Natural Progression of Diabetic Peripheral Neuropathy in the Zenarestat Study Population

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OBJECTIVE — The aim of this study was to report the baseline and natural progression of diabetic peripheral neuropathy over 12 months in a large mild-to-moderate neuropathy population.

RESEARCH DESIGN AND METHODS — Patients from a multicentered trial of zenarestat, an aldose reductase inhibitor, had serial measures of neurologic function, including nerve conduction studies (NCSs), quantitative sensory testing (QST), and clinical neuropathy rating scores at baseline and at 12 months. Baseline population descriptors and changes in neurologic function in placebo-treated patients were analyzed.

RESULTS — Sural sensory velocity ($P = 0.0008$ [95% CI −1.04 to −0.27]), median sensory amplitude ($P = 0.0021$ [−1.3 to −0.29]), median distal motor latency ($P = 0.002$ [0.09–0.28]), cool thermal QST ($P = 0.0005$ [0.27–0.94]), and Michigan Neuropathy Screening Instrument results ($P = 0.0087$ [0.04–0.30]) declined significantly from baseline in the placebo population. NCS changes from baseline were independent of baseline HbA_{1c} stratification.

CONCLUSIONS — The neurologic decline over 12 months is evident when measured by NCS and cool thermal QST. Other measures (vibration QST, neuropathy rating scores, monofilament examination) are insensitive to changes over 12 months in a mild-to-moderate affected population of this size.

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Diabetic peripheral neuropathy (DPN) is a debilitating condition affecting as many as one-half of all patients with diabetes during the course of their disease (1). The progressive, irreversible course of the disease ultimately leads to an increased incidence of ulceration and limb amputations (2).

Currently, therapy is limited to intensive glycemic control and symptomatic treatments. It is critical to identify the appropriate study population within the broad continuum of the disease when evaluating potential therapies. For example, pancreatic islet transplantation work suggests that severe neuropathy is not amenable to therapy (3,4). Defining a mild-to-moderate, perhaps more responsive, DPN population may be helpful in identifying new therapeutic modalities (5).

Objective, yet clinically meaningful, data characterizing the natural progression of mild-to-moderate DPN are also lacking. One issue is the uncertain rate of disease progression (6,7). Another is lack of agreement regarding the clinical relevance of the available scientifically rigorous measures of DPN. The San Antonio neuropathy consensus called for study designs requiring multiple, often expensive electrophysiologic, sensory, and clinical tools to document disease progression and response to therapy (8,9). Only a fraction of these tools translate directly to patient outcomes. None are widely used in clinical practice or are accessible to primary care practitioners.

Increased nerve sorbitol and fructose associated with hyperglycemia remain a hypothesized causal mechanism of DPN. Inhibition of aldose reductase, the enzyme responsible for converting glucose to sorbitol, demonstrates reduced nerve degeneration and improved nerve conduction in animal models and humans (10). Previous aldose reductase inhibitors (ARIs) have been plagued with problems, including occasional marginal efficacy, lack of tissue permeability, and a variety of toxicities lacking a common causal mechanism.

Zenarestat, a highly potent ARI, was evaluated in a large phase 3 trial of mild distal symmetrical DPN, using guidelines provided by the consensus panels (8,9,11). This study was one of the largest long-term, placebo-controlled clinical trials investigating DPN. A significant increase in serum creatinine observed in some zenarestat-treated patients resulted in early termination of the pivotal study and discontinuation of clinical development of zenarestat.

Despite early termination, sufficient data are available to report baseline electrophysiologic, sensory, and neuropathy scores in this large cohort of clinically defined patients with mild-to-moderate DPN. These multiple measures were re-

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Abbreviations: ARI, aldose reductase inhibitor; CRCC, Central Reading and Coordinating Center; DPN, diabetic peripheral neuropathy; MDNS, Michigan Diabetes Neuropathy Score; MNSI, Michigan Neuropathy Screening Instrument; NCS, nerve conduction study; PNSS, Penn Neuropathy Symptom Scale; QST, quantitative sensory testing.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1 —*Summary of baseline demographic characteristics of patients with mild-to-moderate DPN*

Patient characteristic	Placebo	Zenarestat 600 mg/day	Zenarestat 1,200 mg/day
n	472	481	475
Men	276 (58.5)	293 (60.9)	303 (63.8)
White	386 (81.8)	395 (82.1)	404 (85.1)
Hispanic	30 (6.4)	33 (6.9)	29 (6.1)
Black	37 (7.8)	29 (6)	25 (5.3)
Age (years)	51.9 ± 10.3	52.9 ± 9.8	52.5 ± 9.7
Type 2 diabetes	376 (79.7)	399 (83)	386 (81.3)
Duration of diabetes (years)	10.5 ± 9.4 (0.4–52.6)	10.4 ± 10.1 (0.4–60.8)	10.3 ± 9.3 (0.4–49)
Alcohol use (no. drinks/week)	1.1 ± 2.7 (0–21)	1.3 ± 3.2 (0–24)	1.4 ± 3.6 (0–42)
HbA_{1c} (%)	7.7 ± 1.5 (4.8–11.7)	7.8 ± 1.7 (4–12)	7.8 ± 1.5 (4–12.4)
≤8%	275 (62)	284 (62)	284 (62)
	6.7 ± 0.7	6.8 ± 0.8	6.9 ± 0.8
>8%	170 (38)	176 (38)	173 (38)
	9.3 ± 0.9	9.6 ± 0.8	9.5 ± 1.1
Nerve conduction velocity (m/s)*			
n	471	481	475
Median forearm sensory	55.8 ± 4.5 (38.7–75)	55.8 ± 4.2 (42.3–69)	55.9 ± 4.1 (40.6–67)
Peroneal motor	40.2 ± 4.7 (20–56)	40.3 ± 4.5 (16.7–51.3)	40.1 ± 4.8 (18.3–54.7)
Sural sensory†	41.6 ± 5 (21–56)	41.6 ± 5 (29.7–58.3)	41.2 ± 5.2 (23–59)
Amplitude (mV)			
Median sensory	471	481	475
	22.7 ± 12.4 (3.1–71)	22.8 ± 11.8 (4.4–78.2)	22.5 ± 11.5 (2.4–66.1)
Sural sensory	470	481	475
	7.4 ± 4 (−6.9 to 22.5)	7.5 ± 4.2 (1.3–30)	7.5 ± 4 (1.5–26.2)
F-wave latency (m/s)			
Median motor	470	481	473
	29.1 ± 2.5 (22.9–36.5)	29.1 ± 2.5 (21.6–35.3)	29 ± 2.5 (21.9–35.4)
Peroneal motor	402	404	416
	54.6 ± 6.3 (39.4–76.9)	55.1 ± 6.3 (38.6–77.8)	55.1 ± 6.5 (38.8–81.8)
QST ("just noticeable difference")*‡			
n	471	481	475
Cool thermal	14.2 ± 4.5 (4.7–25)	13.9 ± 4.7 (4.7–25)	14.2 ± 4.3 (5.9–25)
Vibratory	19.3 ± 3.2 (7–25)	19.7 ± 3.1 (10.3–25)	19.5 ± 12.9 (7.8–25)
Neuropathy scores/examination			
MDNS (part 1) (0–30 points)	454	470	465
	7.5 ± 4.9 (0–30)	8.1 ± 5.2 (0–28)	7.6 ± 5 (0–28)
Monofilament examination 10 g (0–4 points)	453	469	464
	1.1 ± 1.3 (0–4)	1.1 ± 1.4 (0–4)	1.1 ± 1.3 (0–4)
MNSI (part B) (0–6 points)	469	479	472
	2.6 ± 1.6 (0–6)	2.7 ± 1.6 (0–6)	2.7 ± 1.6 (0–6)
PNSS (part 2,3) (0–14 points)	441	448	442
	3 ± 2.2 (0–14)	3.4 ± 2.1 (0–10)	3.1 ± 2.1 (0–12)

Data are *n* (%), means ± SD, or means ± SD (range). *No response values had a value imputed. See text for details. †Sural sensory nerve conduction was mandatory as entrance criteria. ‡Using Computer-Assisted Sensory Examination-IV.

peated at 12 months, demonstrating the natural progression of placebo patients with mild-to-moderate DPN.

RESEARCH DESIGN AND METHODS

— After signing informed consent, patients were screened by a trained nurse practitioner or physician using physical examination, medical history, and the Penn Neuropathy Symptom Scale (PNSS) to determine whether clinically mild-to-moderate neuropathy was present (12). Patients screened were men or women 18–70 years of age with clinically stable type 1 or type 2 diabetes for at least 6 months, HbA_{1c} <12%, and stable/optimized antidiabetic therapy for at least 3 months. Patients with other neurologic disorders, relevant other diseases, significant laboratory abnormalities, and women who were pregnant, lactating, or of childbearing potential were excluded. This study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee or institutional review board at all 40 study sites.

After the initial screening examination, the presence of mild distal symmetrical DPN was confirmed by a

comprehensive neurologic examination (including nerve conduction studies [NCSs] and quantitative sensory testing [QST]) administered by a board-certified neurologist. NCS and QST data and waveforms were reviewed at the Central Reading and Coordinating Center (CRCC) (University of Pennsylvania, Philadelphia, PA). At least one abnormal NCS or QST measurement was required for enrollment into the study (13). Abnormal NCS was defined as 2.5 SD below the mean for age (velocity, amplitude, and latency), height (velocity and latency), or body surface area (amplitude). Abnormal QST was defined as vibratory and/or cool thermal perception threshold 1.5 SD above the mean for age. Bilateral recordable and CRCC-confirmed sural sensory responses and left median distal motor latency of <4.6 ms (to exclude moderate-to-severe carpal tunnel syndrome) also were required for eligibility.

Patients considered eligible were stratified by baseline HbA_{1c} (≤8 or >8%) and randomized to one of three zenarestat treatment groups (placebo, 600 mg/day, or 1,200 mg/day). The adjustment of antidiabetes medications to achieve American Diabetes Association guidelines was allowed during the study.

The CRCC trained and certified all individuals who performed NCS and QST testing. This included evaluations of the technical quality of normal tracings from each tester. Sites had to pass a CRCC certification process before screening patients. NCS tests were performed or supervised by a certified electromyographer. All NCS and QST data were approved by the CRCC before inclusion into the study database. Technically unsatisfactory studies were repeated.

NCSs were repeated in triplicate on separate days at baseline, month 12, and month 24 using a two-channel Nicolet Viking Quest electromyogram machine (Nicolet Biomedical, Madison, WI). Velocity (median forearm and sural sensory, peroneal motor), F-wave latency (median and peroneal motor), and amplitude (median and sural sensory) were assessed in three left-sided nerves: sural, peroneal, and median. Near-nerve skin temperature was maintained at ≥32°C for the arm and ≥30°C for the leg.

Quantitative sensory threshold testing was conducted in triplicate at baseline, month 12, and month 24 using the Computer-Assisted Sensory Examination IV system (WR Medical Electronics, Stillwater, MN). Both vibration (great toe) and cool thermal (dorsal foot) thresholds on the left were assessed under controlled temperature conditions.

Table 2 —*Summary of electrophysiologic changes from baseline at 12 months in placebo patients*

Measure	Baseline	Change from baseline	*P* (95% CI)*
Nerve conduction velocity (ms)†			
Median forearm sensory	471	360	
	55.8 ± 4.5	−0.05 ± 3.4	0.7703 (−0.04 to 0.03)
HbA_{1c} ≤8%	275	216	
	56.7 ± 4.4	−0.13 ± 3.3	0.5582 (−0.57 to 0.31)
HbA_{1c} >8%, *n*	170	122	
	54.5 ± 4.4	−0.06 ± 3.7	0.8553 (−0.73 to 0.6)
Peroneal motor	471	359	
	40.2 ± 4.7	−0.2 ± 2.2	0.0717 (−0.44 to 0.02)
HbA_{1c} ≤8%	275	216	
	40.8 ± 4.7	−0.2 ± 2.2	0.1992 (−0.49 to 0.10)
HbA_{1c} >8%	170	121	
	39.2 ± 4.6	−0.21 ± 2.1	0.2837 (−0.59 to 0.18)
Sural sensory	471	357	
	41.6 ± 5	−0.65 ± 3.7	0.0008 (−1.04 to −0.27)
HbA_{1c} ≤8%	275	216	
	42.3 ± 5	−0.61 ± 3.7	0.0016 (−1.11 to −0.11)
HbA_{1c} >8%	170	119	
	40.6 ± 4.8	−0.68 ± 3.4	0.0324 (−1.3 to −0.06)
Amplitude (μV)			
Median sensory	471	359	
	22.7 ± 12.4	−0.80 ± 4.86	0.0021 (−1.3 to −0.29)
HbA_{1c} ≤8%	275	216	
	23.1 ± 12.2	−0.59 ± 5.21	0.0983 (−1.29 to 0.11)
HbA_{1c} >8%	170	121	
	22 ± 12.8	−1.03 ± 4.42	0.0116 (−1.82 to −0.23)
Sural sensory	470	355	
	7.4 ± 4	−0.30 ± 3.11	0.0686 (−0.63 to 0.02)
HbA_{1c} ≤8%	275	214	
	7.4 ± 3.9	−0.16 ± 2.66	0.3904 (−0.52 to 0.20)
HbA_{1c} >8%	170	119	
	7.4 ± 4.3	−0.44 ± 3.86	0.2194 (−1.14 to 0.26)
F-wave latency (ms)			
Median motor	470	355	
	29.1 ± 2.5	0.18 ± 0.92	0.002 (0.09 to 0.28)
HbA_{1c} ≤8%	274	214	
	28.9 ± 2.5	0.18 ± 0.89	0.0041 (0.06 to 0.3)
HbA_{1c} >8%	170	119	
	29.4 ± 4.5	0.15 ± 0.97	0.0887 (−0.02 to 0.33)
Peroneal motor	402	276	
	54.6 ± 6.3	0.30 ± 3.08	0.1113 (−0.07 to 0.66)
HbA_{1c} ≤8%	239	170	
	54.1 ± 6.2	0.48 ± 3.28	0.0588 (−0.02 to 0.97)
HbA_{1c} >8%	143	92	
	55 ± 63	0.15 ± 2.14	0.6133 (−0.44 to 0.74)

Data are means ± SD. *None of the change from baseline comparisons between HbA_{1c} strata are statistically different at $P < 0.05$. †No response values had a value imputed. See text for details.

Three neuropathy rating systems, scoring signs, and symptoms were administered. The Michigan Neuropathy Screening Instrument (MNSI) part b was used at 3-month intervals by site person-

Table 3 —*Summary of quantitative sensory changes from baseline at 12 months in placebo patients

Measure	Baseline	Change from baseline	*P* (95% CI)†
Cool thermal	471	360	
	14.16 ± 4.52‡	0.60 ± 3.25	0.0005 (0.27 to 0.94)
HbA_{1c} ≤8%	275	217	
	14.0 ± 4.4	0.4 ± 3.4	0.0844 (−0.05 to 0.85)
HbA_{1c} >8%	170	121	
	14.4 ± 4.7	1 ± 3.1	0.0007 (0.42 to 1.54)
Vibratory	471	359	
	19.31 ± 3.21	0.07 ± 1.70	0.4692 (−0.11 to 0.24)
HbA_{1c} ≤8%	275	216	
	19.5 ± 3.1	−0.02 ± 1.6	0.8424 (−0.24 to 0.20)
HbA_{1c} >8%	170	121	
	19 ± 3.4	0.3 ± 1.8	0.1069 (−0.06 to 1.54)

Data are means ± SD. *No response values had a value imputed. See text for details. †None of the change from baseline comparisons between HbA_{1c} strata are statistically different at $P < 0.05$. ‡Baseline data are in "just noticeable difference" units.

nel (14). The Michigan Diabetes Neuropathy Score (MDNS) part 1 and the PNSS parts 2 and 3 were administered by a board-certified neurologist and site personnel, respectively, at baseline, 12, and 24 months (12,14). A board-certified neurologist performed the monofilament portion of the MDNS using a standardized 10-g filament. This was scored on a 0- to 2-point scale for each limb (total 4-point scale).

The 3-month safety assessments included a physical examination, standard laboratory tests, and query regarding adverse events. A central laboratory was used (Medical Research Laboratory, Highland Heights, KY). Serial chest X rays and electrocardiograms were performed.

Because of early termination of the study, data are presented from baseline and the 12-month assessment. All patients completing the 12-month assessment are included. Change from baseline in the placebo population was analyzed using a paired Student's *t* test within the treatment group and by HbA_{1c} stratification. Comparisons between the two HbA_{1c} strata were performed using two-sample Student's *t* tests. Analyses of the zenarestat-treated patients occurred in the same manner.

NCS or QST recordings considered technically nonevaluable by the CRCC were recorded as missing. Studies not performed were recorded as missing. Technically satisfactory tracings with undetectable responses were imputed as follows: nerve conduction velocity, the 1st percentile of the patient's data at baseline or 12 months for that nerve; sensory amplitude, 0 μV; F-wave latency, missing; and QST, 25 "just noticeable difference." Data presented include the imputed values.

RESULTS — The 2,020 patients identified from prescreening progressed to NCS/QST, from which 1,428 were randomized to one of three treatment groups. The majority were men and had type 2 diabetes. Baseline demographic, NCS, QST, and neuropathy scores are presented in Table 1. Of the 1,428 patients randomized, 472 were in the placebo population. Because of the early termination of the study, 64 placebo patients completed 24 months and 399 (85%) completed 12 months of therapy.

Sixty-two percent of placebo patients were in the baseline HbA_{1c} ≤8% strata. The mean ± SD HbA_{1c} (6.7 ± 0.7%) was statistically different from the >8% strata (9.3 ± 0.9; $P = 0.0001$). Mean ± SD HbA_{1c} at the end of 12 months was 7.2 ± 1.2% and 8.7 ± 1.5% in the two respective strata and continued to be statistically significantly different ($P = 0.0001$).

Table 2 delineates the change from baseline NCS parameters in the placebo patients over 12 months. Very few patients had values below detection requiring imputed values. Sural sensory amplitude and sural sensory nerve conduction values were the most common values below detection, occurring in 20 of 355 and 20 of 357 patients, respectively. In general, nerve conduction declined in all nerves tested, with the decline in sural sensory conduction velocity achieving statistical significance. Decline in NCSs was not statistically different between the two HbA_{1c} strata.

The change from baseline in QST parameters showed slight worsening from baseline in both vibration and cooling thresholds; however, the decline in cool thermal sensation showed the only statistically significant decline (Table 3). QST worsening was not statistically different between the two HbA_{1c} strata.

MNSI was the only neuropathy rating system showing a statistically significant worsening from baseline, a decrease of 0.17 points ($P = 0.0087$ [95% CI −0.04 to 0.30]). This was not considered clinically significant. MDNS declined by a mean of −0.29 points, PNSS increased by 0.05 points, and the monofilament examination declined by −0.16 points, all not statistically significant.

Similar to the placebo group, 62% of 600 mg/day patients and 62% of 1,200 mg/day patients in the zenarestat treatment groups were in the HbA_{1c} ≤8% strata. In the 600 mg/day group at baseline, the mean ± SD HbA_{1c} in the ≤8% strata (6.8 ± 0.8%) was statistically significant from the >8% strata (9.6 ± 0.8%; $P = 0.0001$). At the end of 12 months, mean ± SD HbA_{1c} was 7 ± 1.2% and 8.9 ± 1.6% in the two respective strata ($P = 0.0001$). Baseline mean ± SD in the 1,200 mg/day group was 6.9 ± 0.8% in the ≤8% strata and 9.5 ± 1.1% in the >8% strata. After 12 months, HbA_{1c} mean ± SD values were 7 ± 1.2% and 8.8 ± 1.5%, respectively ($P = 0.0001$).

There was an improvement or lack of progression from baseline in all NCS measures in both zenarestat treatment groups at 12 months (Table 4). The baseline HbA_{1c} had little effect on the NCS change from baseline with the exception of median motor F-wave in the 600 mg/day group (HbA_{1c} ≤8%, mean = 0.099; HbA_{1c} >8%, mean = −0.242; $P = 0.0014$). For both cooling and vibratory QST, the baseline HbA_{1c} stratification showed statistically significant differences in QST worsening from baseline in the 1,200 mg/day group only (cooling HbA_{1c} ≤8% = 0.20; HbA1c >8% = 0.98; $P = 0.0256$; vibration HbA_{1c} ≤8% = 0.13; HbA_{1c} >8% = 0.54; $P = 0.0420$).

CONCLUSIONS — Defining a study population of patients with mild-to-moderate DPN is essential for the efficient

Table 4 —*Summary of changes from baseline in the zenarestat-treated patients*

Measure	Placebo	Zenarestat 600 mg/day	Zenarestat 1,200 mg/day
n	472	481	475
Nerve conduction velocity (ms)*			
Median forearm sensory	360	371	324
	−0.05 ± 3.4	0.8 ± 2.9‡	0.8 ± 2.9‡
HbA_{1c} ≤8%	216	218	194
	−0.13 ± 3.3	0.62 ± 3	0.79 ± 2.9
HbA_{1c} >8%	122	139	115
	−0.06 ± 3.7	0.93 ± 2.7	1 ± 3
Peroneal motor	359	372	324
	−0.21 ± 2.2	0.72 ± 2.3‡	0.81 ± 2.1‡
HbA_{1c} ≤8%	216	219	194
	−0.20 ± 2.2	0.77 ± 2.4	0.71 ± 2
HbA_{1c} >8%	121	139	115
	−0.21 ± 2.1	0.66 ± 2.1	1.1 ± 2.1
Sural sensory†	357	371	324
	−0.7 ± 3.7‡	0.06 ± 4	−0.02 ± 4
HbA_{1c} ≤8%	216	218	194
	−0.61 ± 3.7	0.20 ± 3.9	0.29 ± 4.1
HbA_{1c} >8%	119	139	115
	−0.68 ± 3.4	−0.07 ± 4	0.54 ± 3.6
Amplitude (mV)			
Median sensory amplitude	359	371	324
	−0.8 ± 4.9‡	−0.38 ± 4.5	−0.2 ± 4
HbA_{1c} ≤8%	216	218	194
	−0.59 ± 5.2	−0.12 ± 4.4	−0.03 ± 4
HbA_{1c} >8%	119	139	115
	−1.03 ± 4.4	−0.82 ± 4.7	−0.57 ± 4
Sural sensory amplitude	355	371	323
	−0.3 ± 3.1	−0.44 ± 2.4‡	−0.59 ± 2.7‡
HbA_{1c} ≤8%	214	218	194
	−0.16 ± 2.7	−0.34 ± 2.4	−0.59 ± 2.7
HbA_{1c} >8%	119	139	114
	−0.44 ± 3.9	−0.53 ± 2.4	−0.40 ± 2.3
F-wave latency (ms)			
Median motor	355	370	320
	0.2 ± 0.9‡	−0.06 ± 1	0.02 ± 1
HbA_{1c} ≤8%	214	217§	193
	0.18 ± 0.9	0.10 ± 0.9	0.07 ± 1.0
HbA_{1c} >8%	119	139	114
	0.15 ± 1	−0.24 ± 1.0§	−0.06 ± 0.9
Peroneal motor	276	277	254
	0.3 ± 3.1	−0.13 ± 2.9	−0.34 ± 2.9
HbA_{1c} ≤8%	170	162	156
	0.48 ± 3.3	−0.08 ± 3.2	−0.25 ± 2.8
HbA_{1c} >8%	92	103	85
	0.15 ± 2.9	−0.16 ± 2.1	−0.37 ± 3
QST ("just noticeable difference")*‖			
Cool thermal	360	373	327
	0.6 ± 3.3‡	0.6 ± 3.2‡	0.5 ± 3‡
HbA_{1c} ≤8%	217	220	196
	0.40 ± 3.4	0.42 ± 3.2	0.20 ± 2.9§
HbA_{1c} >8%	121	139	116
	0.98 ± 3.1	0.99 ± 3.1	0.98 ± 3.2§
Vibration	359	374	326
	0.07 ± 1.7	0.2 ± 1.7	0.3 ± 1.7‡
HbA_{1c} ≤8%	216	221	196
	−0.02 ± 1.6	0.14 ± 1.7	0.13 ± 1.6§
HbA_{1c} >8%	121	139	115
	0.27 ± 1.8	0.22 ± 1.6	0.54 ± 1.9§

Data are means ± SD. *No response values had a value imputed. See text for details. †Sural sensory nerve conduction was mandatory as entrance criteria. ‡Statistically significant change from baseline at $P < 0.05$. §Statistically significant change from baseline between HbA_{1c} strata at $P < 0.05$. ‖QST using Computer-Assisted Sensory Examination-IV.

evaluation of DPN therapies. The mild-to-moderate neuropathy population in this study was predominately type 2 diabetic patients with an average HbA_{1c} of 7.8%, mildly decreased nerve conduction velocities, prolonged F-wave latencies, and reduced sensory amplitudes. QST showed loss of large and small fiber-type sensation. Our study population is similar to that of an earlier report that presented results as medians versus our means (15). This is likely to be the patient population most responsive to interventional pharmacotherapy. Any distinguishing features that further characterize subpopulations, which progress more rapidly, or respond more readily to pharmacologic intervention, may have practical importance. Additional efforts are also underway to define a population most responsive to therapy using genetic markers (16).

Determining best methods for measuring neuropathy progression is essential to designing appropriate, cost-effective clinical trials. Currently suggested testing methods from the San Antonio conference are not only labor intensive but extremely costly. The suggested length of said trials (up to 5 years) is expensive and time prohibitive.

The placebo population exhibited a decrease in sensory and motor nerve conduction parameters over 12 months. Too few patients completed 24 months of study to provide reliable conclusions due to the early termination of the study. The only change in sural sensory conduction velocity was statistically significant.

Placebo patients also showed worsening over 12 months as measured by cool thermal threshold. Vibration perception over this period was not statistically different. These findings are consistent with the natural history of DPN, in which small fiber symptoms (measured by cooling) appear before large fiber symptoms (measured by vibration) (17).

Baseline stratification by HbA_{1c} did not appear to significantly affect the disease progression as measured by NCSs or QST, which was surprising. Perhaps this finding is due to exclusion of patients with an HbA_{1c} ≥12% at baseline, improved standards of care with respect to glycemic control in the post-U.K. Prospective Diabetes Study/Diabetes Control and Complications Trial environment, or the small size of the evaluable population with a baseline HbA_{1c} >8% (18). Investigators were encouraged to meet Ameri-

can Diabetes Association HbA_{1c} goals while patients were in the study, and although the strata remained statistically distinct for all of the treatment groups, the difference between strata decreased at the 12-month assessment.

Inability to detect statistically significant changes from baseline was unlikely due to intersite variability. Meticulous attention to training, testing conditions, and use of a central reading center contributed to minimal intersite variability (data not shown) (19).

The neuropathy scores used in this trial had been validated previously for screening only. These methods would be preferable to electrodiagnostic or sensory testing in clinical studies due to the decreased cost and applicability to clinical practice. Only the MNSI showed a statistically significant change in the placebo population over 12 months, but this change is not likely to be clinically meaningful. Whether these tests would show differences over longer study periods is unknown.

The monofilament examination results declined over 12 months but to an extent not clinically or statistically significant. This inability to show a difference was despite performance by trained, board-certified neurologists. The monofilament test results were consistent in defining a baseline population with mild neuropathy (20).

Although clinical development of zenarestat was discontinued because of increased creatinine concentrations in some patients, patients treated with zenarestat showed slowing of or improvement of neuropathy at 12 months as assessed by NCSs. Cool thermal testing showed statistically significant worsening in all populations, including the placebo group. The inability of QST testing to discern treatment differences may be due to the limited number of patients reassessed at 12 months. Power calculations suggest that as many as 450 patients per treatment arm are necessary to show a statistical difference at 24 months. Twelve months of testing may be insufficient to discern changes from baseline, particularly in the case of vibratory testing.

In general, a lack of baseline HbA_{1c} effect on NCS and QST change from baseline over 12 months was seen in both the placebo and treatment groups. Isolated cases of NCSs and QST did discern some limited treatment differences between the two baseline strata; however, none were consistent. This lack of difference in treatment effects between the glycemic strata was unexpected because those individuals with poor glycemic control would be expected to have the highest flux through the polyol pathway. This observation suggests that ARI agents may exert their therapeutic effects at least partially via nonpolyol pathway mechanisms.

After treatment, monofilament and neuropathy scores failed to show any consistent, meaningful change in nerve function. This lack of response may reflect a longer time necessary to show clinical improvement of DPN or the limited number of patients available for assessment after 12 months of ARI treatment.

These data are from the longest and largest trial using multiple methods to assess DPN and the effects of therapy. The results may be useful, in the post-U.K. Prospective Diabetes Study and Diabetes Control and Complications Trial era, for the design of trials aimed at ameliorating the continual progression of neuropathic disease and its complications (21).

NCS abnormalities are the most consistent over 12 months in this mild-to-moderate neuropathy population. Assessments of cool thermal thresholds are able to detect worsening over a 12-month time period in a population of this size. The remaining tests are less useful in showing a decline in nerve function at 12 months or the effects of treatment.

APPENDIX

Participants in the 24-month, double-blind, randomized, placebo-controlled, fixed-dose, parallel-group, multicenter study of zenarestat in the Treatment of Diabetic Neuropathy trial

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