RESEARCH REPORT

Safety and efficacy of ranirestat in patients with mild-to-moderate diabetic sensorimotor polyneuropathy

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Abstract We examined the efficacy and safety of ranirestat in patients with diabetic sensorimotor polyneuropathy (DSPN). Patients (18–75 years) with stable type 1/2 diabetes mellitus and DSPN were eligible for this global, double-blind, phase II/III study (ClinicalTrials.gov NCT00927914). Patients (n = 800) were randomized 1 : 1 : 1 to placebo, ranirestat 40 mg/day or 80 mg/day (265 : 264 : 271). Change in peroneal motor nerve conduction velocity (PMNCV) from baseline to 24 months was the primary endpoint with a goal improvement vs. placebo ≥1.2 m/s. Other endpoints included symptoms, quality-of-life, and safety. Six hundred thirty-three patients completed the study. The PMNCV difference from placebo was significant at 6, 12, and 18 months in both ranirestat groups, but <1.2 m/s. The mean improvement from baseline at 24 months was +0.49, +0.95, and +0.90 m/s for placebo, ranirestat 40 mg and 80 mg, respectively (NS). The treatment difference vs. placebo reached significance when ranirestat groups were combined in a *post hoc* analysis (+0.44 m/s; p = 0.0237). There was no effect of ranirestat on safety assessments, secondary or exploratory endpoints vs. placebo. Ranirestat was well tolerated and improved PMNCV, but did not achieve any efficacy endpoints. The absence of PMNCV worsening in the placebo group underscores the challenges of DSPN studies in patients with well-controlled diabetes.

Key words: aldose reductase, clinical trial, diabetic neuropathy, neuropathy progression

Introduction

Diabetic sensorimotor polyneuropathy (DSPN) is characterized by altered sensation and/or pain usually in the distal legs and feet and can lead to complications such as ulceration and subsequent amputation *(Bril and Buchanan, 2004; Van Acker et al., 2009; Stavniichuk et al., 2012)*. Pathophysiologically, peripheral nerves in patients with diabetes have a reduced ability to regenerate, undergo demyelination and axonal degeneration *(Greene et al., 1992; Polydefkis et al., 2004)*. Directly addressing these causes of complications, rather than treating the resulting symptoms, is an important unmet medical need.

The polyol pathway and the enzyme aldose reductase (AR) are implicated in the pathophysiology of DSPN and other complications of diabetes *(Oates,*

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2008; Ota et al., 2013). AR catalyzes the reduction of aldehyde molecules to sorbitol and then to fructose *(Oates, 2008; Ota et al., 2013)* which are thought to damage cells by mechanisms such as oxidative stress *(Oates, 2008)*. Inhibiting AR may, therefore, improve the oxidative stress profile in susceptible tissues, potentially treating or preventing progress of DSPN *(Oates, 2008; Ota et al., 2013)*.

Ranirestat (AS-3201), a potent, selective, and reversible inhibitor of the AR system, dose-dependently inhibits sorbitol production and improves nerve conduction velocity in animal and human studies of 12 *(Bril and Buchanan, 2004)* and 60 weeks *(Bril and Buchanan, 2006)*. A further clinical study involving patients with mild-to-moderate DSPN showed significant improvements in PMNCV with ranirestat 10–40 mg/day vs. placebo *(Bril et al., 2009)*.

In peripheral nerves, impaired motor nerve conduction velocity is one objective sign of damage and a strong predictor of ulceration in patients with diabetes *(Carrington et al., 2002)*. The US Food and Drug Administration has accepted peroneal motor nerve conduction velocity (PMNCV) as a primary criterion for assessing DSPN treatment, and a rate of decline of 0.6 m/s per year in diabetes has been accepted as standard *(Dyck and O'Brien, 1989; Diabetes Control Complications Trial (DCCT) Research Group, 1995; Partanen et al., 1995; Dyck et al., 1997)*. The current Phase II/III clinical study was powered upon such a rate of decline with the primary objective to determine the effect of ranirestat 40 and 80 mg on PMNCV relative to placebo over 2 years in patients with mild-to-moderate DSPN. Secondary objectives included ranirestat's effects on signs and symptoms of DSPN, safety, and tolerability.

Patients and Methods

Trial design

This double-blind, parallel-group study, randomized patients 1 : 1 : 1 to ranirestat 80 mg or 40 mg, or placebo. Patients were allocated via an interactive voice-response system, according to a pre-defined randomization schedule stratified by site. A 1-month pre-randomization period with two study visits was followed by a 2-year double-blind period with 10 study visits, with a single follow-up visit 1 month after finishing treatment. Outcome measures were assessed at baseline, 6, 12, 18, and 24 months. A change from baseline in PMNCV at month 24 was the primary outcome measure with a goal difference for each ranirestat group vs. placebo of 1.2 m/s or greater.

Patients, investigators, site personnel, and sponsor staff were blinded to treatment codes until database unlock. The study was conducted at 84 sites in Asia, Europe, North America, and Russia between July 20, 2009 and January 10, 2013 after approval by institutional review boards and independent ethics committees. The trial was registered at ClinicalTrials.gov (NCT00927914) and was conducted in accordance with relevant clinical practice guidelines – the Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the European GCP directive and Clinical Trial Directive, and US Code of Federal Regulations. Written, informed consent was obtained from all patients before screening, both for study participation.

Patients

Male and female patients (≥18 and ≤75 years) were eligible if they had a diagnosis of type 1 or type 2 diabetes for ≥12 months before screening (with optimized and stable glycemic control for ≥3 months) and a history of symptomatic distal symmetric polyneuropathy (secondary to diabetes) according to American Academy of Neurology criteria, which include abnormal PMNCV *(England et al., 2005)*.

Exclusion criteria included history of diabetic foot ulcers (Wagner Grade ≥1) or lower extremity amputation, diabetic amyotrophy, or non-diabetic cause of lower limb neuropathy; history of hypothyroidism or B_{12}/folate deficiency; significant cardiovascular or hepatic disease; history of hypoglycemia with loss of consciousness, diabetic ketoacidosis, or hyperglycemic coma in the 3 months before screening; prior participation in a ranirestat study or receipt of investigational medicinal product in the 3 months before screening; and clinically significant illness that would compromise patient safety or ability to assess efficacy.

Study completers were patients who finished the full treatment period, end of treatment visit, and follow-up visit. Patients who discontinued study drug prematurely were encouraged to return for the remaining scheduled visits ("retrieved dropouts").

Assessments and outcomes

An independent data safety monitoring board conducted interim assessments at regular intervals and a futility analysis when most patients had completed 1 year.

Efficacy

The primary efficacy outcome measure was change in mean PMNCV (m/s) from baseline to month 24 in patients taking ranirestat 80 or 40 mg vs. placebo. At each efficacy assessment (baseline, 6, 12, 18, and 24 months), PMNCV was measured bilaterally on two occasions (within a 21-day window), and the mean value was used. Secondary efficacy endpoints included the self-administered Neuropathy

Total Symptom Score-6 (NTSS-6-SA) *(Bastyr et al., 2005)* and the vibration perception threshold (VPT) measured as the mean of three recordings with a standardized and calibrated neurothesiometer (Bailey Instruments, Manchester, UK) on both great toes.

Safety

All adverse events (AEs) and serious AEs (SAEs) were monitored and recorded from the time of consent to final visit. SAEs were collected for 30 days after the last dose. Mood was assessed regularly using the Hospital Anxiety and Depression scale; a physical examination was performed at screening, months 6 and 12, and end of treatment; and vital signs were recorded at screening and all post-randomization visits. Hematology, biochemistry, HbA_{1c}, fasting lipids, urine albumin, and 12-lead electrocardiogram (ECG) were assessed frequently.

Analytical and statistical methods

Sample size calculations were based on the number of patients required to detect a baseline to month 24 PMNCV differences of 1.2 m/s between each dose and placebo. Previous studies with ranirestat indicated a within-group standard deviation (SD) of 3.0 m/s in PMNCV at week 52 *(Bril and Buchanan, 2006; Bril et al., 2009)*. To account for greater variability and allow for robust secondary analyses, a sample size of 750 patients (250 per group) was calculated to detect a clinically important difference of 1.2 m/s (with a common SD of 3.8 m/s), with approximately 90% power at the two-sided 2.5% significance level. This group size was anticipated to provide approximately 80% power to detect a clinically important difference in NTSS-6-SA, assuming an SD of 3.8 *(Bastyr et al., 2005)*, and to detect a difference of 1.31 V in VPT, assuming an SD of 5.2 V (data on file, Eisai Ltd.). Efficacy analyses used the Full Analysis Population. Changes from baseline were analyzed using an analysis of covariance (ANCOVA) model that included terms for treatment and country, and baseline PMNCV as a covariate. Last observation carried forward (LOCF) was used, inputting baseline values for patients without post-baseline data. Least squares means (LSMs) were derived and p-values calculated for ranirestat vs. placebo. Adjustments for multiplicity were made (Dunnett's procedure [*Dunnett, 1955; Dunnett, 1964*]), to maintain the overall alpha at 5% when comparing individual ranirestat doses with placebo.

The Safety Analysis Population included all patients who received at least one dose of study drug and had at least one post-dose safety assessment. Descriptive statistics were used to summarize frequency, severity, duration, and relationship to treatment of AEs that occurred after starting treatment.

The possible saturation of ranirestat effects was not envisaged in the original analysis plan, primarily because the placebo group was anticipated to progress over the 2-year observation period. Therefore, combining the two ranirestat groups was a *post hoc* analysis.

Results

Patient population, baseline data, and exposure

Of 2721 patients screened (Figure S1, Supporting Information), 1921 (71%) were screen failures (91% of whom failed inclusion/exclusion criteria). The remaining 800 were randomized: placebo, 265; ranirestat 40 mg, 264; ranirestat 80 mg, 271. Patients receiving at least one dose of study drug were included in the Full Analysis Population. Baseline data were similar across treatment groups (Table 1).

Overall, 633 patients (79%) completed the study, with similar rates of study discontinuation: placebo, 22%; ranirestat 40 mg, 22%; ranirestat 80 mg, 19%. Of the 800 patients originally randomized, 197 (25%) discontinued treatment before the month-24 assessment (30 continued with study visits as retrieved dropouts). The most common primary reason for discontinuing treatment was the occurrence of AEs (placebo, 5%; ranirestat 40 mg, 4%; and ranirestat 80 mg, 4%). Study discontinuation was the primary reason for missing PMNCV data at a specific visit, with similar percentage of subjects missing data across placebo and ranirestat groups at each time point; approximately 11%, 17%, 21%, and 22% subjects had missing PMNCV data at months 6, 12, 18 and 24, respectively.

Exposure to treatment was similar for patients receiving placebo, ranirestat 40 or 80 mg. Mean exposure durations were placebo, 21 months; ranirestat 40 mg, 21 months; and ranirestat 80 mg, 22 months.

Efficacy

Primary endpoint

Figure 1A shows change from baseline in PMNCV over time. There was a statistically significant treatment difference vs. placebo for both ranirestat 40 and 80 mg at 6, 12, and 18 months. At month 24, the mean (SD) changes from baseline PMNCV were placebo, +0.49 (2.55) m/s; ranirestat 40 mg, +0.95 (2.94) m/s; and ranirestat 80 mg, +0.90 (2.73) m/s. The LSM difference vs. placebo at month 24 was not statistically significant in the individual ranirestat 40 or 80 mg groups when adjusted for multiplicity ($p = 0.07$ and $p = 0.11$, respectively).

When the ranirestat treatment groups were combined in a *post hoc* analysis, there was, a

Table 1. Summary of baseline demographics and clinical characteristics: Safety Analysis Population*.

Characteristic	Placebo (n = 258)	Ranirestat 40 mg (n = 259)	Ranirestat 80 mg (n = 268)	Ranirestat Total (n = 527)	Combined total (n = 785)
Mean age, years (SD)†	58.2 (8.9)	57.3 (10.0)	57.3 (10.2)	57.3 (10.1)	57.6 (9.7)
Female sex, n (%)	84 (32.6)	95 (36.7)	98 (36.6)	193 (36.6)	277 (35.3)
Mean BMI, kg/m^2 (SD)	30.4 (5.0)	30.3 (4.9)	30.7 (5.1)	30.5 (5.0)	30.5 (5.0)
Mean HbA_{1c}, % (mmol/mol; SD)	7.8 (62; 1.7)	7.9 (63; 1. 7)	8.0 (64; 1.8)	8.0 (64; 1.8)	7.9 (63; 1.7)
Type 2 diabetes, n (%)	229 (88.8)	234 (90.3)	228 (85.1)	462 (87.7)	691 (88.0)
DM duration, years (SD)‡	12.4 (9.7)	11.5 (7.7)	13.7 (9.6)	12.6 (8.8)	12.6 (9.1)
DSPN duration, years (SD)	4.6 (4.2)	4.4 (3.9)	4.6 (4.6)	4.5 (4.3)	4.5 (4.2)
Any diabetic treatment, n (%)	249 (96.5)	255 (98.5)	264 (98.5)	519 (98.5)	768 (97.8)
Prior insulin	2 (0.8)	4 (1.5)	2 (0.7)	6 (1.1)	8 (1.0)
Concomitant insulin	142 (55.0)	144 (55.6)	170 (63.4)	314 (59.6)	456 (58.1)
Prior OHA	5 (1.9)	5 (1.9)	3 (1.1)	8 (1.5)	13 (1.7)
Concomitant OHA	192 (74.4)	196 (75.7)	188 (70.1)	384 (72.9)	576 (73.4)

BMI, body mass index; DM, diabetes mellitus; DSPN, diabetic sensorimotor polyneuropathy; OHA, oral hypoglycemic agent; SD, standard deviation.
*The Safety Analysis Population included all patients from the Full Analysis Population (n = 800) who had ≥1 safety assessment; as 15 patients were lost to follow-up between randomization and the month-1 visit, the Safety Analysis Population comprised 785 patients.
†Age at informed consent.
‡One patient was not included in the 80 mg group for this baseline measure, giving 267 patients in this group, 528 in the combined ranirestat groups, and 784 in total.

significant difference in PMNCV vs. placebo at month 24 (+0.44 m/s vs. placebo; p = 0.0237) although this did not meet the target of 1.2 m/s.

We assessed the effect of statin and angiotensin-converting enzyme (ACE) inhibitor use given evidence that these factors may influence DPN *(Malik et al., 1998; Ziegler et al., 2011; Davis et al., 2008; Vinik et al., 2008)*. Placebo-treated subjects who were taking a statin or ACE inhibitor had similar degrees of improvement in PMNCV over 24-months compared to those who were not (0.32 vs. 0.5 m/s) and (0.45 vs. 0.70 m/s), respectively.

Secondary endpoints

Baseline NTSS-6-SA scores were 9.4–9.6, and improvements from baseline were seen by month 6 and sustained through month 24 in all treatment groups. However, no statistically significant differences were observed with ranirestat vs. placebo at 24 months (Fig. 1B). At baseline, VPT was 17.1 V in the placebo group, 16.4 V in the ranirestat 40 mg group, and 16.8 V in the 80 mg group. There was a trend toward worsening VPT over time (i.e., increased perception threshold) in all three groups; however, there was no statistical difference for either ranirestat group vs. placebo at month 6, 12, 18, or 24 (Fig. 1C).

Secondary and exploratory measures including signs and symptoms of DSPN, sensory capacity, quality of life, pain, and various electrophysiological parameters did not show a trend toward treatment effect (Appendix S1 and Table S1).

Frequency of complications

Complications due to DSPN were minimal (placebo, 3%; ranirestat 40 mg, 4%; ranirestat 80 mg, 1%); the rates and time to event did not differ between treatment groups.

Safety

Adverse events

AE incidence was similar across treatment groups: 87% placebo and 84% ranirestat combined (Tables 2 and 3). The placebo and combined ranirestat groups both had 8% of patients with an AEs leading to discontinuation. The only AE that led to discontinuation in >2 patients in any treatment group was depression (five patients, ranirestat). Most AEs were of mild or moderate severity. SAEs occurring in ≥2 patients were coronary artery disease, angina pectoris, cataract, dyspnea, and gastroenteritis. Two deaths occurred in the placebo group and two each in the ranirestat 40 and 80 mg groups. One patient in the ranirestat 80 mg group died due to hypertensive heart disease considered possibly related to study drug; the other three deaths were considered to be related to underlying comorbidities.

Vital signs, ECG parameters, and mean laboratory values

There were no clinically important difference between placebo and ranirestat treated groups over the course of the study with respect to $HbA_{1c,}$ percentage of subjects with an HbA_{1c} change from baseline ≥1% at any point during the study, blood pressure (BP), or low-density lipoprotein (LDL) levels.

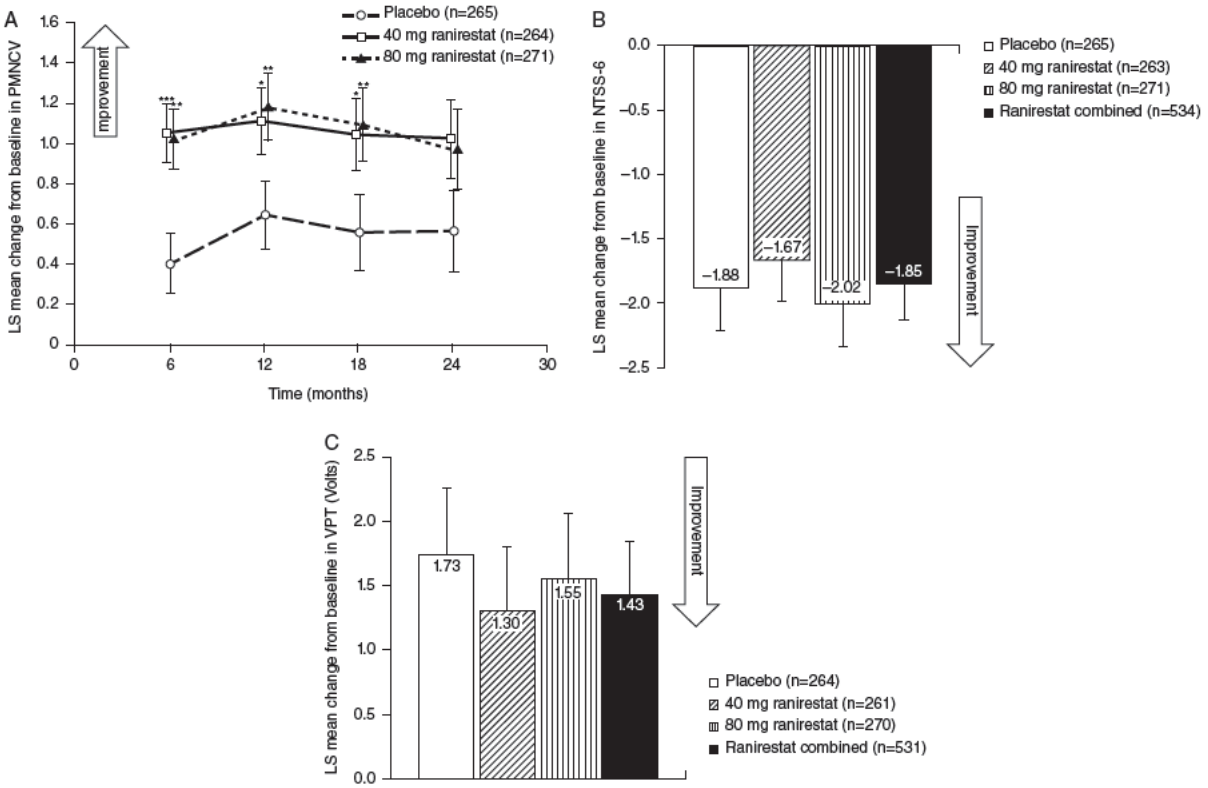

Figure 1. Change from baseline in efficacy measures: Full Analysis Population (last observation carried forward, LOCF). Least squares (LS) mean change (±standard error of the mean [SEM]): (A) in peroneal motor nerve conduction velocity (PMNCV) (m/s) over time (LOCF, Full Analysis Population), based on analysis of covariance (ANCOVA). p-values vs. placebo (not adjusted for multiplicity, except at 24 months), *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$. Error bars have been staggered for clarity; ○ = placebo (n = 265); □ = 40 mg ranirestat (n = 264); ▲ = 80 mg ranirestat (n = 271). When ranirestat groups were combined at month 24 in a *post hoc* analysis, there was a significant difference vs. placebo ($p = 0.0237$).(B) from baseline to month 24 in mean self-administered Neuropathy Total Symptom Score-6 (NTSS-6-SA); all treatment differences vs. placebo were non-significant; □placebo (n = 265); ▨40 mg ranirestat (n = 263); ▥80 mg ranirestat (n = 271); ■ranirestat combined (n = 534); (C) from baseline to month 24 in mean vibration perception threshold (VPT) (V); all treatment differences vs. placebo were non-significant; □placebo (n = 264); ▨40 mg ranirestat (n = 261); ▥80 mg ranirestat (n = 270); ■ranirestat combined (n = 531).

Table 2. Overview of treatment-emergent adverse events: Safety Analysis Population*.

Category, n (%)	Placebo (n = 258)	Ranirestat		
		40 mg (n = 259)	80 mg (n = 268)	Total (n = 527)
Any AEs	225 (87.2)	212 (81.9)	228 (85.1)	440 (83.5)
Treatment-related AEs	71 (27.5)	64 (24.7)	71 (26.5)	135 (25.6)
Severe AEs	34 (13.2)	46 (17.8)	43 (16.0)	89 (16.9)
AEs leading to discontinuation of study drug	21 (8.1)	24 (9.3)	17 (6.3)	41 (7.8)
AEs leading to study drug dose interruption	26 (10.1)	33 (12.7)	31 (11.6)	64 (12.1)
Serious AEs	62 (24.0)	49 (18.9)	52 (19.4)	101 (19.2)
Death	2 (0.8)	2 (0.8)	2 (0.7)	4 (0.8)

*Includes only adverse events (AEs) that were considered treatment-emergent, that is, started or increased in severity on or after the first dose of study drug, up to and including 30 days after the final dose of study drug.

A *post hoc* analysis of the association of change in BP and PMNCV was performed using baseline and month 24 data and revealed that increases in DBP were associated with improvements in PMNCV ($p < 0.001$) (Fig. 2).

Discussion

This phase II/III clinical study evaluated the efficacy and safety of ranirestat (40 and 80 mg) in patients with mild-to-moderate DSPN. There was a consistent

Table 3. Treatment-emergent adverse events in ≥5% in any treatment group: Safety Analysis Population*.

Category, n (%)	Placebo (n = 258)	Ranirestat		
		40 mg (n = 259)	80 mg (n = 268)	Total (n = 527)
Nasopharyngitis	20 (7.8)	22 (8.5)	21 (7.8)	43 (8.2)
Diarrhea	19 (7.4)	24 (9.3)	17 (6.3)	41 (7.8)
Pain in extremity	16 (6.2)	23 (8.9)	17 (6.3)	40 (7.6)
Arthralgia	16 (6.2)	18 (6.9)	19 (7.1)	37 (7.0)
Upper respiratory tract infection	16 (6.2)	13 (5.0)	23 (8.6)	36 (6.8)
Edema peripheral	20 (7.8)	17 (6.6)	18 (6.7)	35 (6.6)
Hypertension	12 (4.7)	18 (6.9)	16 (6.0)	34 (6.5)
Back pain	13 (5.0)	19 (7.3)	8 (3.0)	27 (5.1)
Musculoskeletal pain	10 (3.9)	14 (5.4)	10 (3.7)	24 (4.6)
Nausea	14 (5.4)	9 (3.5)	15 (5.6)	24 (4.6)
Headache	12 (4.7)	13 (5.0)	9 (3.4)	22 (4.2)

*Includes only adverse events that were considered treatment-emergent, that is, started or increased in severity on or after the first dose of study drug, up to and including 30 days after the final dose of study drug.

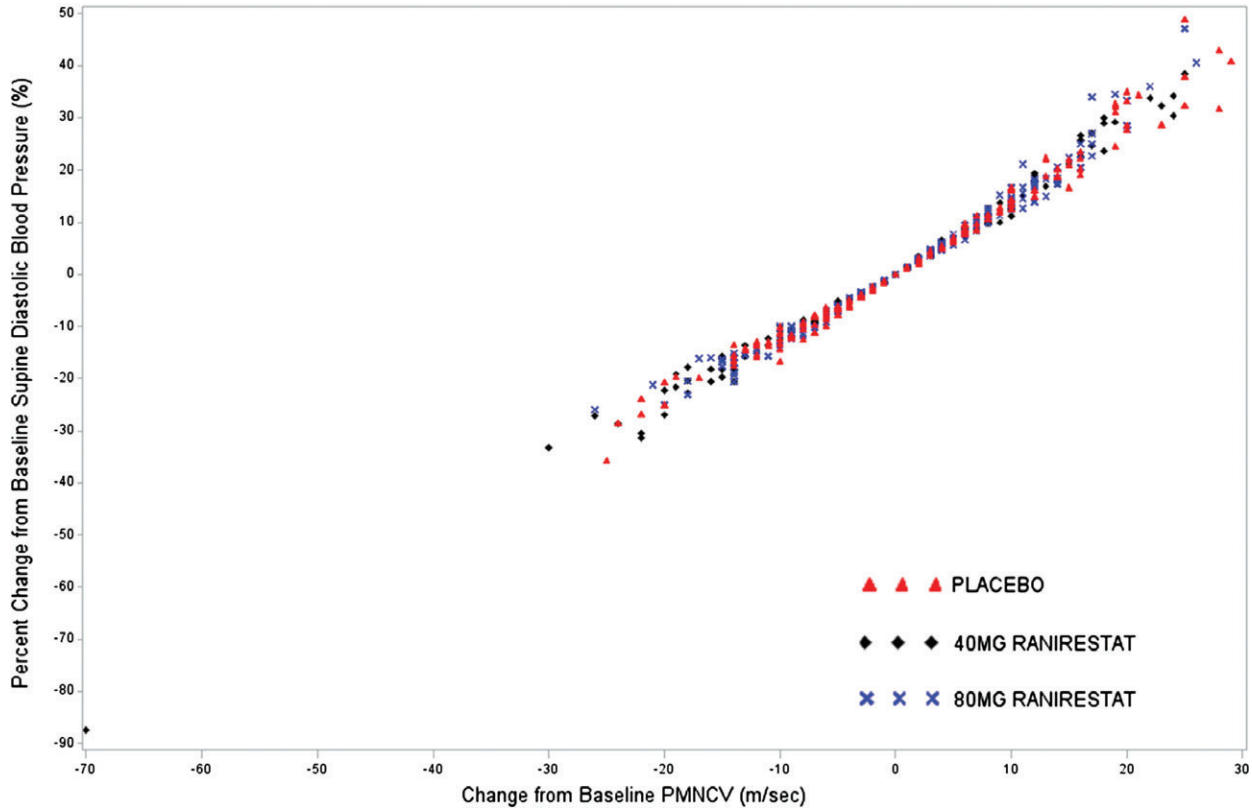

Figure 2. Relationship between change from baseline in diastolic blood pressure and peroneal motor nerve conduction velocity (PMNCV) at month 24.

but small improvement from baseline to 24 months in PMNCV with ranirestat 40 and 80 mg/day vs. placebo although the magnitude of improvement never reached the primary endpoint goal of 1.2 m/s. Similarly, none of the secondary measures demonstrated a treatment benefit. The lack of progression in the placebo group contributed to ranirestat not meeting the primary endpoint goal of a 1.2 m/s improvement in PMNCV. Even when we combined the ranirestat 40 and 80 mg dose groups and found a significant change from baseline to 24 months vs. placebo (+0.44 m/s; p = 0.0237), this change was still below the established threshold of a 1.2 m/s difference vs. placebo.

Unexpectedly, PMNCV improved rather than declined *(Diabetes Control Complications Trial (DCCT) Research Group, 1995; Partanen et al., 1995)* over time in the placebo group (+0.49 m/s at 24 months). A similar pattern of paradoxical improvement or

modest progression with placebo has been seen in several recent large multicenter clinical trials of DSPN. In the Nathan I study, PMNCV improved in the placebo group by 0.18 m/s after 2 years (N = 207) and decreased by 0.06 m/s after 4 years (N = 207) *(Ziegler et al., 2011)*. Conversely, there was a decline of 0.38 m/s in PMNCV in placebo patients (N = 262) from two identical 1-year ruboxistaurin clinical trials *(Tesfaye et al., 2007)*. A longitudinal 3-year cohort study of 62 subjects with well-controlled diabetes and stable risk factor control did not observe a change in NCV but did demonstrate worsening in measures of small fiber function *(Gibbons et al., 2013)*. Reasons for this relative lack of disease progression compared with historical rates may include better control of diabetes in the intensively monitored clinical trial environment. HbA_{1c} was stable over time, averaging 7.8%–8.0% (62–64 mmol/mol). An *ad hoc* analysis of placebo patients with baseline $HbA_{1c} \geq 9\%$ (≥75 mmol/mol) did show a worsening of PMNCV of $0.06 \text{ m/s} \pm 0.45$ at 2 years compared with an improvement of 0.62 ± 0.171 in subjects with baseline $HbA_{1c} < 9\%$. This modest worsening of PMNCV in subjects with poor glycemic control is closer to the historical data upon which this study was powered *(Diabetes Control Complications Trial (DCCT) Research Group, 1995; Partanen et al., 1995)*. This could suggest that rates of DPN progression have changed over time as diabetes control and treatment of comorbidities has improved. Indeed, the average HbA_{1c} of the older studies in which PMNCV decreased more prominently was 9.3% while the average HbA_{1c} in this study was 7.8% compared with 8.8% in the NATHAN 1 study *(Ziegler et al., 2011)*, 7.6% in the ruboxistaurin studies *(Tesfaye et al., 2007)*, and 7.2% in the Gibbons and colleagues study *(Gibbons et al., 2013)*. The fact that we were able to detect differences between placebo and treatment groups despite the lack of progression in the placebo group is likely due to the lower than anticipated variability in PMNCV (a PMNCV SD of 2.6 across treatment groups vs. an expected SD of 3.8 m/s).

Unexpectedly, a *post hoc* analysis of change in supine diastolic blood pressure (DBP) and PMNCV between baseline and month 24 showed a very strong association between drop of DBP and reduction (worsening) of PMNCV. The observed decrease in DBP may reflect a loss of sympathetic muscle tone associated with progressive loss of sympathetic nerve function, which may explain the strong association with impairment of PMNCV. The association of falling DBP and worsening PMNCV may potentially compound the risk of developing diabetic complications such as ulceration, and therefore could justify more intense clinical management of subjects with falling DBP. As suggested by the similar incidences of change in DBP between treatment and placebo groups, ranirestat did not appear to have any impact on DBP.

Dropouts over time and the LOCF approach may have underestimated efficacy measures in this study. Of the 265 placebo and 535 ranirestat patients, 209 (79%) and 427 (80%), respectively, continued treatment and contributed data (observed data) to the 24-month time point. Using observed data, the combined ranirestat change from baseline PMNCV at 24 months was +1.14 m/s (vs. +0.56 m/s with placebo). The LOCF approach assigns the previous recorded observation (or baseline value in the absence of post-baseline assessments) for missing data, and this approach reduces the ranirestat (combined) change from baseline PMNCV to +0.93 m/s. The LOCF approach for handling missing data was selected following regulatory agency interactions.

Regardless of the analysis method used, PMNCV changes were small, and the lack of a sequential improvement beyond 6 months argues against a disease-modifying effect on large-fiber nerve function with ranirestat. This is reinforced by the lack of treatment effect on signs and symptoms of DSPN or vibration sensation. This lack of observable clinical benefit could suggest that an improvement of +0.44 m/s in PMNCV above placebo is insufficient to cause perceptible difference in DSPN signs and symptoms; active progression is required to demonstrate an effect with placebo; or PMNCV is not necessarily the appropriate surrogate for neuropathy progression. AR inhibitors are hypothesized to slow the progress of neuropathy by limiting sorbitol accumulation, so the absence of disease progression in the placebo group limited the ability to observe clinical changes or pathologic changes related to ranirestat treatment.

Incorporating a dedicated measure of small caliber fiber such as skin biopsy was considered although ultimately not used due to the fact that regulatory authorities did not accept a change in this measure as a criterion for approval. Future studies should include additional measures of small fiber structure or function such as skin biopsy and more contemporary longitudinal data are needed using these measures.

Ranirestat was well tolerated and improved PMNCV vs. placebo, but not to the 1.2 m/s threshold. Ranirestat did not result in any detectable symptom benefit over placebo. The lack of neuropathy progression as measured by PMNCV in the placebo group highlights the challenges of conducting multinational DSPN trials.

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Supporting Information

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