Oral Treatment With α-Lipoic Acid Improves Symptomatic Diabetic Polyneuropathy

The SYDNEY 2 trial

DAN ZIEGLER, MD, FRCPE[1]
ALEXANDER AMETOV, MD[2]
ALEXEY BARINOV, MD[3]
PETER J. DYCK, MD[4]
IRINA GURIEVA, MD[5]
PHILLIP A. LOW, MD[4]
ULLRICH MUNZEL, PHD[6]
NIKOLAI YAKHNO, MD[3]
ITAMAR RAZ, MD[7]
MARIA NOVOSADOVA, MD[5]
JOACHIM MAUS, MD[6]
RUSTEM SAMIGULLIN, MD[6]

OBJECTIVE — The aim of this trial was to evaluate the effects of α-lipoic acid (ALA) on positive sensory symptoms and neuropathic deficits in diabetic patients with distal symmetric polyneuropathy (DSP).

RESEARCH DESIGN AND METHODS — In this multicenter, randomized, double-blind, placebo-controlled trial, 181 diabetic patients in Russia and Israel received once-daily oral doses of 600 mg ($n = 45$) (ALA600), 1,200 mg ($n = 47$) (ALA1200), and 1,800 mg (ALA1800) of ALA ($n = 46$) or placebo ($n = 43$) for 5 weeks after a 1-week placebo run-in period. The primary outcome measure was the change from baseline of the Total Symptom Score (TSS), including stabbing pain, burning pain, paresthesia, and asleep numbness of the feet. Secondary end points included individual symptoms of TSS, Neuropathy Symptoms and Change (NSC) score, Neuropathy Impairment Score (NIS), and patients' global assessment of efficacy.

RESULTS — Mean TSS did not differ significantly at baseline among the treatment groups and on average decreased by 4.9 points (51%) in ALA600, 4.5 (48%) in ALA1200, and 4.7 (52%) in ALA1800 compared with 2.9 points (32%) in the placebo group (all $P < 0.05$ vs. placebo). The corresponding response rates (≥50% reduction in TSS) were 62, 50, 56, and 26%, respectively. Significant improvements favoring all three ALA groups were also noted for stabbing and burning pain, the NSC score, and the patients' global assessment of efficacy. The NIS was numerically reduced. Safety analysis showed a dose-dependent increase in nausea, vomiting, and vertigo.

CONCLUSIONS — Oral treatment with ALA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. An oral dose of 600 mg once daily appears to provide the optimum risk-to-benefit ratio.

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From the [1]German Diabetes Clinic, German Diabetes Center, Leibniz Institute at the Heinrich Heine University, Düsseldorf, Germany; the [2]Russian Medical Academy for Advanced Studies, Moscow, Russia; the [3]Neurology Clinic, Moscow Medical Academy, Moscow, Russia; the [4]Department of Neurology, Mayo Clinic, Rochester, Minnesota; the [5]Federal Center for Diabetic Foot, Moscow, Russia; [6]MEDA Pharma, Bad Homburg, Germany; and [7]Hadassah University, Jerusalem, Israel.

Address correspondence and reprint requests to Prof. Dan Ziegler, MD, FRCPE, Deutsche Diabetes-Klinik, Deutsches Diabetes-Zentrum, Leibniz-Institut an der Heinrich-Heine-Universität, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany. E-mail: dan.ziegler@ddz.uni-duesseldorf.de.

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Abbreviations: ALA, α-lipoic acid; DSP, distal symmetric polyneuropathy; NIS, Neuropathy Impairment Score; NSC, Neuropathy Symptoms and Change; TSS, Total Symptom Score.

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

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At least one of four diabetic patients is affected by distal symmetric polyneuropathy (DSP), which represents a major health problem. DSP may be associated with excruciating neuropathic pain and is responsible for both substantial morbidity and increased mortality (1–4). Neuropathic pain affects 16% of diabetic patients (5) and exerts a substantial impact on the quality of life, particularly by causing interference of sleep and enjoyment of life (6). Pain is a subjective symptom of major clinical importance that often motivates patients to seek health care. However, the pharmacologic treatment of chronic painful DSP remains a challenge for the physician (7).

Based on the pathogenetic mechanisms of DSP (8), several therapeutic approaches have been developed including antioxidants such as α-lipoic acid (ALA) to diminish increased oxidative stress (3,9–13). These drugs have been designed to favorably influence the underlying pathophysiology of the disorder, not solely to relieve pain. It is likely that in the foreseeable future, near normoglycemia will not be achievable in the majority of diabetic patients. Hence, these compounds could offer the advantage of being effective despite persistent hyperglycemia.

A recent meta-analysis comprising 1,258 diabetic patients with symptomatic DSP from four randomized clinical trials (14) including the first Symptomatic Diabetic Neuropathy (SYDNEY) study (15) suggested that treatment with ALA using 600 mg i.v. as a daily infusion for 3 weeks reduced pain, paresthesia, and numbness to a clinically meaningful degree. This effect was accompanied by an improvement of neuropathic deficits, assuming a potential of the drug to favorably influence the underlying neuropathy. However, apart from a small oral pilot study (ORPIL) using 600 mg ALA t.i.d (16), the efficacy and dose response of oral treatment with ALA on neuropathic symptoms and deficits in patients with symptomatic DSP have not yet been established. Therefore, we conducted a four-arm, randomized,

double-blind, placebo-controlled, dose-response trial using ALA (600, 1,200, and 1,800 mg q.d.) treatment over 5 weeks after a 1-week placebo run-in period.

RESEARCH DESIGN AND METHODS

— The SYDNEY 2 trial was a four-arm, parallel group, randomized, double-blind, placebo-controlled, multicenter trial using three oral doses of ALA (Thioctacid HR; MEDA Pharma, Bad Homburg, Germany). The primary end point was a confirmatory comparison of each group receiving ALA versus placebo using the change in Total Symptom Score (TSS) from baseline.

After obtaining the approvals by the Ethics Committees of Hadassah University, Jerusalem, Israel, and the Wolfson Medical Center, Holon, Israel, and the National Ethics Committee of the Ministry of Health, Moscow, Russia, and written informed consent, 181 patients with diabetes and symptomatic DSP were recruited from two centers in Israel and three centers in Russia. All patients were exposed to once-daily placebo treatment for 1 week (single-blind run-in phase). Thereafter, eligible patients were randomly assigned to receive the following treatments once daily over 5 consecutive weeks: ALA 600 mg (ALA600), 1,200 mg (ALA1200), 1,800 mg (ALA1800), or placebo (double-blind treatment phase). A 5-week treatment duration was chosen because, in previous studies, no plateau in the TSS response was observed after 3 weeks of intravenous ALA treatment and a slower onset of efficacy was assumed for oral therapy.

Inclusion criteria at the screening visit were age between 18 and 74 years, diabetes (type 1 or 2) defined by American Diabetes Association criteria, duration of diabetes ≥1 year, HbA_{1c} (A1C) <10%, symptomatic DSP attributable to diabetes after a thorough evaluation for other causes of neuropathy, TSS >7.5 points, Neuropathy Impairment Score (NIS) subscore for lower limbs ($NIS_{[LL]}$) ≥2 points, and pain sensation according to the pinprick test absent or decreased. At the randomization visit after the 1-week run-in, subjects had to comply with all of the following criteria: TSS ≥5 points; TSS range (maximum TSS − minimum TSS during the run-in period) <3 points; more than one of the four symptoms of the TSS had to have occurred continuously over the last 3 months, sufficient compliance 85–100%. Among others, exclusion criteria were confounding neurologic disease or neuropathy; myopathy of any cause; peripheral vascular disease severe enough to cause intermittent claudication ischemic ulcers or limb ischemia; significant hepatic or renal disease, antioxidant therapy, or pentoxyphylline within the last month; and use of ≥50 mg ALA or use of γ-linolenic acid–containing substances within the last 3 months.

Outcome measures

Primary outcome measure. The primary end point was the TSS, which is a summation of presence, severity, and duration of the four main positive neuropathic sensory symptoms: lancinating/stabbing pain, burning pain, paresthesia, and asleep numbness. The TSS was assessed at screening, at baseline before start of study treatment, and after 1, 2, 3, 4, and 5 weeks of treatment. All other parameters (see below) were determined at screening and at the end of the study.

Secondary outcome measures. The NIS and the Neuropathy Symptoms and Change (NSC) score were assessed according to the Clinical Neuropathic Assessment as previously described (15). The NIS is the sum score of a standard group of examinations of muscle strength (0 = normal to 4 = paralyzed), reflexes (0 = normal to 2 = absent with reinforcement), and touch-pressure, vibration, joint position and motion, and pinprick (0 = normal to 2 = absent for each modality) of the index finger and great toe and is scored for both sides of the body. The NSC scores (number, severity, and change) are derived from answers to 38 questions (muscle weakness, questions 1–19; sensation, questions 20–29; and autonomic symptoms, questions 30–38) (15).

Moreover, nerve conduction studies (amplitude, velocity, and latency of the tibial and peroneal nerves and amplitude and latency of the sural nerve) were performed. All neurological assessments were done by trained and certified neurologists. All answered Clinical Neuropathic Assessment booklets were reviewed by the Reading and Quality Assurance Center at the Mayo Clinic, Rochester, Minnesota. The global estimate of efficacy was rated by the patient as very good/good, satisfactory, or insufficient.

DSP was staged according to Dyck et al. (17,18): stage 0 (no neuropathy), stage 1 (asymptomatic neuropathy), stage 2a (symptomatic neuropathy: walking on heels possible), stage 2b (symptomatic neuropathy: walking on heels impossible), and stage 3 (disabling neuropathy).

Safety parameters

Vital signs including systolic/diastolic blood pressure and heart rate after 3 min of sitting, body weight, and standard laboratory parameters were monitored at the beginning and end of the study. Adverse events were monitored throughout the entire study.

Statistical analysis

The confirmatory analysis was based on the comparison of the changes in TSS from baseline to the end of treatment among the ALA groups and placebo including center effects but no treatment-center interactions. A treatment difference of 1.83 points of TSS (a half-range of a maximal single symptom) was considered as a clinically meaningful response to treatment. For all efficacy variables, the analyses of the intention-to-treat population were primary. To reduce variance, ANCOVA was applied with the baseline as covariate. In the case of missing data for study end (week 5), the last value carried forward principle was applied. To determine the onset of action, each time point was analyzed analogously to the primary analysis. Moreover, responder rates (≥50% improvement in TSS) were compared among treatment groups by applying the center-adjusted Cochran-Mantel-Haenszel test. Among the secondary variables, the subscores of the TSS and NSC scores were analyzed in analogy to the confirmatory analysis. The level of significance (two sided) was set at $\alpha = 0.05$.

RESULTS

— Of the 227 patients screened, 40 were found to be ineligible to enter the run-in phase mainly because of A1C ≥10% or concomitant serious hepatic or renal disease. Thus, 187 patients entered the run-in phase. Among these, six patients were not randomly assigned because of unstable TSS or withdrawal of consent. Among the 181 patients randomly assigned, a total of 15 (8%) subjects discontinued during the treatment period, and 166 patients completed the trial. Most patients (12) discontinued because of adverse events: 1 in the placebo group, 0 in the ALA600 group, 5 in ALA1200, and 6 in ALA1800. One patient in the ALA1800 group did not complete the trial because of lack of efficacy; another one patient each in the ALA1200

Table 1—*Clinical characteristics in the intention-to-treat population*

	Placebo	ALA600	ALA1200	ALA1800
n	43	45	47	46
Age (years)	57 ± 11	56 ± 12	59 ± 12	59 ± 9
Sex (% male)	35	44	40	41
BMI (kg/m^2)	29.1 ± 4.4	28.7 ± 3.9	30.9 ± 4.5	28.4 ± 4.8
Systolic blood pressure (mmHg)	134 ± 19	134 ± 16	141 ± 17	135 ± 10
Systolic blood pressure (mmHg)	81 ± 9	80 ± 10	83 ± 7	82 ± 9
Heart rate (bpm)	73 ± 9	74 ± 12	73 ± 10	72 ± 8
Diabetes type (% type 2)	84	82	83	85
Duration of diabetes (years)	14 ± 10	13 ± 8	14 ± 10	15 ± 11
Insulin treatment (%)	42	60	53	57
Treatment with oral antidiabetic agents (%)	74	67	64	50
A1C (%)	7.53 ± 1.18	7.58 ± 1.09	7.85 ± 1.31	7.81 ± 1.14
Smokers (%)*	0	11	11	9
Hypertension (%)	61	69	68	72
Polyneuropathy stage (% stage 2a)	93	82	89	98
Duration of neuropathy (years)	4.9 ± 3.2	4.8 ± 3.9	5.0 ± 3.8	4.9 ± 4.0
Retinopathy (%)	51	67	75	74
Nephropathy (%)	26	20	17	22

Data means ± SD unless otherwise indicated. *Smoker within the last 2 years.

and ALA1800 group discontinued for other reasons.

The clinical characteristics of the patients are shown in Table 1. As a sign of homogeneity, no significant differences among the groups were noted for any of the parameters listed, except for treatment with oral antidiabetic agents ($P = 0.018$) and BMI ($P = 0.036$, Table 1).

There were also no significant differences among the groups in the mean baseline TSS and its individual subscores. After 5 weeks of treatment, a significant reduction in the mean TSS and its subscores for stabbing/lancinating and burning pain was observed in all active arms compared with the placebo arm (all $P < 0.05$) (Table 2). No significant differences among the three ALA groups and the placebo group were noted for paresthesia and numbness.

The mean TSS levels during the placebo run-in and the randomized double-blind period of the trial are illustrated in Fig. 1. TSS was significantly reduced in the ALA600, ALA1200, and ALA1800 groups versus placebo at weeks 2–5 ($P < 0.05$) and in the ALA1800 group versus placebo at week 1 ($P < 0.05$).

No significant differences were observed among the three ALA groups for the changes in mean TSS at any of the time points examined. The response rates defined as ≥50% reduction in TSS after 5 weeks were 62% in ALA600, 50% in ALA1200, and 56% in ALA1800 compared with 26% after placebo ($P < 0.05$). The mean levels of the NSC scores, NIS, and $NIS_{[LL]}$ at screening and their changes after 5 weeks of treatment are given in Table 3. There were no significant differences among the groups at screening. A similar significant improvement in NSC number, severity, and change was found in all ALA groups compared with the pla-

Table 2—*Baseline levels and changes from baseline (negative values correspond to improvement) in the TSS and its individual subscores after 5 weeks of treatment (last value carried forward)*

	Placebo	ALA600	ALA1200	ALA1800
TSS				
Baseline	9.27 ± 1.56	9.44 ± 1.86	9.40 ± 1.64	9.02 ± 1.61
Change	−2.92 ± 3.18	−4.85 ± 3.03*	−4.50 ± 3.28*	−4.70 ± 3.54*
Stabbing pain				
Baseline	2.21 ± 0.77	2.32 ± 0.94	2.38 ± 0.89	2.03 ± 0.88
Change	−0.83 ± 1.14	−1.40 ± 1.15*	−1.56 ± 1.07*	−1.46 ± 1.20*
Burning pain				
Baseline	2.11 ± 0.87	2.21 ± 1.07	2.17 ± 1.05	2.15 ± 1.03
Change	−0.50 ± 1.15	−1.32 ± 1.07*	−1.09 ± 1.19*	−1.15 ± 1.41*
Paresthesia				
Baseline	2.21 ± 0.63	2.32 ± 0.80	2.12 ± 0.80	2.17 ± 0.69
Change	−0.80 ± 1.17	−1.16 ± 1.26	−0.85 ± 1.21	−1.12 ± 1.20
Numbness				
Baseline	2.74 ± 0.67	2.58 ± 0.67	2.73 ± 0.66	2.67 ± 0.72
Change	−0.79 ± 1.09	−0.97 ± 1.06	−0.99 ± 1.13	−0.98 ± 1.16

Data are means ± SD. *$P < 0.05$ vs. placebo.

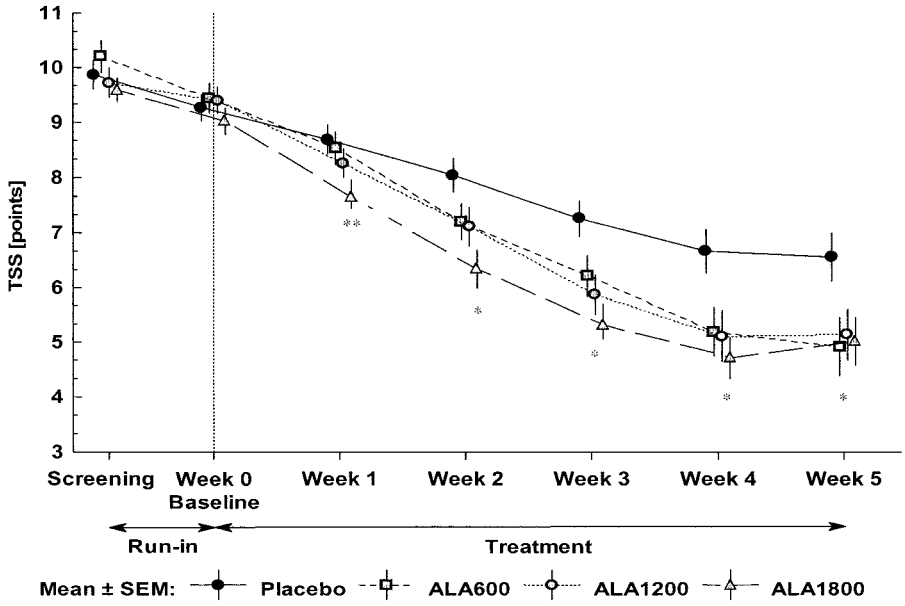

Figure 1—*Mean TSS levels on a weekly basis during the placebo run-in and the randomized double-blind period of the trial. *P < 0.05 for ALA600, ALA 1200, and ALA1800 vs. placebo; **P < 0.05 for ALA1800 vs. placebo.*

cebo group (all $P < 0.05$, except for NSC number in ALA1800: $P = 0.08$). For the changes of NIS, a significant improvement was noted in ALA1200 ($P < 0.05$) and a borderline improvement in ALA1800 versus placebo ($P = 0.055$). Regarding the changes in $NIS_{[LL]}$, a trend for borderline significance was found in the ALA600 group ($P = 0.07$ vs. placebo). Focusing on $NIS_{[LL]}$ sensory function, a significant difference between ALA600 and placebo ($P < 0.05$) and a borderline improvement in ALA1200 compared with placebo ($P = 0.09$) were noted. No significant differences among the groups were noted for any of the nerve conduction studies (data not shown). The percentages for the global estimate of efficacy rated by the patients as very good/good, satisfactory, and insufficient were 29, 40, and 32%, respectively, for the placebo group, 62, 27, and 11% for the ALA600 group, 56, 31, and 13% for the ALA1200 group, and 71, 21, and 9% for the ALA1800 group ($P < 0.05$ for all ALA doses vs. placebo).

The rates of treatment-emergent adverse events were 9 (21%) in the placebo group, 12 (27%) in the ALA600 group ($P = 0.53$ vs. placebo), 20 (43%) in the ALA1200 group ($P = 0.03$ vs. placebo), and 25 (54%) in the ALA1800 group ($P = 0.001$ vs. placebo). The rates of treatment-emergent adverse events in World Health Organization preferred terms (>10% in any group) increased with escalating doses and were nausea 0, 6 (13%), 10 (21%), and 22 (48%) ($P < 0.05$ for all ALA groups vs. placebo); vomiting 0, 1 (2%), 2 (4%), and 12 (26%) ($P < 0.05$ for ALA1800 vs. placebo); vertigo 0, 2 (4%), 2 (4%), and 5 (11%), respectively ($P = 0.056$ for ALA1800 vs. placebo).

CONCLUSIONS — The results of the SYDNEY 2 trial demonstrate that oral treatment with ALA over 5 weeks improved the positive sensory symptoms scored by the TSS in diabetic patients with DSP. This overall effect was not dose dependent, as there were no differences in the changes in mean TSS among all active groups. A significant improvement in TSS was noted as soon as after 1 week with ALA1800 and after 2 weeks with ALA600 and ALA1200. Among the individual TSS symptoms, improvement in pain but not paresthesia and numbness was observed. Moreover, ALA ameliorated the NSC and neuropathy impairment scores (NIS and $NIS_{[LL]}$).

Table 3—*Screening levels and changes from screening in NSC scores, NIS, and $NIS_{[LL]}$ after 5 weeks of treatment (last value carried forward)*

	Placebo	ALA600	ALA1200	ALA1800
NSC number				
Screening	6.8 ± 1.7	7.0 ± 1.6	7.1 ± 1.5	6.6 ± 1.5
Change	−1.7 ± 2.1	−2.8 ± 2.1*	−2.8 ± 2.2*	−2.7 ± 2.5†
NSC severity				
Screening	14.1 ± 4.3	14.4 ± 4.4	14.7 ± 4.5	13.5 ± 3.5
Change	−4.9 ± 4.3	−7.4 ± 4.6*	−7.2 ± 5.0*	−7.6 ± 4.2*
NSC change				
Screening	−0.1 ± 0.7	0.0 ± 0.3	−0.2 ± 0.6	0.0 ± 0.3
Change	+5.4 ± 4.6	+8.6 ± 5.6*	+8.5 ± 5.3*	+9.5 ± 5.1*
NIS				
Screening	19.2 ± 17.1	19.4 ± 17.6	18.7 ± 14.1	17.6 ± 15.8
Change	−2.38 ± 6.06	−3.80 ± 4.61	−3.85 ± 4.57*	−3.85 ± 6.49‡
$NIS_{[LL]}$				
Screening	14.5 ± 14.6	15.4 ± 14.4	15.0 ± 11.1	13.0 ± 11.6
Change	−2.08 ± 5.57	−3.75 ± 4.41§	−2.63 ± 3.28	−2.70 ± 5.33
$NIS_{[LL]}$ sensory function				
Screening	7.05 ± 3.21	6.80 ± 3.76	7.21 ± 2.82	6.53 ± 2.79
Change	−1.05 ± 1.99	−2.25 ± 2.27*	−1.73 ± 1.72‖	−1.55 ± 1.81

Data are means ± SD. Negative values correspond to improvement. *$P < 0.05$, †$P = 0.08$, ‡$P = 0.055$, §$P = 0.07$, and ‖$P = 0.09$ (each vs. placebo).

The mechanisms of the rapid improvement in both neuropathic symptoms and deficits may be related to an improvement in nerve blood flow mediated by the antioxidant action of ALA (19–26). In the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study, oral administration of 300 mg ALA per day as monotherapy and in combination with irbesartan (150 mg/day) to patients with the metabolic syndrome resulted in a significant increase in endothelium-dependent flow-mediated vasodilation of the brachial artery by 44 and 75%, respectively, compared with placebo treatment after 4 weeks. This effect was accompanied by reductions in plasma levels of interleukin-6 and plasminogen activator-1, suggesting that the drug may improve endothelial dysfunction via anti-inflammatory and antithrombotic mechanisms (27). Intravenous infusion of 600 mg ALA exerts an acute effect on microcirculation in patients with diabetic polyneuropathy (28,29). The impairment of nitric oxide–mediated vasodilation in diabetes has been attributed to increased vascular oxidative stress. At this point, acute infusion of ALA improved nitric oxide–mediated endothelium-dependent vasodilation in diabetic patients (30).

The safety analysis revealed an overall favorable safety profile for the low dose. None of the patients with ALA600 discontinued the study, whereas with the higher doses 5 of 47 (11%) and 6 of 46 (13%) patients dropped out because of adverse events during treatment with ALA1200 and ALA1800, respectively. The most frequent adverse event was a dose-dependent increase in the incidence of nausea. Whereas at ALA600, this rate was slight (13%), it was markedly higher at 1,200 mg q.d. and 1,800 mg q.d., reaching 21 and 48%, respectively. The rate of adverse events with 1,200 mg q.d. (21%) is somewhat higher than that previously reported in the α-Lipoic Acid in Diabetic Neuropathy (ALADIN II) study in 7% of the patients receiving 1,200 q.d. orally (31) and that observed in the ALADIN study in 15% of the patients given 1,200 q.d. intravenously (32). However, a direct comparison of these studies is not possible because of the different routes of administration and oral drug formulations used. The oral HR (high release) formulation of ALA used in this study was specifically developed to reduce the relatively high variability in drug plasma levels after oral administration of the conventional formulation. The coefficient of variation was reduced from 59% for the drinking solution to 22% for the HR formulation (R. Hermann, unpublished observations).

In view of previous studies using analgesics in neuropathic pain, we believe that a response of at least 50% reduction in neuropathic symptoms after 3 weeks is clinically meaningful. According to this definition, the response rates were 50–62% in patients treated with ALA and 26% in those receiving placebo. The number needed to treat for the 600-mg dose of oral ALA q.d. is 2.7. Whether the observed favorable short-term effect of ALA on neuropathic symptoms and deficits can be translated into slowing the progression of diabetic polyneuropathy in the long term is unknown. However, our finding that neuropathic deficits such as impaired sensory function were improved is encouraging, because these are major risk factors in the development of neuropathic foot ulcers (33).

In summary, this trial demonstrated that the magnitude of efficacy of oral once-daily treatment with ALA using doses of 600–1,800 mg over 5 weeks on neuropathic symptoms is comparable to that resulting from intravenous treatment using 600 mg/day over 3 weeks as previously reported (14). It is notable that this improvement is clinically meaningful and demonstrable within 1–2 weeks. In the absence of a dose response and because the higher doses resulted in increased rates of gastrointestinal side effects, 600 mg once daily seems to be the most appropriate oral dose.

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