Ranirestat for the Management of Diabetic Sensorimotor Polyneuropathy

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Background Aldose reductase inhibitors (ARIs) are potential disease modifiers for diabetes complications. We aimed to determine whether ranirestat, an ARI, could slow or reverse the course of diabetic sensorimotor polyneuropathy (DSP).

Methods 549 patients with DSP were randomized to treatment with placebo or ranirestat 10, 20, or 40 mg/d for 52 weeks in this multicenter, double-blind study. Efficacy was evaluated by nerve conduction studies (NCS), the modified Toronto Clinical Neuropathy Score (mTCNS), and quantitative sensory tests (QST).

Results At Week 52, the summed sensory (bilateral sural plus proximal median sensory) nerve conduction velocity (NCV) did not show significant changes from baseline (placebo 2.0 m/s compared to ranirestat 3.2-3.8 m/s). Significant improvement in the summed motor (peroneal, tibial, and median) NCV was observed with ranirestat 20 and 40 mg/d treatment at Week 12 (p ≤ 0.05), and at Week 24 and 36, and in the peroneal motor NCV at Weeks 36 and 52 (p ≤ 0.05) for the ranirestat 20 mg/d group. The mTCNS and QST did not differ between groups during the study. Ranirestat was well tolerated with no pertinent differences in drug-related adverse events, or effects on clinical laboratory parameters, vital signs, or ECGs between the four groups.

Conclusions Treatment with ranirestat appears to have an effect on motor nerve function in mild to moderate DSP, but the results of this study failed to show a statistically significant difference in sensory nerve function relative to placebo.
Sensorimotor polyneuropathy is one of the major complications of diabetes with a prevalence of about 50% in both type 1 and type 2 diabetes. Although the biochemical mechanisms underlying the development of DSP are complex and still controversial, the polyol pathway is an important factor. Elevated blood glucose in diabetes patients leads to increased activity of aldose reductase (AR), an enzyme that converts glucose to sorbitol, one of the alcohol sugars. The result is accumulation of sorbitol within nerves which is associated with oxidative stress and nerve damage. ARIs block the polyol pathway and should be effective in preventing the progression of DSP. In fact, an earlier study showed that inhibition of nerve sorbitol levels was associated with improved motor NCV and an increase in the density of small-diameter sural nerve myelinated fibers.

Although a number of ARIs have been developed, none have achieved clinical success for diverse reasons, one being that not all ARIs penetrate human peripheral nerve. Ranirestat, (previously known as AS-3201), an ARI developed by Dainippon Sumitomo Pharma, Ltd. (Osaka, Japan) has demonstrated 65 and 84% inhibition of sorbitol accumulation in sural nerve from patients treated for 12 weeks with 5 and 20 mg/d, respectively ($P < 0.001$). In a 48 week extension study, the sensory NCV improved by $\geq 1$ m/s relative to baseline ($P < 0.05$).

Building on these phase II study results, we aimed to determine whether ranirestat would safely slow or reverse the progression of DSP when compared to placebo treatment for 52 weeks.

**METHODS**

We performed a multicenter, double-blind, randomized, placebo-controlled study in which patients were assigned to ranirestat 10 mg/d, 20 mg/d, 40 mg/d, or placebo administered as a once daily dosage for 52 weeks. The 40 mg/d dose was selected to determine whether a higher ranirestat dose, with presumed greater sorbitol inhibition, would improve the efficacy observed in the phase 2 study with a maximum dose of 20 mg/d. The institutional review boards at the participating centers reviewed and approved the study before the start of any study procedures. All patients provided written informed consent prior to screening procedures.

**Patients:** 549 patients were enrolled in the study using the Interactive Voice Response System (IVRS). Entry criteria were: 18–70 years of age, type 1 or 2 diabetes for at least 6 months, glycemic control stable for at least 3 months before entry, HbA1c $\geq 7.0\%$, and the presence of bilateral sural nerve potential amplitude responses of at least 1.0 $\mu$V. DSP was diagnosed by the modified San Antonio Criteria requiring the presence of 2 of the following 4 criteria: 1) symptoms of DSP, 2) signs of DSP, 3) abnormal NCS with at least 2 abnormal nerves, and 4) abnormal VPT. The presence of either of the latter 2 criteria was required. Patients with nondiabetic neuropathy or severe neuropathy (sural nerve amplitude $< 1.0 \mu$V) were excluded. The results of NCS, VPT and the entry criteria for each patient were reviewed and approved by the Central Core Laboratory before a patient could be randomized to ensure consistency of study procedures and high-quality data.

**Procedures:** Screening included a medical history, physical and neurological examinations, NCS, QST including VPT, cold detection threshold (CDT), and monofilament sensitivity. The mTCNS was used as a potentially more sensitive measure for clinical change than the validated TCNS. The NCS, QST, and mTCNS were repeated at Weeks 12, 24, 36 and 52.
The primary endpoint was the summed change in sensory NCV from baseline of bilateral sural and proximal median sensory nerves. Secondary endpoints were the changes for individual sensory NCV, summed and individual motor NCV, F wave latencies, QST, and the mTCNS.

1. **Electrophysiology measurements**: Testing was standardized for temperature, side of testing, stimulation protocol, averaging of sensory potentials, and measurement of latencies and amplitudes. Unilateral NCS were performed on the nondominant median motor, dominant peroneal motor, and nondominant median sensory nerves. Bilateral sural NCS were performed. Sensory NCS were performed antidromically. Measurements of distances, response latencies, and amplitudes were performed using onset latencies and baseline-to-peak amplitudes. Measurements from the initial positive peak, if present, to negative peak were made for sensory NCS. F waves were obtained for all motor nerves and the minimal reproducible latency was measured. Conduction velocities were calculated for motor and sensory nerves.

2. **mTCNS**: The mTCNS consists of graded symptom and sensory test scores caused by DSP in the judgment of the examiner. Details of the mTCNS have been presented previously in a validation study. The individual symptoms and signs evaluated are identical with the original, validated TCNS. The scale varies from 0 (no signs or symptoms of DSP) to 33 (maximal symptoms and signs of DSP) with a maximum of 18 symptom points and 15 sensory test points.

3. **QST**: The VPT and CDT were measured at the first toe by the method of limits using the Neuro Sensory Analyzer Model TSA-II (Medoc Ltd., Advanced Medical Systems, Ramat, Yishai, Israel).

4. **Biochemical Measurements**: Tandem Laboratories, Salt Lake City, UT, performed the ranirestat plasma assays. Samples were prepared by a solid-phase extraction procedure and were analyzed by liquid chromatography/tandem mass spectrometry. Calibration standards were prepared by spiking blank, homogenized human plasma with the appropriate spiking solutions provided by Dainippon Sumitomo Pharma, Ltd. The API 3000 was operated in the selected-reaction monitoring mode under optimized conditions for detection of ranirestat negative ions formed by TurboIonSpray ionization.

**Statistical analyses**: Demographic and baseline characteristics were analyzed for homogeneity using the Kruskal-Wallis $\chi^2$ test. An intention-to-treat analysis was performed. Within-group comparisons between the baseline and end of treatment value were assessed using the Student’s paired $t$ test. ANCOVA was constructed to test for effects of treatment. Comparisons of groups were assessed using an ANCOVA model including baseline values as covariates. Medically meaningful predefined covariates were not included in the model if they were found to be homogeneous at baseline. Because of differences in the number of patients between dose groups and between centers, the changes are expressed as Least Squares Means (LSM) and statistically analyzed with baseline as a covariate. P-values are adjusted for multiplicity using Dunnett’s procedure. Missing observations were handled by the last observation carried forward method.

**RESULTS**

1,645 patients were screened; 549 patients fulfilling the entry criteria were randomized: 134 to placebo, 138 to ranirestat 10 mg/d, 132 to ranirestat 20 mg/d, and 145 to the ranirestat 40 mg/d. Two patients assigned to ranirestat 10 mg/d were not included in safety and efficacy evaluation because they did not take any study medication. The patient demographic data are shown in Table 1. No significant differences
were observed between the treatment groups for gender, age, BMI, type of diabetes, duration of diabetes, duration of DSP, or HbA1c. For all patients, the mean baseline BMI was 33.1 kg/m² and most patients (83%) had type 2 diabetes for 14.5 years and DSP for 4.9 years. Their baseline HbA1c was 8.3%. NCS and mTCNS data at screening are also shown in Table 1. The mean value of each symptom in the mTCNS was approximately 1 and was somewhat higher for each sensory test introducing a floor effect.

Patient commitment was shown by the 85.7% who completed the entire 12-month study. The most common cause for discontinuation was voluntary withdrawal in 5.5%. Other reasons for not completing the study were: adverse events in 1.8%, lack of compliance 2.2%, lost to follow-up 2.2%, failed to continue to meet entry criteria 2.2%, and other 0.4%. There was no difference in reasons for withdrawal across the different treatment groups. The average compliance per visit was greater than 94% in each treatment group.

For the summed sensory NCV of the bilateral sural and proximal median sensory nerves, the observed mean changes (± SD) from baseline to week 52 were 2.0 (± 7.98) m/s in the placebo group, 3.2 (± 7.98) m/s in the 10 mg/d group, 3.8 (± 8.45) m/s in the 20 mg/d group, and 3.6 (± 9.33) m/s in the 40 mg/d group. For the purposes of inferential statistical analysis by the Least Square Means (LSM) method, these changes are 1.17, 1.55, 2.55 and 2.50 m/s for placebo, ranirestat 10, 20, 40 mg/d respectively at week 52. These differences did not achieve statistical significance between treatment groups. Figure 1 shows the LSM change from baseline for the summed sensory NCV.

Figure 2 shows the LSM change from baseline in the summed motor NCV of the tibial, peroneal, and median nerves. A mean decrease (deterioration) in the summed motor NCV occurred at Week 12 in the placebo group compared with mean increases (improvement) in all ranirestat groups. There were significant differences between ranirestat 20 mg/d and placebo (p=0.028) and between ranirestat 40 mg/d and placebo (p=0.002) at Week 12, when the LSM changes from baseline were -0.54 m/s in the placebo group, 0.65 m/s in the 10 mg/d group, 1.35 m/s in the 20 mg/d group, and 1.94 m/s in the 40 mg/d group. These results remained consistent at subsequent visits.

The peroneal motor NCV improved with ranirestat treatment significantly at Weeks 36 (p<0.05 to p<0.01) and 52 (p=0.014, 0.015 and 0.108 for ranirestat 10, 20 and 40 mg/d respectively) with ranirestat treatment compared to a slight deterioration of the LSM 0.1 m/s at Week 52 in the placebo group (Figure 3). The F-wave latencies also increased (worsened) in the placebo group compared with decreased latencies (improvement) in the ranirestat 20 and 40 mg/d groups at most visits (data not shown).

The mTCNS total, symptom and sensory test scores tended to decrease (improve) in all treatment groups (including placebo) resulting in no statistically significant differences. A decrease in mTCNS (improvement) was observed in all groups as early as 12 weeks and the decrease in mTCNS persisted (or decreased more) during the study in all groups to Week 52 without significant differences between groups. The decrease in the mTCNS at Week 52 was -2.75 points in placebo and varied from -2.4 to -2.75 in ranirestat groups (data not shown).

Both VPT and CDT improved at every visit in all groups, but the differences did not achieve statistical significance between ranirestat and placebo.

Ranirestat plasma levels were proportional to dose, an indication of linear pharmacokinetics. The mean values were consistent over time, without evidence of ranirestat accumulation or auto-induction.
The incidence of adverse events was comparable in all groups and led to premature withdrawal of 2.2% patients in the placebo group, 1.5% patients in the 10 mg/d group, 2.3% patients in the 20 mg/d group, and 1.4% patients in the 40 mg/d group. Ranirestat had no clinically relevant effects on clinical laboratory parameters including liver and renal function tests.

DISCUSSION

The results of this study did not show a significant difference between ranirestat and placebo treatment in the primary efficacy endpoint (change in summed sensory NCV) perhaps due to the unexpected placebo improvement. In the previous phase II study, the changes in the summed sensory NCV with placebo treatment at Week 12 ranged from -0.21 to 0.20 m/s, whereas a change from baseline of 2.1m/s was observed at 12 weeks in the placebo group in the current study. The explanation of the differences in behavior of the placebo groups between the 2 studies is obscure because the patient populations are similar with the same entry criteria and only a small difference in BMI between the two study populations was noted. A placebo response has been observed in other recent studies of DSP, and may result from lifestyle modification by the patients as they enter a clinical trial. Future studies need to examine lifestyle behavior in much more detail (such as regular assessment of weight and BMI during the study) than was done in the current study in order to determine if this was the full explanation for the placebo group behavior. A Phase II proof-of-concept study completed in Japan demonstrated a significant improvement in the summed sensory NCV with ranirestat compared to placebo after 26 weeks of treatment although the placebo group in this study also improved. (personal communication)

The changes in motor and sensory nerve conduction parameters differed in this study and there is no good explanation of this observation. Both summed and individual motor NCS parameters showed improvements with ranirestat treatment compared with deterioration in patients treated with placebo. The improved peroneal motor NCV with ranirestat treatment suggests clinical benefit since an abnormal peroneal motor NCV has been associated with the development of foot ulcers and mortality. One possible reason for the differences observed in sensory and motor NCV results in this study and compared to the earlier phase II study are that sensory NCS are more challenging to perform technically than motor NCS because of the magnitude of the signals (sensory potential amplitudes are measured in µV compared to motor potential amplitudes measured in mV). As a result, factors such as limb edema may have more of an impact on sensory recordings than on motor recordings. The sural nerve is the most challenging (of the nerves tested in this study) to evaluate due to anatomic variations and the small size of the sural nerve response. As the number of study sites increased and the BMI of the patients increased from the phase II study, it is possible that these factors played a role in the results consistent with the observed higher standard deviations of the baseline parameters in this study. The use of a central core laboratory can minimize, but not eliminate, technical barriers in DSP studies; standardization of procedures across centers is also essential. The balance between including many centers to decrease the recruitment time for the study and including fewer centers with tightly controlled procedures needs to be kept in mind for future studies in DSP.

The mTCNS did not show a difference between the placebo and ranirestat treatment groups. In addition to an unexpected placebo effect perhaps due to lifestyle modification, another possible explanation for the lack of differences in the mTCNS response could be the floor effect. There are six symptoms
evaluated in the mTCNS and the mean symptom score on entry was about 5. This means that each symptom was about 1 at entry; this level leaves very little room for a significant change with treatment; i.e.: there is a floor effect. Similar comments apply to the sensory tests. Current criteria are set to capture patients at a stage of DSP that will respond to treatment. Abnormalities in NCS and/or QST are required for entry but symptoms and signs are not essential although the great majority of patients have both when they enter these clinical trials. DSP is at a mild-moderate stage using these entry criteria as shown by sural nerve morphology from prior studies, so the study population desired has been captured, but it is likely that clinical changes cannot be expected after only 12 months of treatment and that longer treatment intervals are essential to demonstrate clinical effects. Alternatively, only patients with marked symptoms might be recruited, but then it is uncertain that the severity would be uniform as symptoms are a poor guide to the underlying pathology in DSP. To determine a drug effect on harder end-points (such as frequency of foot ulceration) requires much larger study cohorts, patients with more advanced stages of DSP when foot ulceration is more likely to occur, and much longer durations of treatment such as 5 year studies.

The results of this study lend support to the importance of the polyol pathway in the pathophysiology of DSP and show that inhibition of the polyol pathway by the ARI ranirestat improves motor nerve function parameters. The placebo response and appropriate efficacy variables remain continuing challenges in ARI development and important lessons have been learned from the current study. Ranirestat continues to hold promise for the treatment of patients with DSP.

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REFERENCES


### Table 1 Patient Baseline Demographic Information

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<th>Placebo (N=134)</th>
<th>10 mg/Day (N=136)</th>
<th>20 mg/Day (N=132)</th>
<th>40 mg/Day (N=145)</th>
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<td>74 (55.2)</td>
<td>94 (69.1)</td>
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<td>BMI [kg/m²]</td>
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<td>32.9 (6.9)</td>
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<td>33.5 (7.5)</td>
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<td>Type II [%]</td>
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<td>14.6 (9.0)</td>
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<td>Sensory Tests</td>
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Data shown are number (%) for gender and type of diabetes, and mean (standard deviation) for other parameters.

The p-values for gender and type of diabetes were obtained from χ² tests. P values for the other parameters were obtained from one-way analyses of variance.

Symptoms and sensory tests are domains of the mTCNS. Symptoms range from 0-18 and sensory tests from 0-15.
**Figure 1** Changes from Baseline in the Summed Sensory NCV

Summed sensory NCV includes bilateral sural and proximal median sensory nerves. Data shown are LS Mean (± SE) Change from Baseline for LOCF. Adjusted p-value: placebo vs 10 mg (p=0.962), 20 mg (p=0.246), 40 mg (p=0.369) at Week 52.

**Figure 2** Changes from Baseline in the Summed Motor NCV

The summed motor NCV includes the median, peroneal and tibial nerves. Data shown are LS Mean (± SE) Change from Baseline for LOCF. Adjusted p-value: placebo vs 10 mg (p=0.247), 20 mg (p=0.028), 40 mg (p=0.002) at Week 12, placebo vs 10 mg (p=0.296), 20 mg (p=0.152), 40 mg (p=0.036) at Week 24, placebo vs 10 mg (p=0.188), 20 mg (p=0.029), 40 mg (p=0.013) at Week 36, placebo vs 10 mg (p=0.913), 20 mg (p=0.123), 40 mg (p=0.162) at Week 52.
**Figure 3** Changes from Baseline in Peroneal Motor NCV

* p < 0.05, ** p < 0.01

Data shown are LS Mean (± SE) Change from Baseline for LOCF. Adjusted p values; placebo vs ranirestat all doses at Week 36, (p≤0.035), placebo vs 10 mg (p=0.014), 20 mg (p=0.015) and 40 mg (p=0.108) at Week 52.