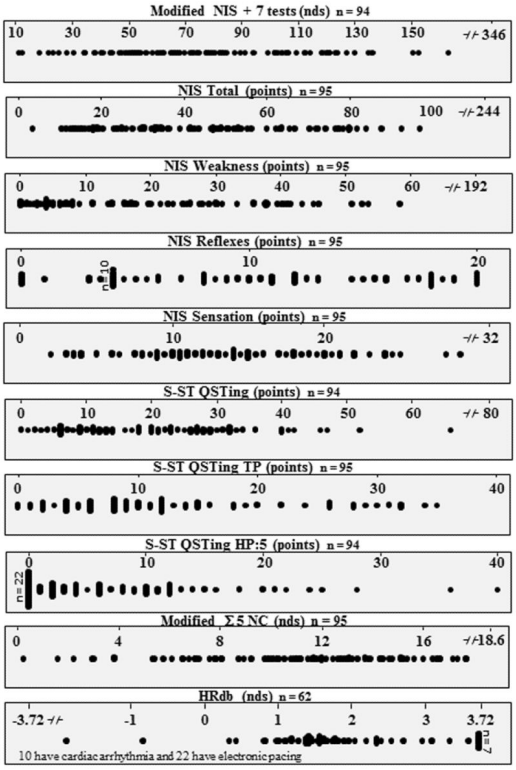

Figure 1.

The distribution of the measured values (mean of the 2 assessments) of the components of mNIS+7_{Ionis} of the first 100 patients entered into IONIS-TTR_{RX} Phase 3 FAP trial. Note that the clinical measures of weakness, muscle stretch reflexes, and clinical sensation scale abnormality with only a small ceiling effect observed for NIS reflexes. Among the clinical neurophysiological tests, scaling is robust for most tests, but approximately one-fourth of patients have no abnormality of Somatotopically assessed heat as pain 5 (HP5). Heart rate decrease with deep breathing was at ceiling in 7 patients. The data in this figure illustrate that mNIS+7_{Ionis} represents the kind and range of severities of functional polyneuropathy abnormalities that occur in FAP. While muscle weakness, muscle stretch reflexes, and sensation loss of both large and small sensory fibers are broadly represented in the score, autonomic dysfunction is inadequately represented, because of frequent cardiac arrhythmias and electronic pacing.

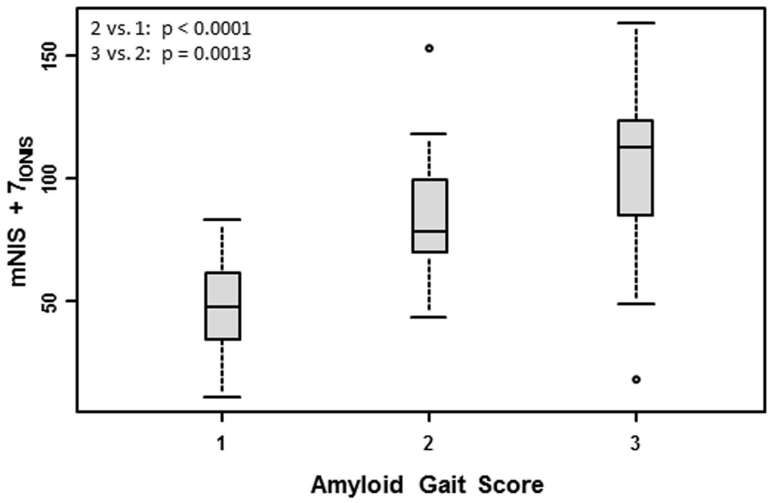

Figure 2.
The mNIS+7_{Ionis} score values of patients who have stage 1, 2, and 3 PND abnormalities.

Table 1

The Test/Re-test Reproducibility of Baseline Values of Neuropathy Signs, Nerve Conduction Tests, Smart Somatotopic Quantitative Sensation Tests, and Heart Rate Decrease with Deep Breathing

Test	Baseline 1			Baseline 2			α †	95% CI
	n*	Median	Range	n*	Median	Range		
NIS Total (points)	94	43.5	4.0 - 102.8	93	42.0	3.0 - 92.5	0.97	(0.96, 0.98)
mod. Σ 5 NC (nds)	94	11.9	1.2 - 17.7	94	11.6	−0.7 - 17.7	0.98	(0.97, 0.99)
S ST QST (points)	91	20.0	0.0 - 76.0	89	20.0	0.0 - 58.0	0.57	(0.36, 0.75)
S ST QST TP (points)	91	10.0	0.0 - 40.0	89	10.0	0.0 - 38.0	0.44	(0.22, 0.65)
S ST QST HP:5 (points)	91	4.0	0.0 - 40.0	89	4.0	0.0 - 40.0	0.65	(0.51, 0.78)
HRdb (nds)	57	−1.7	−3.7 - 1.9	56	−1.6	−3.7 - 0.7	0.93	(0.88, 0.96)
INCAT from NSC (points)	96	3.0	0.0 - 10.0	97	3.0	0.0 - 10.0	0.94	(0.91, 0.96)

*Missing values account for the numbers being <100. For NIS (points) and NSC (INCAT) a single or double evaluation has been performed on all 100 patients. For the other listed endpoint, a somewhat lesser number is used.

†Krippendorff alpha

Table 2

Correlation Coefficients and Statistical Significance of Individual Neuropathy Signs and Neurophysiologic Tests Using Spearman Rank Correlations in ISIS Baseline Study of 100 FAP Patients (n = 94 or 95)

Test			Mean Fibular CMAP[§] nd	Mean Tibial CMAP nd	Mean Ulnar CMAP nd	Mean S ST QSTing[¶] TP Hand pts	Mean S ST QSTing TP Foot pts	Mean S ST QSTing HP:5 Hand pts	Mean S ST QSTing HP:5 Foot Pts
Mean Values of Neuropathic Signs (NIS 23, 21, 22, 24, 15, 30, 34, 31 and 35) or Symptoms (NSC 20 and 21)	NIS # 23	r*	−0.62						
		p†	<0.0001						
	NIS # 21	r*	−0.56						
		p†	<0.0001						
	NIS # 22	r*		−0.41					
		p†		<0.0001					
	NIS # 24	r*		−0.35					
		p†		0.0005					
	NIS # 15	r*			−0.47				
		p†			<0.0001				
	NIS # 30	r*				0.16			
		p†				0.1268			
	NIS # 34	r*					0.47		
		p†	NIS # 23 = toe extensors #21 = ankle dorsiflexors #22 = ankle plantar flexors #24 = toe flexors #15 = finger spread #30 = touch pressure (finger) #34 = touch pressure (toe) #31 = pin-prick (finger) #35 = pink-prick (toe) NSC # 20 = loss of touch # 22 = loss of pain sensation				<0.0001		
	NIS # 31	r*						0.19	
		p†						0.0666	
	NIS # 35	r*							0.39
		p†							<0.0001
	NSC Severity # 20	r*					0.38		
		p†					0.0002		
	NSC Severity # 22	r*							0.57
		p†							<0.0001

*Spearman rank correlations

†Shaded *P*-values indicate the test was significant at the 0.05 level. If a Bonferroni correction for multiple tests is used, the cutoff is 0.0045.

§CMAP = compound muscle action potential amplitudes

[¶]S ST QSTing = smart quantitative sensation testing

Table 3

Correlation Coefficients and Statistical Significance of Composite Scores of Polyneuropathy Signs (NIS) or Symptoms (NSC), and Neurophysiologic Tests (n = 100)

Test	r.p[a]					
	Mean Modified + 7 tests (nds and pts)	Mean modified Σ 5 NC[c] (nds)	Mean VDT (nd)[d]	Mean S-ST QSTing[e] TP[f] (pts)	Mean S-ST QSTing HP:5[g] (pts)	Mean HRdb[h] (pts)
Mean NIS Total (pts)	1	1	2	1	NS	NS
Mean NIS Weakness (pts)	1	1	3	1	NS	NS
Mean NIS Reflexes (pts)	5	4	NS	3	NS	NS
Mean NIS Sensation (pts)	1	1	1	2	3	NS
Mean INCAT from NSC (pts)	2	2	NS	2	NS	NS
Mean NSC Weakness severity (pts)	2	3	NS	1	NS	NS
Mean NSC Sensation severity (pts)	2	3	2	2	NS	NS
Mean NSC PNSS[i] severity (pts)	NS	NS	5	3	NS	NS
Mean NSC Pain severity (pts)	NS	NS	NS	NS	NS	NS
Mean NSC Autonomic severity (pts)	2	2	NS	3	5	3

[a] r.*P* statistical category from Spearman rank correlations and *P*-values:
r category: 1 = r ≥ 0.5 or r ≤ −0.5; 2 = r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5; 3 = r > −0.25 to r < 0.25.
P-value category: 1 = $P \leq 0.0001$; 2 = $P > 0.0001$ to p ≤ 0.005; 3 = $P > 0.005$ to p ≤ 0.05; NS = $P > 0.05$.
r.*P* category: 1 if 1,1 (r category, *P*-value category); 2 if 1,2 or 2,1; 3 if 2,2; 4 if 2,3 or 3,2; 5 if 3,3.

[b] Σ 5 NCs (nds) = the sum of the normal deviates from percentiles of fibular nerve compound muscle action potential (CMAP) amplitudes, motor nerve conduction velocities (MNCV) and motor nerve distal latency (MNDL), tibial MNDL, and sural nerve action potential (SNAP) amplitudes.

[c] modified Σ 5 NCs (nds) = the sum of the normal deviates from percentiles of ulnar, fibular, and tibial nerve CMAPs and ulnar and sural SNAPs.

[d] VDT = Vibratory Detection Threshold

[e] S ST QSTing = Smart Somatotopic Quantitative Sensation Testing

[f] TP = Touch Pressure

[g] HP:5 = Heat as Pain 5 QSTing Threshold

[h] HRdb = Heart Rate Response to Deep Breathing

[i] PNSS = Positive Neuropathic Sensory Symptoms

Table 4

Correlation Coefficients and Statistical Significance of Composite Scores of Polyneuropathy Signs (NIS), Symptoms (NSC), or Neurophysiologic Tests and Health Scores (n=100)

Test	r.P*				
	Norfolk Score	Amyloid Gait Stage (PND)	Dyck/ Rankin Score	Mean INCAT from NSC (pts)	SF-36 Health Score Physical Health Summary Measure
Mean Modified NIS + 7 tests (nds and pts)	1	1	1	1	2
Mean NIS Total (pts)	2	1	1	1	2
Mean NIS Weakness (pts)	2	1	1	1	2
Mean NIS Reflexes (pts)	3	3	3	3	5
Mean NIS Sensation (pts)	3	1	2	2	4
Mean NSC Weakness severity (pts)	1	1	1	1	1
Mean NSC Sensation severity (pts)	1	3	3	2	2
Mean NSC PNSS† severity (pts)	1	NS	5	3	2
Mean NSC Pain severity (pts)	1	NS	NS	5	3
Mean NSC Autonomic severity (pts)	3	NS	2	2	2
Mean Σ 5 NC§	NS	3	3	NS	NS
Mean S-ST QSTing¶; TP** (pts)	1	2	3	2	2
Mean S-ST QSTing HP:5†† (pts)	NS	NS	NS	NS	NS

* r.*P* statistical category from Spearman rank correlations and *P*-values: r category: 1 = r ≥ 0.5 or r ≤ −0.5; 2 = r ≥ 0.25 to r < 0.5 or r ≤ −0.25 to r > −0.5; 3 = r > −0.25 to r < 0.25 *P*-value category: 1 = *P* ≤ 0.0001; 2 = *P* > 0.0001 to *P* ≤ 0.005; 3 = *P* > 0.005 to *P* ≤ 0.05; NS = *P* > 0.05 r.p category: 1 if 1,1 (r category, p-value category); 2 if 1,2 or 2,1; 3 if 2,2; 4 if 2,3 or 3,2; 5 if 3,3

† PNSS = Positive Neuropathic Sensory Symptoms

§ Σ 5 NCs (nds) = the sum of the normal deviates from percentiles of fibular nerve compound muscle action potential (CMAP)

¶ S ST QSTing = Smart Somatotopic Quantitative Sensation Testing

** TP = Touch Pressure

†† HP:5 = Heat as Pain 5 QSTing Threshold