# Challenges in Design of Multicenter Trials

## End points assessed longitudinally for change and monotonicity

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**OBJECTIVE** — Assessing clinimetric performance of diabetic sensorimotor polyneuropathy (DSPN) end points in single and multicenter trials.

**RESEARCH DESIGN AND METHODS** — Assessed were placebo-treated patients with DSPN in the Viatris and Eli Lilly trials and an epidemiologic cohort.

**RESULTS** — Test reproducibility in clinical trial cohorts ($r_I \sim 0.7–0.85$) approached that in the epidemiologic cohort ($r_I \sim 0.85–0.95$). Associations between pairs of end points explained <10% of the variability of data (sometimes 15–35%), being higher in the epidemiologic cohort and the Viatris trial than in the Lilly trial. Most end points did not show monotonic worsening over 4 years. However, sural nerve amplitude and peroneal motor conduction velocity did. A nerve conduction score ($\Sigma$ 5 NC nds [5 attributes of nerve conduction expressed as normal deviates]) did not show monotonic worsening in established DSPN. In the epidemiologic cohort followed for 9.5 years, monotonic worsening of small magnitude occurred for sural amplitude, vibration detection threshold, and especially for composite quantitative sensation.

**CONCLUSIONS** — The main reason why it is difficult to demonstrate monotonic worsening of neuropathic end points appears to be a very slow worsening of DSPN, a placebo effect for symptoms and signs, and measurement noise. Demonstrating disease progression in controlled trials of DSPN is more likely when 1) patients with developing rather than established DSPN are selected, 2) type 1 diabetic patients are preferentially recruited, 3) patients are selected who cannot or will not achieve ideal glycemic control, 4) end points chosen are known to show monotonic worsening, and 5) a restricted number of centers and expert examiners (trained, certified, using standard approaches, and reference values and interactive surveillance of tests) are used.

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Rigorous control of glycemia retards or ameliorates diabetic sensorimotor polyneuropathy (DSPN), but long and expensive trials are needed (1–4). No adjuvant treatment, in addition to glycemic control, has achieved sufficient efficacy, considering side effects, to obtain regulatory approval (e.g., by the Food and Drug Administration) (5–13). This contrasts to interventions ameliorating sensory symptoms of pain or autonomic symptoms (gastric atony, diarrhea, and sexual dysfunction) receiving approval (14–20). Therefore, we ask, are controlled clinical trials of ancillary treatments doable, which end points should be used, and how long and rigorous do the trials need to be? Assuming that adjuvant efficacious treatments exist, why has it been so difficult to demonstrate efficacy? Possibilities are 1) interventions are not efficacious; 2) present diabetes care inhibits development of complications; 3) other diabetic complications (hypertension, hyperlipidemia, renal disease, and other) with possible adverse effects on DSPN (21) are now managed better; 4) the wrong kind, stage, or duration of DSPN is studied; 5) end points chosen are insufficiently sensitive, specific, monotonic (measuring a consistent trend of worsening or improvement with time), or generalizable (for study at many medical centers); 6) excessive recruitment of type 2 diabetic patients showing little change with time and excessive variability of measured end points; 7) both placebo and treated patients receive better than usual medical treatment (e.g., of hyperglycemia) while in the trial; and 8) studies are insufficiently powered.

The present studies focus on the performance of neuropathy end points in a longitudinal epidemiology survey in Rochester, Minnesota (22), and in placebo arm patients of two pharmaceutical trials, the Viatris trial and the Eli Lilly trial, of mild severity DSPN in type 1 and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Patient cohorts studied

The three cohorts studied are dissimilar in important ways but are alike in having mild or moderate severity DSPN (stage 2B and 3 [23] are excluded), and severity of neuropathy was evaluated by the same approaches and criteria. Minimal criteria for the diagnosis of DSPN were the same: i.e., $\Sigma$ 5 NC nds (5 attributes of nerve conduction expressed as normal deviates) ≥95th percentile, neuropathy impairment score of lower limbs [NIS(LL)] ≥2 points, or Diabetes Control and Complications Trial (DCCT) criteria (two approaches).

The epidemiologic study patients are consenting individuals with diabetes and distal symmetric DSPN from Rochester, and

later Olmsted County, Minnesota (Rochester Diabetic Neuropathy Study) (22).

The Viatris trial patients (Nathan 1, Viatris) are placebo-treated individuals from a prospective double-blind multicenter trial of oral α-lipoic acid (600 mg/day) for 4 years. A total of 38 medical centers from the U.S. and Europe participated. Entry criteria were somewhat different from the epidemiologic cohort: *1*) the neuropathy impairment score of lower limbs + 7 tests (NIS[LL] + 7 tests) ≥97.5th percentile; *2*) NIS(LL) ≥2 points; and *3*) two additional criteria: an abnormality (>99th percentile) of at least one attribute of nerve conduction (NC) in two leg nerves tested and a total symptom score ≥5 points.

The Lilly trial patients are placebo-treated individuals of two prospective double-blind multicenter trials (B7A-MC-MBCW and MBBP) of LY 333531 (a specific protein kinase C-β inhibitor) for the symptoms of DSPN during a 1-year period. The criteria for study entry were as follows: diagnosis of DSPN, neuropathic symptoms (a symptom score >6 points), vibration detection threshold of the great toe using CASE IV ≥95th percentile, a sural nerve sensory amplitude ≥1 μV, and an A1C level <12%. A total of 71 medical centers from six countries (in the U.S., Europe, Middle East, and Asia) participated.

### Personnel and performance of tests

The same clinical instruments, end points, instructions, and reference values were used for the epidemiologic cohort, the Viatris trial, and the Lilly trial. All tests were to be done independently, without taking previous or concurrent examination and test results into account.

In the epidemiologic cohort, one of us (P.J.D.) performed all clinical evaluations. In the Viatris and Lilly trials, trained and certified (for the study) neurologists or diabetologists did the examinations. Nerve conductions were performed by neurologists or electromyography technicians under the supervision of physicians. Quantitative sensation testing was done by technicians using CASE IV (a computer-based system using standard and calibrated stimuli, predetermined and validated algorithms of testing, and null stimuli and reference values [percentiles and normal deviates] from the Rochester Diabetic Neuropathy Study cohort of healthy subjects) (24,25).

All neurological evaluation sheets (Clinical Neuropathy Assessment, see below) were sent to a central reading and quality assurance center to interactively recognize omissions and errors, to electronically calculate scores, and to enter data into an electronic database (26).

### Use of standard and independent tests

In the epidemiologic cohort, all evaluations were performed independently without availability of earlier or concurrent tests. In the Viatris trial, ~40% of respondents reported that they had always, or sometimes, reviewed previous or concurrent medical information or tests, probably improving the estimate of reproducibility and associations. Information was not available for the Lilly trial.

### Analyses

Neuropathy impairment was expressed as NIS(LL) points and symptoms as neuropathy symptom and change score (NSC) severity points. Individual attributes of nerve conduction were recorded as measured values and as normal deviates (nds) (from percentiles correcting for age and other applicable variables) (25). The composite nerve conduction score (Σ 5 NC nds) consists of peroneal nerve amplitude, velocity and distal latency, tibial distal latency, and sural amplitude. The normal deviates of the measurable (when amplitude is 0, velocity and latency cannot be estimated) attributes of the five attributes listed above were summed, divided by the number of measurable attributes and multiplied by 5. Results of quantitative sensation tests (QST) and reduction of heart rate with deep breathing were given as normal deviates (from percentiles corrected for applicable variables).

For reproducibility, intraclass correlations were used. For concordance between tests, Spearman rank-order correlations were used. For change with time, neuropathic end points were regressed on time and the derived slope was tested for statistical significance.

### Study limitation

Factors that might affect results of any trial, and therefore the extent to which results from others might be disparate from ours, include *1*) methods of data analyses used, including adjustment using normative values and whether classic or Bayesian statistics are used; *2*) restriction on enrollments, defining the population to which inferences are to be made; and *3*) the nature of any drug effect, including the magnitude of any effect and whether the effect is to show deterioration or to reverse decline.

## RESULTS

### Demographic and disease characteristics

In patients from the untreated (the epidemiologic study) and placebo arm (the Viatris and Lilly trials), glycemic control (A1C ~8–9%) was not ideal (Table 1). All patients studied had mild-severity DSPN. However, by the criteria of the median values of NIS(LL), Σ 5 NC nds, Σ 3 QST tests nds, and heart rate with deep breathing nds, the Viatris trial cohort was most severe, followed by the Lilly trial and then by the epidemiologic cohort. By the criteria of symptoms (NSC severity) and Σ DCCT criteria (summated values giving equal weights for decreased ankle reflexes, clinical vibration of toes, and neuropathic symptoms [from NSC]), the order of most to least severe was the Lilly trial, the Viatris trial, and the epidemiologic cohorts.

### Reproducibility of nerve tests

Reproducibility of neuropathy end points could only be assessed for the Viatris trial and the Lilly trial. Generally, reproducibility was in the range of $r_{\mathrm{I}} = 0.7$–0.85 (Table 2), somewhat lower than previously published values mainly from the epidemiologic cohort.

### Concordance ($r^2$ as percentages) between pairs of neuropathy end points

There is considerable variability of associations between pairs of end points and among cohorts (Table 3). For many pairs of end points, the percent variability explained by the data are <10%; but for others, it was in the range of 15–35%. For the epidemiologic cohort, the Viatris trial, and the Lilly trial, neurological signs (NIS[LL]) were correlated with symptoms to a substantial degree, i.e., 6, 12, and 15% at the first and 15, 24, and 16% at the last examination, respectively. By comparison, Σ 5 NC and NIS(LL) had values of 11, 17, and 0% and 14, 19, and 1%, respectively—a low correlation in the Lilly trial at both examinations. The mean values of the percent correlations were similar between the epidemiologic cohort and the Viatris trial at first and at last evaluations. It was lower for the Lilly trial cohort. In all cases, mean correlations were higher at the last examination than at the first examination.

**Table 1—***Clinical characteristics of patients in the Rochester, Viatris, and Lilly cohorts at first evaluation using inclusion criteria of $\Sigma$ 5 NC tests $\geq$95th percentile*

| | Rochester | | | | | Viatris | | | | | Lilly | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cohort | n | % | Mean | Median | SD | n | % | Mean | Median | SD | n | % | Mean | Median | SD |
| Age (years) | 108 | | 57.8 | 58.0 | 13.3 | 191 | | 53.7 | 55.0 | 7.8 | 130 | | 48.3 | 50.0 | 9.1 |
| Sex (M) | 108 | 56.5 | | | | 191 | 68.1 | | | | 130 | 53.1 | | | |
| Type 1 diabetes | 108 | 36.1 | | | | 191 | 23.0 | | | | 130 | 31.5 | | | |
| DSPN (stage 2a) | 108 | 36.1 | | | | 191 | 96.3 | | | | 130 | 97.7 | | | |
| A1C (%) | 108 | | 8.2 | 8.0 | 1.5 | 190 | | 8.9 | 8.8 | 1.9 | 130 | | 8.0 | 7.8 | 1.5 |
| Creatinine (mg/dl) | 108 | | 1.1 | 1.1 | 0.3 | 190 | | 0.9 | 0.9 | 0.3 | | | | | |
| Ankle reflexes (0–4 pts) | 108 | | 2.0 | 2.0 | 1.9 | 191 | | 2.0 | 2.0 | 1.1 | 130 | | 1.7 | 2.0 | 1.3 |
| Great toe vibration (0–4 pts) | 108 | | 0.2 | 0.0 | 0.5 | 191 | | 2.3 | 2.0 | 1.2 | 130 | | 1.9 | 2.0 | 1.1 |
| NIS(LL) (pts) | 108 | | 2.2 | 2.0 | 2.9 | 191 | | 10.1 | 10.0 | 5.2 | 130 | | 7.6 | 6.5 | 5.2 |
| NSC(LL) severity (pts) | 108 | | 1.0 | 0.0 | 2.8 | 191 | | 4.7 | 4.0 | 3.5 | 130 | | 8.8 | 8.0 | 5.0 |
| $\Sigma$ DCCT criteria (0–12 pts) | 108 | | 1.4 | 0.7 | 1.7 | 191 | | 5.2 | 4.8 | 1.8 | 130 | | 4.9 | 5.1 | 2.1 |
| Peroneal motor amplitude nd | 108 | | 1.4 | 1.3 | 0.7 | 191 | | 1.7 | 1.9 | 0.8 | 130 | | 1.1 | 1.1 | 0.9 |
| Peroneal motor CV nd | 106 | | 3.2 | 2.1 | 2.8 | 174 | | 4.4 | 3.2 | 3.6 | 130 | | 3.2 | 2.3 | 2.2 |
| Peroneal motor DL nd | 106 | | 0.9 | 0.8 | 0.9 | 174 | | 1.2 | 1.2 | 1.3 | 130 | | 0.9 | 0.9 | 0.9 |
| Tibial motor DL nd | 108 | | 1.2 | 1.1 | 0.8 | 183 | | 1.9 | 1.9 | 1.0 | 130 | | 1.9 | 1.9 | 0.8 |
| Sural SNAP nd | 106 | | 1.7 | 1.9 | 0.8 | 191 | | 2.3 | 2.8 | 0.8 | 130 | | 2.3 | 1.4 | 11.8 |
| $\Sigma$ 5 NC tests nd | 108 | | 8.3 | 6.8 | 3.9 | 191 | | 11.5 | 10.4 | 5.2 | 130 | | 9.4 | 7.8 | 12.0 |
| VDT nd | 108 | | 1.3 | 1.2 | 1.5 | 191 | | 3.3 | 2.9 | 2.1 | 130 | | 4.0 | 3.8 | 1.4 |
| $\Sigma$ 3 QST nd | 107 | | 1.6 | 0.7 | 3.9 | 191 | | 8.6 | 7.9 | 5.6 | | | | | |
| HRDB nd | 105 | | 0.9 | 1.0 | 1.3 | 190 | | 1.6 | 1.5 | 1.6 | 129 | | 1.4 | 1.2 | 1.5 |

$\Sigma$ 3 QST, summated normal deviates of VDT, cooling detection threshold and heat-pain 5 threshold, using CASE IV; $\Sigma$ 5 NC tests, summated normal deviates of peroneal motor nerve amp, CV and DL, tibial motor DL, and sural SNAP; $\Sigma$ DCCT criteria, summated abnormalities of ankle reflexes, clinical vibration sensation of the great toes, and neuropathic symptoms of the lower limb (as described in RESEARCH DESIGN AND METHODS); CV, conduction velocity; DL, distal latency; HRDB, heart rate decrease with deep breathing; nd, normal deviate, all given in the upper tail of the normal distribution (see RESEARCH DESIGN AND METHODS); NSC(LL) severity, neuropathy symptoms, and change severity of lower limbs; pts, points; SNAP, sensory nerve action potential; VDT, vibration detection threshold using CASE IV.

## Consistency of end point worsening over time (monotonicity)

Estimates of monotonicity varied somewhat depending on criteria for diagnosis of DSPN (Table 4). Therefore, it was assessed using three criteria for the diagnosis of DSPN, i.e., NIS[LL] $\geq$2 points, $\Sigma$ 5 NC nds $\geq$95th, and DCCT with two or more of three criteria (two varieties). By these criteria, sural sensory nerve amplitude performed best, significantly worsening eight of a possible nine times, with the ninth time not showing a significant change. Peroneal nerve motor conduction velocity showed significant worsening in two of nine cases. Heart rate change with deep breathing showed neither worsening nor improvement. Improvement was found for ankle reflexes (significantly four

of nine times); NSC(lower limbs) severity also showed significant improvement (three of nine times). Summated DCCT criteria showed significant improvement in three of nine cases. Tibial motor distal latency showed significant improvement in three cases.

These results were confirmed and strengthened by assessment of longitudinal data in patients in the epidemiologic cohort with DSPN for the full duration of study (median 9.5 years) (Table 5, available from the authors upon request). The end points showing consistent monotonic worsening without improvement were as follows: sural sensory amplitude, clinical vibration of toe (significant two of four times), and $\Sigma$ 3 QST nds (significant four of four times).

## Testing for the effect of restricting entry into study by a percentile value of an end point and then following course using the same but unrestricted end point

The possible effect was tested using $\Sigma$ 5 NC nds in triplicate measures at baseline of the Viatris trial cohort patients. At first (of triplicate measures), only patients with $\Sigma$ 5 NC nds values $\geq$95th percentile were included and the same patients assessed at the second and third occasion— all three tests done within a week of each other. Comparing $\Sigma$ 5 NC nds median values of the second and third to that of the first examination, the median values were 10.4 nds, 10.7 nds (NS), and 10.2 nds ($P$ = 0.03). Because nerve conductions in DSPN have not significantly

**Table 2—*Reproducibility of neuropathic end point measurements at onset of Viatris and Lilly controlled clinical trials of DSPN***

| | ICC | | | |
| --- | --- | --- | --- | --- |
| | Viatris | | Lilly | |
| | First and second exam | First and third exam | First and second exam | First and third exam |
| Ankle reflexes (0–4 pts) | 0.82 | 0.80 | — | 0.83 |
| Great toe vibration (0–4 pts) | 0.77 | 0.73 | — | 0.88 |
| NIS(LL) (pts) | 0.82 | 0.82 | — | 0.89 |
| NSC(LL) severity (pts) | — | 0.80 | — | 0.81 |
| $\Sigma$ DCCT criteria (0–12 pts) | — | 0.77 | — | 0.88 |
| Peroneal motor CV nd | 0.85 | 0.85 | 0.84 | 0.80 |
| Tibial motor DL nd | 0.66 | 0.53 | 0.66 | 0.70 |
| Sural SNAP nd | 0.91 | 0.87 | 0.69 | 0.65 |
| $\Sigma$ 5 NC tests nd | 0.84 | 0.82 | 0.78 | 0.80 |
| VDT nd | 0.73 | 0.76 | 0.67 | 0.58 |
| CDT nd | 0.86 | 0.86 | — | — |
| HP:5 nd | 0.84 | 0.83 | — | — |
| $\Sigma$ 3 QST tests nd | 0.85 | 0.85 | — | — |
| HRDB nd | 0.81 | 0.83 | 0.72 | 0.73 |

Abbreviations are given in Table 1. Additional abbreviations: CDT, cooling detection threshold using CASE IV; HP:5, heat pain 5, severity of the pain experience from 1 (least) to 10 (most).

changed in a few days, the significant improvement found at the third examination is due to restriction at first evaluation and using the same end point (without restriction) for the subsequent two evaluations.

**CONCLUSIONS** — This study does not directly address all of the possible reasons why it has been difficult to demonstrate efficacy from adjuvant treatments of DSPN but deals with issues of reproducibility, concordance between pairs of tests, monotonicity, and the rate of worsening over prolonged times in mild DSPN. Our results show that the main reason is that DSPN worsens very slowly and that many end points are not sufficiently sensitive, accurate, representative, reproducible, and especially monotonic to reliably recognize the small worsening occurring over a period of 4 years. The magnitude of worsening measured over a period of 4 years was very small and was not accompanied by increased neurological signs or symptoms, both showing improvement (albeit small) rather than worsening. One possible explanation for why only a slight deterioration was observed might be our use of the commonly used practice in controlled clinical trials to "carry last observations forward" with the consequence of underestimating actual deterioration. Here, it was not the reason for the low rate of worsening, since results were essentially unchanged with

deletion of "carried forward" data. Because this slow rate of worsening was found for all three cohorts and had also been observed previously in DCCT studies (1,2), we attribute it to very slow worsening of DSPN.

Assuming that DSPN worsens very slowly and that adjuvant treatments are unlikely to improve nerve function to a greater degree than from euglycemia, end points needed to detect a difference between treatment and placebo must have excellent clinimetric characteristics. If, on the other hand, an adjuvant treatment causes a greater improvement than that from institution of euglycemia, one assumes that present monitoring approaches or analyses would be able to recognize and track improvement. Many of the end points studied were reasonably reproducible and concordant. By the criteria of monotonicity, some of the end points performed poorly. This was especially true for symptoms and neurological signs, which typically showed significant improvement rather than worsening. The failure of these clinical measures to perform well raises a serious question about the adequacy of the recently published research case definition of polyneuropathy (27). The end points that performed best were sural nerve amplitude and to a lesser degree peroneal motor conduction velocity, both showing monotonic worsening. This worsening is all the more meaning-

ful, as we had corrected for the influence of change in age and weight. Considering the epidemiologic cohort patients with DSPN followed for the full duration of study (median 9.5 years), sural nerve amplitude continued to show significant monotonic worsening three of four times. By contrast, peroneal motor conduction velocity did not show monotonic worsening. The composite score ($\Sigma$ 3 QST nds) showed monotonic worsening four of four times.

What inferences about the conduct of future therapeutic trials of DSPN can be drawn from the present analysis, and are multicenter trials doable? Several important insights about how to improve future trials can be inferred. First, since near euglycemia prevents or ameliorates DSPN, success is more likely if patients who cannot, or will not, achieve good chronic glycemic control are included. Second, end points should be chosen differing on whether patients without or with DSPN are to be recruited for study—composite scores of NC and heart rate with deep breathing emphasized for the former and the two attributes of NC and composite score of QSTs identified here for the latter. Third, studies will need to be done for long times to show a treatment effect. Perhaps the best stage of DSPN for conduct of trials is patients on the verge of developing DSPN. These patients showed monotonic worsening of composite scores of nerve conduction and, to a lesser degree, of heart rate variability with deep breathing (28). Type 1 diabetic patients are preferable to type 2 diabetic patients because there is less variability of normal test results due to their younger age and because polyneuropathy worsens to a greater degree in type 1 diabetes (25,29). However, we acknowledge that selection of other patients, other stages of complication, or other methods of analyses may be shown to improve study performance unlike that shown here.

The monotonic improvement of clinical signs and symptoms in placebo arm trial patients of controlled clinical trials demonstrated here is of concern, especially in light of their historical use in DSPN (30,31) and their importance in the recently published case definition of polyneuropathy (27). We judge the observed improvement we observed in the placebo arm of trials is mainly due to a placebo effect. Measures of neurological signs and symptoms, although good enough to demonstrate a large therapeutic response

**Table 3—***Percent Spearman rank-order correlations ($r^2$) between pairs of neuropathic end points explained by the data in the Rochester (R), Viatris (V), and Lilly (L) cohorts at first and last evaluation*

| Cohort | Ankle reflexes (0–4 pts) | | | Vibration great toe (0–4 pts) | | | NIS(LL) (pts) | | | NSC(LL) severity (pts) | | | NSC(LL) negative symptom severity (pts) | | | NSC(LL) positive symptom severity (pts) | | | Σ DCCT criteria | | | Peroneal motor CV nd | | | Sural SNAP nd | | | Σ 5 NC tests nd | | | Σ 3 QST nd | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L | R | V | L |
| **First evaluation** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ankle reflexes (0–4 pts) | — | — | — | 2 | 0 | 5 | — | — | — | 5 | 1 | 5 | 0 | 1 | 5 | 7 | 0 | 3 | — | — | — | 1 | 3 | 0 | 9 | 5 | 0 | 0 | 4 | 0 | 6 | 2 | — |
| Great toe vibration (0–4 pts) | 2 | 0 | 5 | — | — | — | — | — | — | 5 | 7 | 3 | 3 | 17 | 11 | 3 | 0 | 1 | — | — | — | 3 | 5 | 1 | 7 | 7 | 0 | 4 | 8 | 1 | 3 | 7 | — |
| NIS(LL) (pts) | — | — | — | — | — | — | — | — | — | 6 | 12 | 15 | 5 | 31 | 15 | 4 | 1 | 9 | — | — | — | 8 | 13 | 2 | 16 | 11 | 0 | 11 | 17 | 0 | 10 | 20 | — |
| NSC(LL) severity (pts) | 5 | 1 | 5 | 5 | 7 | 3 | 6 | 12 | 15 | — | — | — | — | — | — | — | — | — | — | — | — | 0 | 6 | 4 | 15 | 4 | 5 | 1 | 5 | 5 | 5 | 5 | — |
| Σ DCCT criteria (0–12 pts) | — | — | — | — | — | — | — | — | — | 9 | 28 | 23 | 16 | 5 | 9 | — | — | — | — | — | — | 4 | 11 | 1 | 17 | 13 | 0 | 4 | 15 | 0 | 10 | 8 | — |
| Peroneal motor CV nd | 1 | 3 | 0 | 3 | 5 | 1 | 8 | 13 | 2 | 0 | 6 | 4 | 0 | 6 | 1 | 1 | 3 | 4 | 4 | 11 | 1 | — | — | — | 4 | 1 | 1 | — | — | — | 11 | 9 | — |
| Tibial motor DL nd | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 2 | 0 | 0 | 1 | 1 | 6 | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | — | — | — | 0 | 1 | — |
| Sural SNAP nd | 9 | 5 | 0 | 7 | 7 | 0 | 16 | 11 | 0 | 15 | 4 | 5 | 9 | 5 | 10 | 8 | 1 | 3 | 17 | 13 | 0 | 4 | 1 | 1 | — | — | — | — | — | — | 15 | 2 | — |
| Σ 5 NC tests nd | 0 | 4 | 0 | 4 | 8 | 1 | 11 | 17 | 0 | 1 | 5 | 5 | 2 | 7 | 4 | 0 | 2 | 4 | 4 | 15 | 0 | — | — | — | — | — | — | — | — | — | 13 | 12 | — |
| VDT nd | 11 | 2 | 1 | 11 | 7 | 0 | 26 | 11 | 0 | 9 | 0 | 5 | 3 | 4 | 5 | 1 | 7 | 1 | 27 | 5 | 1 | 18 | 4 | 6 | 22 | 2 | 1 | 16 | 8 | 0 | — | — | — |
| Σ 3 QST nd | 6 | 2 | — | 3 | 7 | — | 10 | 20 | — | 5 | 5 | — | 3 | 18 | — | 5 | 0 | — | 10 | 8 | — | 11 | 9 | — | 15 | 2 | — | 13 | 12 | — | — | — | — |
| HRDB nd | 4 | 4 | 0 | 1 | 0 | 0 | 5 | 4 | 0 | 10 | 1 | 1 | 7 | 1 | 2 | 6 | 0 | 0 | 8 | 2 | 1 | 1 | 2 | 2 | 6 | 1 | 5 | 1 | 3 | 2 | 11 | 7 | — |
| NSC(LL) negative symptom severity (pts) | 0 | 1 | 5 | 3 | 17 | 11 | 5 | 31 | 15 | — | — | — | — | — | — | 11 | 2 | 10 | 9 | 28 | 23 | 0 | 6 | 1 | 9 | 5 | 10 | 2 | 7 | 4 | 3 | 18 | — |
| NSC(LL) positive symptom severity (pts) | 7 | 0 | 3 | 3 | 0 | 1 | 4 | 1 | 9 | — | — | — | 11 | 2 | 10 | — | — | — | 16 | 5 | 9 | 1 | 3 | 4 | 8 | 1 | 3 | 0 | 2 | 4 | 5 | 0 | — |
| Mean | 4 | 2 | 2 | 4 | 5 | 2 | 9 | 12 | 5 | 6 | 4 | 5 | 4 | 10 | 8 | 6 | 1 | 4 | 11 | 10 | 5 | 4 | 5 | 2 | 11 | 4 | 2 | 5 | 8 | 2 | 8 | 8 | — |
| **Last evaluation** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ankle reflexes (0–4 pts) | — | — | — | 11 | 1 | 4 | — | — | — | 8 | 0 | 4 | 5 | 0 | 9 | 1 | 0 | 3 | — | — | — | 1 | 5 | 1 | 15 | 0 | 1 | 5 | 3 | 0 | 5 | 2 | — |
| Great toe vibration (0–4 pts) | 11 | 1 | 4 | — | — | — | — | — | — | 14 | 14 | 4 | 18 | 22 | 9 | 4 | 5 | 2 | — | — | — | 1 | 14 | 0 | 14 | 10 | 0 | 12 | 17 | 1 | 7 | 21 | — |
| NIS(LL) (pts) | — | — | — | — | — | — | — | — | — | 15 | 24 | 16 | 18 | 34 | 33 | 3 | 7 | 10 | — | — | — | 2 | 12 | 2 | 30 | 14 | 0 | 14 | 19 | 1 | 16 | 23 | — |
| NSC(LL) severity (pts) | 8 | 0 | 4 | 14 | 14 | 4 | 15 | 24 | 16 | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 5 | 4 | 11 | 4 | 0 | 3 | 7 | 2 | 8 | 10 | — |
| Σ DCCT criteria (0–12 pts) | — | — | — | — | — | — | — | — | — | 19 | 31 | 31 | 11 | 13 | 21 | — | — | — | — | — | — | 3 | 18 | 1 | 27 | 10 | 0 | 8 | 20 | 1 | 16 | 22 | — |
| Peroneal motor CV nd | 1 | 5 | 1 | 1 | 14 | 0 | 2 | 12 | 2 | 1 | 5 | 4 | 5 | 7 | 4 | 0 | 2 | 4 | 3 | 18 | 1 | — | — | — | 9 | 5 | 2 | — | — | — | 6 | 22 | — |
| Tibial motor DL nd | 0 | 0 | 0 | 4 | 1 | 4 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 3 | 4 | 1 | 4 | 2 | 4 | — | — | — | 1 | 2 | — |
| Sural SNAP nd | 15 | 0 | 1 | 14 | 10 | 0 | 30 | 14 | 0 | 11 | 4 | 0 | 18 | 6 | 0 | 3 | 1 | 0 | 27 | 10 | 0 | 9 | 5 | 2 | — | — | — | — | — | — | 21 | 8 | — |
| Σ 5 NC tests nd | 5 | 3 | 0 | 12 | 17 | 1 | 14 | 19 | 1 | 3 | 7 | 2 | 8 | 10 | 3 | 0 | 2 | 2 | 8 | 20 | 1 | — | — | — | — | — | — | — | — | — | 11 | 24 | — |
| VDT (CASE IV) nd | 10 | 2 | 0 | 16 | 26 | 1 | 33 | 24 | 1 | 14 | 11 | 6 | 24 | 21 | 5 | 3 | 2 | 5 | 29 | 27 | 2 | 15 | 23 | 4 | 30 | 10 | 8 | 19 | 27 | 7 | — | — | — |
| Σ 3 QST nd | 5 | 2 | — | 7 | 21 | — | 16 | 23 | — | 8 | 10 | — | 15 | 25 | — | 3 | 1 | — | 16 | 22 | — | 6 | 22 | — | 21 | 8 | — | 11 | 24 | — | — | — | — |
| HRDB nd | 3 | 0 | 3 | 9 | 10 | 1 | 11 | 6 | 2 | 6 | 1 | 2 | 2 | 3 | 4 | 4 | 0 | 1 | 14 | 8 | 3 | 4 | 5 | 1 | 6 | 2 | 1 | 8 | 8 | 2 | 12 | 11 | — |
| NSC(LL) negative symptom severity (pts) | 5 | 0 | 9 | 18 | 22 | 9 | 18 | 34 | 33 | — | — | — | — | — | — | 11 | 17 | 27 | 19 | 31 | 31 | 5 | 7 | 4 | 18 | 6 | 0 | 8 | 10 | 3 | 15 | 25 | — |
| NSC(LL) positive symptom severity (pts) | 1 | 0 | 3 | 4 | 5 | 2 | 3 | 7 | 10 | — | — | — | 11 | 17 | 27 | — | — | — | 11 | 13 | 21 | 0 | 2 | 4 | 3 | 1 | 0 | 0 | 2 | 2 | 3 | 1 | — |
| Mean | 6 | 1 | 3 | 10 | 13 | 3 | 14 | 17 | 7 | 8 | 8 | 4 | 12 | 15 | 11 | 4 | 4 | 7 | 14 | 17 | 8 | 4 | 10 | 2 | 16 | 6 | 1 | 9 | 14 | 2 | 10 | 14 | — |

—, Test not available or not appropriate for comparison. Abbreviations are given in Table 1. The complete table with columns of percent correlation for tibial motor DL, VDT, and HRDB can be obtained on written request.

*Design of multicenter trials*

**Table 4—Median regression slopes ($\bar{b}$) of various neuropathic end points over time in the Rochester, Viatris, and Lilly cohorts using different criteria for the diagnosis of polyneuropathy**

| Cohort | Rochester $\bar{b}$ per 4 years | P* | Viatris $\bar{b}$ per 4 years | P | Lilly $\bar{b}$ per year | P |
|---|---|---|---|---|---|---|
| Entry criteria | NIS(LL) ≥2 points | | | | | |
| Number of patients (mode) | 83 | | 191 | | 234 | |
| Ankle reflexes† (0–4 pts) | −0.35 | 0.02 | −0.27 | <0.01 | 0.24 | 0.73 |
| Great toe vibration† (0–4 pts) | 0.40 | <0.01 | 0.12 | 0.30 | −0.25 | <0.01 |
| NIS(LL)† (pts) | 0.82 | 0.99 | 0.16 | 0.81 | 0.35 | 0.02 |
| NSC(LL) severity† (pts) | −0.13 | 0.29 | −0.52 | 0.23 | −3.27 | <0.01 |
| Σ DCCT criteria† (0–12 pts) | −0.21 | 0.21 | −0.27 | 0.10 | −0.38 | <0.01 |
| Peroneal motor CV nd | 0.08 | 0.33 | −0.00 | 0.54 | 0.05 | 0.05 |
| Tibial motor DL nd | −0.11 | 0.27 | −0.10 | 0.09 | −0.04 | 0.10 |
| Sural SNAP nd | 0.23 | <0.01 | +0.00 | 0.05 | 0.14 | <0.01 |
| Σ 5 NC tests nd | −0.20 | 0.44 | −0.21 | 0.05 | 0.29 | 0.05 |
| VDT (CASE IV) nd | 0.53 | 0.02 | +0.00 | 0.34 | −0.40 | <0.01 |
| Σ 3 QST nd | 2.48 | <0.01 | −0.28 | 0.02 | | |
| HRDB nd | +0.00 | 0.67 | 0.05 | 0.55 | 0.10 | 0.13 |
| Entry criteria | Σ 5 NC tests nd ≥95th | | | | | |
| Number of patients (mode) | 108 | | 191 | | 130 | |
| Ankle reflexes† (0–4 pts) | −0.10 | 0.28 | −0.27 | <0.01 | −1.22 | 0.07 |
| Great toe vibration† (0–4 pts) | 0.38 | <0.01 | 0.12 | 0.30 | −0.08 | 0.42 |
| NIS(LL)† (pts) | 1.04 | 0.03 | 0.16 | 0.81 | −1.42 | 0.07 |
| NSC(LL) severity† (pts) | 0.05 | 0.78 | −0.52 | 0.23 | −2.38 | <0.01 |
| Σ DCCT criteria† (0–12 pts) | 0.17 | 0.28 | −0.27 | 0.10 | −1.73 | <0.01 |
| Peroneal motor CV nd | 0.14 | 0.83 | −0.00 | 0.54 | +0.00 | 0.82 |
| Tibial motor DL nd | −0.38 | <0.01 | −0.10 | 0.09 | −0.07 | 0.05 |
| Sural SNAP nd | 0.11 | 0.03 | +0.00 | 0.05 | 0.11 | 0.03 |
| Σ 5 NC tests nd | −0.52 | 0.08 | −0.21 | 0.05 | −0.37 | 0.26 |
| VDT (CASE IV) nd | 0.38 | 0.01 | +0.00 | 0.34 | −0.52 | <0.01 |
| Σ 3 QST nd | 2.10 | <0.01 | −0.28 | 0.02 | | |
| HRDB nd | +0.00 | 0.66 | 0.05 | 0.55 | 0.04 | 0.50 |
| Entry criteria | DCCT ≥2 of 3 criteria | | | | | |
| Number of patients (mode) | 30 | | 187 | | 222 | |
| Ankle reflexes† (0–4 pts) | −0.11 | 0.97 | −0.28 | <0.01 | 0.26 | 0.73 |
| Great toe vibration† (0–4 pts) | −0.07 | 0.90 | 0.10 | 0.37 | −0.27 | <0.01 |
| NIS(LL)† (pts) | 0.90 | 0.48 | 0.04 | 0.89 | 0.63 | 0.04 |
| NSC(LL) severity† (pts) | −0.28 | 0.15 | −0.55 | 0.21 | −3.35 | <0.01 |
| Σ DCCT criteria† (0–12 pts) | −0.54 | 0.21 | −0.31 | 0.07 | −0.39 | <0.01 |
| Peroneal motor CV nd | 0.94 | 0.56 | −0.00 | 0.51 | 0.05 | 0.05 |
| Tibial motor DL nd | −0.09 | 0.59 | −0.09 | 0.12 | −0.05 | 0.05 |
| Sural SNAP nd | 0.10 | 0.34 | +0.00 | 0.05 | 0.12 | <0.01 |
| Σ 5 NC tests nd | 0.05 | 0.57 | −0.16 | 0.07 | 0.28 | 0.09 |
| VDT (CASE IV) nd | 0.52 | 0.12 | +0.00 | 0.36 | −0.38 | <0.01 |
| Σ 3 QST nd | 2.14 | 0.01 | −0.28 | 0.02 | | |
| HRDB nd | −0.00 | 0.98 | 0.05 | 0.50 | 0.08 | 0.14 |

Abbreviations are given in Table 1. For all the cohorts studied, the patients who were included in analysis had DSPN by the entry criteria shown and were evaluated at baseline and on at least one additional evaluation. Patients who terminated studies early (dropouts) are not significantly different from ones who did not by the criteria of glycemic control (type of diabetes, A1C, or creatinine) or severity of neuropathy [NIS(LL), NSC(LL) severity, or Σ 5 NC tests nd]. *P = Wilcoxon's signed rank test to determine whether the median slope differs from 0. †The mean slope is reported for this variable.

(e.g., in immune neuropathies [32,33]), are not as able to do so in DSPN with low rates of worsening.

Finally, we note that restricting entry into study by use of a percentile abnormality of an end point and then using the same end point to measure change may result in a spurious estimate of improvement. Therefore, it is advisable to either incorporate a run-in phase and subsequent baseline measurements for analyses or use different criteria for entry into study than used for purposes of follow-up.

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