
Treatment of symptomatic diabetic polyneuropathy with the antioxidant α -lipoic acid: A meta-analysis

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Running title:

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Abstract

Aims: To determine the efficacy and safety of 600 mg of α -lipoic acid given i.v. over 3 weeks in diabetic patients with symptomatic polyneuropathy.

Methods: We searched the database of VIATRIS GmbH, Frankfurt, Germany, for clinical trials of α -lipoic acid according to the following prerequisites: randomized, double-masked, placebo-controlled, parallel-group trial using α -lipoic acid infusions of 600 mg i.v. per day for 3 Weeks, except for weekends, in diabetic patients with positive sensory symptoms of polyneuropathy which were scored by the Total Symptom Score (TSS) in the feet on a daily basis. Four trials (ALADIN I, ALADIN III, SYDNEY, NATHAN II) comprised n=1258 patients (α -lipoic acid: n=716; placebo: n=542) met these eligibility criteria and were included in a meta-analysis based on the intention-to-treat principle. Primary analysis involved a comparison of the differences in TSS from baseline to the end of i.v. treatment between the groups treated with α -lipoic acid or placebo. Secondary analyses included daily changes in TSS, responder rates ($\geq 50\%$ improvement in TSS), individual TSS components, Neuropathy Impairment Score (NIS), NIS of the lower limbs (NIS-LL), individual NIS-LL components, and the rates of adverse events.

Results: After 3 weeks the relative difference in favour of α -lipoic acid vs placebo was 24.1 (13.5-33.4)% (geometric mean with 95% confidence interval) for TSS and 16.0 (5.7-25.2)% for NIS-LL. The responder rates were 52.7% in patients treated with α -lipoic acid and 36.9% in those on placebo ($p < 0.05$). On a daily basis there was a continuous increase in the magnitude of TSS improvement in favour of α -lipoic acid vs placebo which was noted first after 8 days of treatment. Among the individual components of the TSS, pain, burning, and numbness decreased in favour of α -lipoic acid as compared with placebo, while among the NIS-LL components pin-prick and touch-pressure sensation as well as ankle reflexes were

improved in favour of α -lipoic acid after 3 weeks. The rates of adverse events did not differ between the groups.

Conclusions: The results of this meta-analysis provide evidence that treatment with α -lipoic acid (600 mg/day i.v.) over 3 weeks is safe and significantly improves both neuropathic symptoms and deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.

Key words: Diabetic polyneuropathy, Total Symptom Score, Neuropathy Impairment Score, α -lipoic acid, meta-analysis

Abbreviations: ALADIN: Alpha-lipoic Acid in Diabetic Neuropathy, SYDNEY: Symptomatic Diabetic Neuropathy, NATHAN: Neurological Assessment of Thiocctic Acid in Neuropathy, TSS: Total Symptom Score, NIS: Neuropathy Impairment Score, NIS-LL: Neuropathy Impairment Score of the lower limbs, QUOROM: Quality of Reporting of Meta-analyses, ITT: intention-to-treat, NNT: number needed to treat, CBV: capillary blood cell velocity, TESS: treatment-emergent signs and symptoms, NO: nitric oxide,

Introduction

Diabetic neuropathy represents a major health problem, as it is responsible for substantial morbidity, increased mortality, and impaired quality of life (1-6). Although near-normoglycaemia is now generally accepted as the primary approach to prevention and treatment of diabetic complications, it is not achievable in a considerable number of patients. Moreover, in contrast to trials aimed at improvement in glycaemic control in Type 1 diabetic patients, those conducted in Type 2 diabetic patients did not provide unequivocal evidence for a favourable effect on diabetic polyneuropathy (7). In the past two decades several medical treatments that exert their effects despite hyperglycaemia have been derived from the experimental pathogenetic concepts of diabetic neuropathy and tested in clinical trials (8). In contrast to drugs solely aimed at symptomatic pain relief, such compounds have been designed to ideally improve or slow the progression of both the neuropathic process and corresponding symptoms.

A substantial body of evidence suggests that oxidative stress resulting from enhanced free-radical formation and/or defects in anti-oxidant defence plays a major role among the putative pathogenetic mechanisms of diabetic neuropathy (9-10). Consequently, antioxidants such as α -lipoic acid (thioctic acid) have been shown to improve experimental diabetic neuropathy (11,12). α -Lipoic acid was introduced in Germany as soon as in 1959 to treat acute poisoning, i.e. liver failure associated with ingestion of *amanita phalloides*, and shortly thereafter it was also prescribed to treat neuropathic complaints (13). More recently, several randomized placebo-controlled clinical trials, some but not all of which have been published, evaluated the efficacy and safety of α -lipoic acid in patients with diabetic polyneuropathy focussing on i.v. infusion treatment over 3 weeks (14-17). Because the results of the individual trials varied and, hence, made a conclusive interpretation more difficult, we undertook a comprehensive analysis of trials with

comparable designs which met specific eligibility criteria for a meta-analysis to obtain a more precise estimate on the efficacy and safety of α -lipoic acid in diabetic patients with symptomatic polyneuropathy.

Methods

We searched the database of VIATRIS GmbH, Frankfurt, Germany, for clinical trials conducted by this company with α -lipoic acid according to the following prerequisites: 1.) randomized, double-masked trial, 2.) placebo-controlled, parallel-group trial, 3.) α -Lipoic acid infusion of 600 mg i.v. per day, 4.) i.v. treatment duration of 3 weeks, without treatments on Saturdays and Sundays, 5.) daily assessment of the Total Symptom Score (TSS), except for Saturdays and Sundays, and 6.) diabetic patients with symptomatic polyneuropathy. Trials were eligible for inclusion in the meta-analysis only if all these six criteria were fulfilled. According to the QUOROM Statement flow diagram (18) four potentially relevant trials were identified and screened for retrieval, retrieved for more detailed information, considered potentially appropriate to be included in the meta-analysis, and finally, these four trials were included in the meta-analysis with usable information, by outcome. No trial was excluded.

The ALADIN (**A**lpha-lipoic **A**cid in **D**iabetic **N**europathy) I (14) and ALADIN III studies (15) were multicenter trials including out-patients from 38 and 71 diabetes centres and general practitioners in Germany, respectively. The SYDNEY (**S**ymptomatic **D**iabetic **N**europathy) Study (16) was a monocenter trial including in-patients from a hospital in Moscow, Russia. The NATHAN (**N**eurological **A**ssessment of **T**hiocctic **A**cid in **N**europathy) II Study (17) was a multicenter trial including out-patients from 33 diabetes centres in the USA, Canada, and Europe. Comparative analyses were performed on an intention-to-treat basis including n=1258 patients. The intention-to-treat population in the individual trials and in total in the groups treated with α -lipoic acid or placebo were as follows: ALADIN I: n=77/81; ALADIN III: n=338/165; SYDNEY: n=60/60; NATHAN II: n=241/236; Total: n=716/542.

Assignment: In each trial individual patients were randomized according to their entry sequence following a central computerized randomization list.

Masking (blinding): Intravenous infusion of the trometamol salt solution containing 600 mg of α -lipoic acid (Thioctacid[®] T, VIATRIS GmbH, Frankfurt am Main, Germany) or placebo in 250 ml 0.9% isotone saline solution over 30 min once daily was administered over two periods of 5 days (Monday to Friday) and one period of 4 days (Monday to Thursday) during 3 consecutive weeks. Ampules containing 10 ml (250 mg) and 4 ml (100 mg) α -lipoic acid or placebo were used. Each patient received 6 ampules (4 ampules with 10 ml each and 2 ampules with 4 ml each). Because of the yellow color of the α -lipoic acid containing solution, riboflavin (0.00375 mg/ml) was added to placebo to obtain preparations looking alike. All investigators and participants were blinded to the randomization of the study drug assignments.

Outcome measures:

Total Symptom Score (TSS): At baseline (day 1) and each visit (days 2-5, 8-12, and 15-19) prior to infusion, neuropathic symptoms in the foot (pain, burning, paresthesiae, and numbness) were scored by the physician or a trained nurse regarding their intensity as described previously (14). The comparison of the changes from baseline to day 19 or last available value, respectively, in the TSS, ranging from 0 (no symptoms) to a maximum of 14.64 points (all symptoms are severe and [almost] continuously present), between the groups receiving α -lipoic acid and placebo was used as the primary outcome measure.

Neuropathy Impairment Score (NIS): The NIS was completed in the ALADIN III, SYDNEY, and NATHAN II studies according to Dyck et al. (19) at baseline and day 19 by the physicians who had been trained prior to the start of the trial by an experienced neurologist. In brief, a standard group of muscles were evaluated for

weakness and muscle stretch reflexes (biceps, triceps, brachioradialis, knee, ankle) and perceptions to touch-pressure, vibration (128 Hz tuning fork), joint position, and pinprick perceptions were graded on index finger and great toe as normal (0), decreased (1), or absent (2). For evaluating the NIS of the lower limbs (NIS-LL), only neurologic abnormalities of the lower limb were tallied (27). In the ALADIN I study only components of the Neuropathy Disability Score (NDS) (20) were available and therefore, NIS and NIS-LL could not be computed.

Laboratory methods and adverse events

Glycosylated hemoglobin (HbA_{1c}) was determined at baseline and day 19 with the HPLC technique using a Diamat analyzing system (Bio-Rad, Munich, Germany). The normal range is <6.3% of total hemoglobin. Treatment emergent adverse events were classified on the basis of the body systems using WHO preferred terms.

Statistical analysis:

The patients' clinical characteristics and baseline neurological parameters are presented mean±SD.

Primary analysis involved a comparison of the relative differences in TSS from baseline to the end of i.v. treatment between the groups treated with α -lipoic acid or placebo. Secondary analyses included daily changes in TSS, responder rates ($\geq 50\%$ improvement in TSS), individual TSS components, Neuropathy Impairment Score (NIS), NIS of the lower limbs (NIS-LL), individual NIS-LL components, and the rates of adverse events. The aforementioned efficacy outcome measures were analyzed as ratio R of the last value divided by baseline. These ratios were considered to be lognormally distributed. (Handling of "0" was resolved by substitution of "0" by "1/15", i.e. the reciprocal of the TSS maximum.) Descriptive statistics were performed for each study separately and for the pooled data. Pooling was performed using a two-way ANOVA with study as random and

treatment as fixed factor. The point estimates for the treatment difference (i.e. for the ratio of treatment effects in the re-transformed variable) and the 2-sided 95% confidence intervals were derived from t-tests for each study separately and from ANOVAs for the pooled data. The presented “relative differences” are estimates of the effect ratios $(R_P - R_T)/R_P * 100$ (with R_P , R_T being the ratios for placebo and α -lipoic acid, respectively), indicating superiority of α -lipoic acid if >0 (and limited by 100% for a 100% treatment effect) and inferiority if <0 .

In addition, the response rates for the TSS were computed as follows: responder: ‘Yes’ ($1 - \text{last value/baseline} \geq 50\%$), i.e. more than 50% decrease in TSS from baseline, and ‘No’ ($1 - \text{last value/baseline} < 50\%$). Descriptive frequencies were given for each study separately and the pooled data. Point estimates of odds ratios and confidence intervals were computed for each study separately and the pooled data. Logistic regression using study and treatment as covariates was applied to the responder criterion. The individual components of the NIS-LL were analyzed analogously. All these analyses were based on the ITT population.

Adverse events were coded according to WHO-ART. Global incidence for treatment emergent adverse events is presented as well as the incidence for the most frequent preferred terms.

Results

The clinical characteristics and outcome measures at baseline in the pooled groups given α -lipoic acid and placebo are shown in Table 1. The variables listed were comparable between the groups.

The mean HbA_{1c} levels decreased from 8.8±1.9% at baseline to 8.5±1.7% after 3 weeks in the pooled group treated with α -lipoic acid and similarly from 8.9±1.9% at baseline to 8.6±1.7% after 3 weeks in the pooled group given placebo.

The relative differences in TSS between the groups given α -lipoic acid as compared with placebo after 3 weeks for the individual trials and the pooled data are shown in Fig. 1. Positive values indicate benefit for α -lipoic acid, while negative values are in favour of placebo. After 3 weeks the relative difference in TSS was 24.1 (13.5-33.4)% in favour of α -lipoic acid for the pooled data. Individual trial analysis indicated improvements in the TSS in favour of α -lipoic acid vs placebo in the SYDNEY, NATHAN II, and ALADIN I studies, whereas in the ALADIN III Study the point estimate was around zero.

The relative daily differences in TSS between the pooled α -lipoic acid and placebo groups are shown in Fig. 2. There was a continuous increase in the magnitude of TSS improvement in favour of α -lipoic acid vs placebo with confidence intervals excluding zero noted first after 8 days of treatment which was maintained until the end of treatment.

The responder rates in the groups given α -lipoic acid and placebo after 3 weeks are shown for the individual trials and the pooled data in Fig. 3. In all four trials the response rates were higher for α -lipoic acid than placebo, reaching statistical significance in the ALADIN I and SYDNEY trials as well as for the pooled data. The pooled response rates of 52.7% in patients treated with α -lipoic acid and 36.9% in those on placebo correspond to a number needed to treat of 6.3. As for

the relative differences, the SYDNEY Study showed the most pronounced difference between α -lipoic acid and placebo.

The pooled relative differences between α -lipoic acid and placebo at 3 weeks for the individual neuropathic symptoms and the TSS for comparison are illustrated in Fig. 4. All the individual symptoms were improved in favour of α -lipoic acid, but the CI for paraesthesiae crossed the zero line, while the remaining three symptoms did not. The greatest difference in favour of α -lipoic acid was observed for burning pain.

The relative differences in NIS between the groups given α -lipoic acid as compared with placebo after 3 weeks for the individual trials and the pooled data are shown in Fig. 5. After 3 weeks the relative difference in NIS was 17.1 (6.8-26.2)% in favour of α -lipoic acid for the pooled data. Individual trial analysis indicated improvements in NIS in favour of α -lipoic acid vs placebo in the SYDNEY Study, while in the NATHAN II and ALADIN III studies the point estimates favoured α -lipoic acid but the 95% CI crossed the vertical zero line.

The relative differences in NIS-LL between the groups given α -lipoic acid as compared with placebo after 3 weeks for the individual trials and the pooled data are illustrated in Fig. 6. After 3 weeks the relative difference in NIS-LL was 16.0 (5.7-25.2)% in favour of α -lipoic acid for the pooled data. As for NIS, individual trial analysis indicated improvements in NIS-LL in favour of α -lipoic acid vs placebo in the SYDNEY Study, while in the NATHAN II and ALADIN III studies the point estimates favoured α -lipoic acid but the 95% CI crossed the vertical zero line.

In the pooled analysis among the individual components of the NIS-LL the variables of pin-prick and touch-pressure sensations as well as ankle reflexes were improved in favour of α -lipoic acid as compared to placebo after 3 weeks (Table 2). Regarding the individual studies pin-prick sensation was improved in

SYDNEY and NATHAN II studies, while ankle reflexes were improved in the SYDNEY Study only. However, the point estimates were >1 , thus favouring α -lipoic acid, except for touch-pressure sensation in the NATHAN II Study. No differences between the pooled groups were noted for the remaining NIS-LL components (data not shown).

The percentages of treatment-emergent signs and symptoms (TESS) and most frequent TESS in preferred terms (headache and nausea) during the 3-week treatment period are listed in Table 3. TESS, headache, and nausea did not differ between the groups.

Discussion

This meta-analysis comprising 1258 diabetic patients from four controlled clinical trials demonstrates that treatment with α -lipoic acid given 600 mg i.v. per day for 3 weeks significantly reduces the chief symptoms of diabetic polyneuropathy to a clinically meaningful degree. A statistically significant difference in the Total Symptom Score (TSS) between α -lipoic acid and placebo was observed from the second week of treatment onward and was continuously increasing until the end of treatment. Treatment with α -lipoic acid i.v. also significantly improved the neuropathic deficits assessed by the Neuropathy Impairment Scores (NIS, NIS-LL) driven by improving pin-prick sensation, touch-pressure sensation, and ankle reflexes. Moreover, treatment with α -lipoic acid was associated with rates of adverse events not exceeding those of placebo.

When comparing the results of the individual trials it becomes obvious that the most prominent favourable effects α -lipoic acid on neuropathic symptoms and deficits were found in the SYDNEY Study as compared with the other three trials. There are several possible explanations for this finding. First, this study was conducted as a monocentre trial, thus eliminating the risk of inter-centre

variability. Indeed, in the ALADIN III Study which did not show a difference in TSS between α -lipoic acid and placebo, the number of participating centres was highest and there was evidence of markedly increased inter-centre variability for the TSS assessment. Second, a placebo run-in phase was included in the SYDNEY Study, thus minimising the risk of extreme placebo responses which could be excluded prior to randomisation. Once again by comparison, the placebo response was highest in the ALADIN III Study. Third, the SYDNEY Study was more rigorous due to pre-training and certification of investigators, use of reading and quality assurance of neuropathic endpoints, and use of in-patients with very few drop-outs. On the other hand, a conservative approach of excluding the SYDNEY Study from the meta-analysis did not significantly alter the beneficial effect of α -lipoic acid on the TSS (data not shown), suggesting that the SYDNEY Study has not exerted major bias in this meta-analysis.

The rapid nature of improvement in both neuropathic symptoms and deficits is of interest. The exact mechanisms are unknown, but may be related to rapid improvement in nerve blood flow mediated by the antioxidant action of the drug (11,12,21-26). In fact, i.v. infusion of 600 mg α -lipoic acid acutely accelerated time to peak capillary blood cell velocity (CBV) during postocclusive hyperaemia in patients with diabetic polyneuropathy) indicating that the drug exerts an acute effect on microcirculation (27). Impairment in the neurovascular reflex arc defined as a lacking decrease in CBV after cooling of the contralateral hand was improved with a decrease in CBV by 12.3% after 3 weeks of i.v. treatment with α -lipoic acid in diabetic patients with polyneuropathy (28). The impairment of nitric oxide (NO)-mediated vasodilation in diabetes has been attributed to increased vascular oxidative stress. At this point, acute infusion of α -lipoic acid improved NO-mediated endothelium-dependent vasodilation in diabetic patients (29). This effect was positively related to plasma levels of malondialdehyde and inversely related to

levels of ubiquinol-10, suggesting that oxidative stress contributes to endothelial dysfunction.

The magnitude of the effect of α -lipoic acid on the TSS deserves comment. 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 52.7% in patients treated with α -lipoic acid and 36.9% in those on placebo. Thus, the number needed to treat is 6.3. This number is reasonable given the considerable placebo response probably due to the subjective nature of neuropathic symptoms and the potentially high suggestive power of a daily i.v. intervention. Moreover, this number has to be seen in the light of the favourable safety profile of this drug, the relatively rapid onset of symptom reduction, the fact that not only neuropathic pain but also numbness is improved, and that not only neuropathic symptoms but also functional deficits are reduced.

Whether the favourable short-term effect of α -lipoic acid on neuropathic deficits observed in the pooled group can be translated into slowing the progression of diabetic polyneuropathy in the long term is unknown (30), but certainly this finding is encouraging given the fact that neuropathic deficits such as those shown improved herein (e.g. impaired pin-prick sensation) are major risk factors in the development of neuropathic foot ulcers (6). In conclusion, this meta-analysis including the largest sample of diabetic patients ever that have been treated with a single drug or even a class of drugs to reduce neuropathic symptoms demonstrates that treatment with α -lipoic acid (600 mg/day i.v.) over 3 weeks is superior to placebo in ameliorating both neuropathic symptoms and deficits. It is notable that this improvement is clinically meaningful, demonstrable within one week, and achieved in the absence of adverse events.

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References

1. Shaw JE, Zimmet PZ. The epidemiology of diabetic neuropathy. *Diabetes Rev* 1999; 7: 245-252.
2. Resnick HE, Vinik AI, Schwartz AV, Leveille SG, Brancati FL, Balfour J, Guralnik JM. Independent effects of peripheral nerve dysfunction on lower-extremity physical function in old age. The Women's Health and Aging Study. *Diabetes Care* 2000; 23: 1642-1647.
3. Galer BS, Gianas A, Jensen MP. Painful diabetic neuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract* 2000; 47: 123-128.
4. Forsblom CM, Sane T, Groop PH, Totterman KJ, Kallio M, Saloranta C, et al. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia* 1998; 41:1253-1262.
5. Coppini DV, Bowtell PA, Weng C, Young PJ, Sönksen PH. Showing neuropathy is related to increased mortality in diabetic patients – a survival analysis using an accelerated failure time model. *J Clin Epidemiol* 2000; 53: 519-523.
6. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJM. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care* 1998; 21: 1071-1075.
7. Ziegler D. Glycaemic control. In: Gries FA, Cameron NE, Low PA, Ziegler D, eds. *Textbook of Diabetic Neuropathy*. Stuttgart, New York: Thieme, 2003; 157-160.
8. Ziegler D, Luft D. Clinical trials for drugs against diabetic neuropathy. Can we combine scientific needs with clinical practicalities? In: Tomlinson DR, ed. *Neurobiology of diabetic neuropathy*. San Diego, CA: Elsevier Science, Academic Press, 2002; 431-463.

9. Low PA, Nickander KK, Tritschler HJ: The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. *Diabetes* 1997; 46, Suppl 2: S38-S42.
10. Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 2001; 44: 1973-1988.
11. Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritschler HT, Low PA. Lipoic acid improves nerve blood flow, reduces oxidative stress and improves distal nerve conduction in experimental diabetic neuropathy. *Diabetes Care* 1995; 18: 1160-1167.
12. Cameron NE, Cotter MA, Horrobin DH, Tritschler HJ. Effects of α -lipoic acid on neurovascular function in diabetic rats: interaction with essential fatty acids. *Diabetologia* 1998; 41: 390-399.
13. Bock E, Schneeweiss J: Ein Beitrag zur Therapie der Neuropathia diabetica. *Münchener Med. Wochenschrift* 1959; 43: 1911-1912.
14. Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schütte K, Nehrdich D, Dannehl K, Gries FA, the ALADIN Study Group: Treatment of symptomatic diabetic peripheral neuropathy with the antioxidant α -lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). *Diabetologia* 1995; 38: 1425-1433.
15. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R, and the ALADIN III Study group: Treatment of symptomatic diabetic polyneuropathy with the antioxidant α -lipoic acid. A 7-month multicenter randomized controlled trial (ALADIN III Study). *Diabetes Care* 1999; 22: 1296-1301.
16. Low PA, Dyck PJ, Ziegler D, Stokov I, Novosadova M, Samigullin R, SYDNEY Study Group. Intravenous alpha-lipoic acid improves positive neuropathic symptoms

in hospitalised diabetic patients: the SYDNEY trial. *Diabetologia* 2002; 45: Suppl 2, A334.

17. NATHAN II Study. VIATRIS GmbH, data on file.

18. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses*. *Lancet* 1999; 354: 1896-900.

19. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC: Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 1997; 49: 229-239.

20. Young MJ, Boulton AJM, Macleod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993; 36: 150-154.

21. Nickander KK, McPhee BR, Low PA, Tritschler H: Alpha-lipoic acid: antioxidant potency against lipid peroxidation of neural tissues in vitro and implications for diabetic neuropathy. *Free Rad Biol Med* 1996; 21: 631-639.

22. Mitsui Y, Schmelzer JD, Zollman PJ, Mitsui M, Tritschler HJ, Low PA. Alpha-lipoic acid provides neuroprotection from ischemia-reperfusion injury of peripheral nerve. *J Neurol Sci* 1999; 163: 11-16.

23. Coppey LJ, Gallett JS, Davidson EP, Dunlap JA, Lund DD, Yorek MA. Effect of antioxidant treatment of streptozotocin-induced diabetic rats on endoneurial blood flow, motor nerve conduction velocity, and vascular reactivity of epineurial arterioles of the sciatic nerve. *Diabetes* 2001; 50: 1927-1937.

24. Kunt T, Forst T, Wilhelm A, Tritschler H, Pfoetzner A, Harzer O, Engelbach M, Zschaebitz A, Stofft E, Beyer J. Alpha-lipoic acid reduces expression of vascular cell adhesion molecule-1 and endothelial adhesion of human monocytes after stimulation with advanced glycation end products. *Clin Sci (Lond)* 1999; 96: 75-82.

25. Borcea V, Nourooz-Zadeh J, Wolff SP, Klevesath M, Hofmann M, Ulrich H, Wahl P, Ziegler R, Tritschler H, Halliwell B, and Nawroth PP: α -Lipoic acid decreases oxidative stress even in diabetic patients with with poor glycemic control and albuminuria. *Free Radical Biology and Medicine*, 1999, 22: 1495-1500.
26. Androne L, Gavan NA, Veresiu IA, Orasan R. In vivo effect of lipoic acid on lipid peroxidation in patients with diabetic neuropathy. *In Vivo* 2000; 14: 327-330.
27. Haak E, Usadel KH, Kusterer K, Amini P, Frommeyer R, Tritschler HJ, Haak T. Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. *Exp Clin Endocrinol Diabetes* 2000; 108: 168-74.
28. Haak ES, Usadel KH, Kohleisen M, Yilmaz A, Kusterer K, Haak T. The effect of alpha-lipoic acid on the neurovascular reflex arc in patients with diabetic neuropathy assessed by capillary microscopy. *Microvasc Res* 1999; 58: 28-34.
29. Heitzer T, Finckh B, Albers S, Krohn K, Kohlschutter A, Meinertz T. Beneficial effects of alpha-lipoic acid and ascorbic acid on endothelium-dependent, nitric oxide-mediated vasodilation in diabetic patients: relation to parameters of oxidative stress. *Free Radic Biol Med* 2001; 31: 53-61.
30. Ziegler D, Reljanovic M, Mehnert H, Gries FA. α -Lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. *Exp Clin Endocrinol Diabetes* 1999; 107: 421-430.

Table 1: Baseline clinical characteristics of the pooled intention-to-treat population.

	α-Lipoic acid	Placebo
n	716	542
Sex (m/f)	367 (51.3)/349 (48.7)	286 (52.8)/256 (47.2)
Age (years)	56.3±8.3	56.9±7.8
BMI (kg/m ²)	29.3±5.2	30.1±5.5
Type 1/Type 2 diabetes	58 (8.1)/658 (91.9)	45 (8.3)/497 (91.7)
Duration of diabetes (years)	12.3±8.5	12.8±8.8
Duration of neuropathy (years)	3.6±3.9	3.7±3.5
HbA _{1c} (%)	8.8±1.9	8.9±1.9
Insulin treatment	453 (63.3)	321 (59.2)
Smokers	106 (14.8)	81 (15.0)
Retinopathy	277 (38.8)	218 (40.2)
Nephropathy	116 (16.2)	75 (13.8)
Total Symptom Score (TSS)	8.1±2.9	8.0±3.0
Neuropathy Impairment Score (NIS)	15.8±10.6 (n=639)	16.1±10.5 (n=461)
Neuropathy Impairment Score Lower Limbs (NIS-LL)	12.4±7.2 (n=639)	12.6±7.4 (n=461)

Values are mean±SD or n (%).

Table 2: Odds ratio (OR) point estimates and 95% confidence limits (CI) for three individual components of the Neuropathy Impairment Score of the lower limbs (NIS-LL).

	Pin-Prick Sensation (Great Toe) OR (95% CI)	Touch-Pressure Sensation (Great Toe) OR (95% CI)	Ankle Reflexes OR (95% CI)
ALADIN I	1.32 (0.61-2.86)	1.78 (0.87-3.65)	1.38 (0.49-3.91)
ALADIN III	1.12 (0.75-1.68)	1.22 (0.82-1.82)	1.08 (0.69-1.68)
SYDNEY	2.56 (1.13-5.80)	1.17 (0.49-2.79)	5.07 (1.36-18.88)
NATHAN II	1.65 (1.03-2.66)	0.99 (0.62-1.56)	1.70 (0.84-3.46)
<i>Meta-Analysis</i>	1.57 (1.21-2.05)	1.35 (1.05-1.75)	1.69 (1.22-2.35)

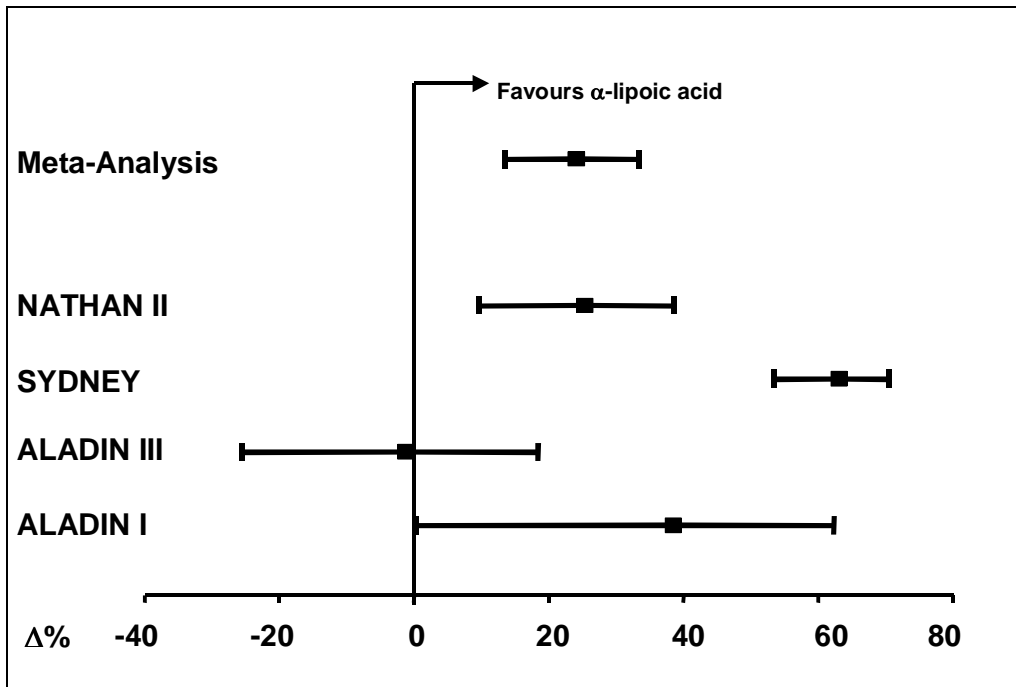
Values >1 favour α -lipoic acid

Values <1 favour placebo

Table 3: Percentages of treatment -emergent signs and symptoms (TESS) and most frequent TESS in preferred terms.

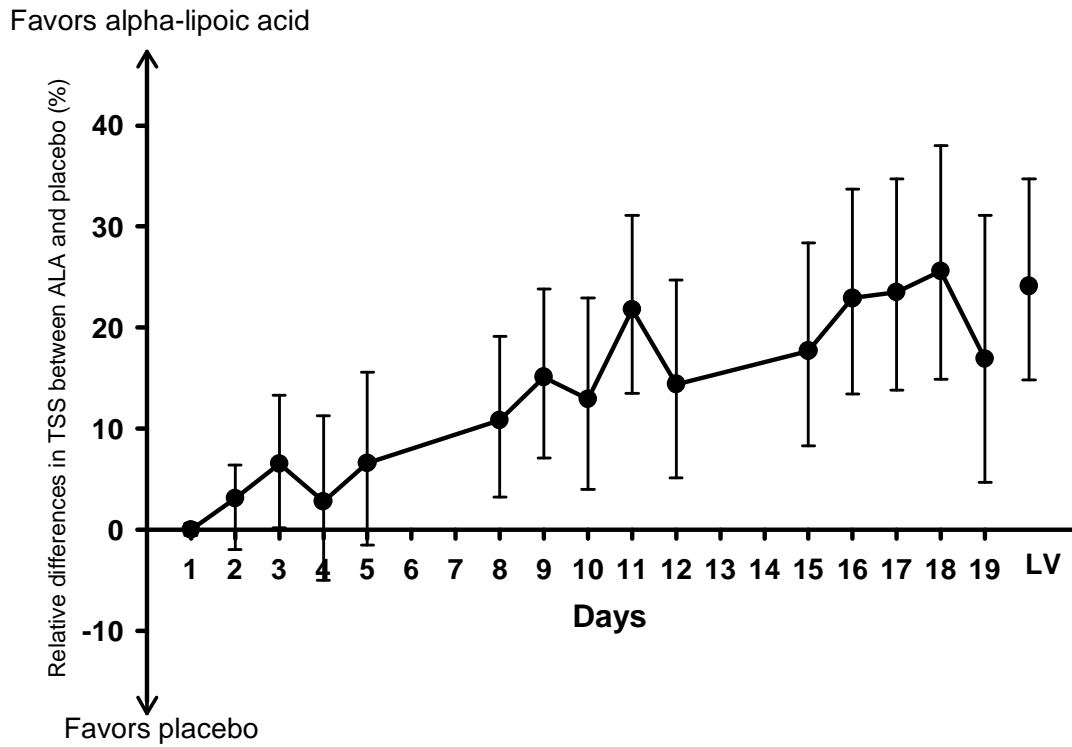
	TESS		Headache		Nausea	
	α -Lipoic Acid	Placebo	α -Lipoic Acid	Placebo	α -Lipoic Acid	Placebo
ALADIN I	18.2	19.8	7.8	8.6	2.6	1.2
ALADIN III	51.8	57.0	3.3	2.4	3.6	3.6
SYDNEY	1.7	3.3	0	0	0	0
NATHAN II	54.8	50.8	11.2	13.1	6.2	4.7
Meta-Analysis	45.0	42.8	6.1	7.7	4.1	3.3

Fig. 1: Relative differences in the Total Symptom Score (TSS) between α -lipoic acid and placebo at 3 weeks vs baseline shown for the pooled data and the four individual trials.



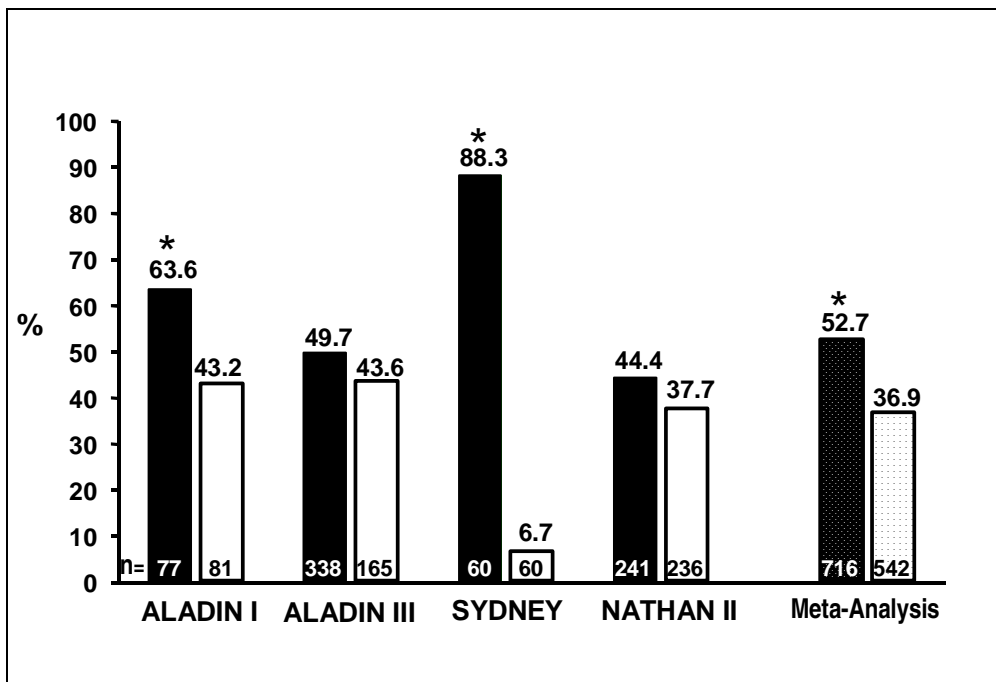
Displayed are point estimates for $\Delta\% = 1 - \text{ratio of the geometric means}$ with 95% CI. CI > 0 favours α -lipoic acid.

Fig 2: Relative daily differences in the Total Symptom Score (TSS) between α -lipoic acid and placebo.



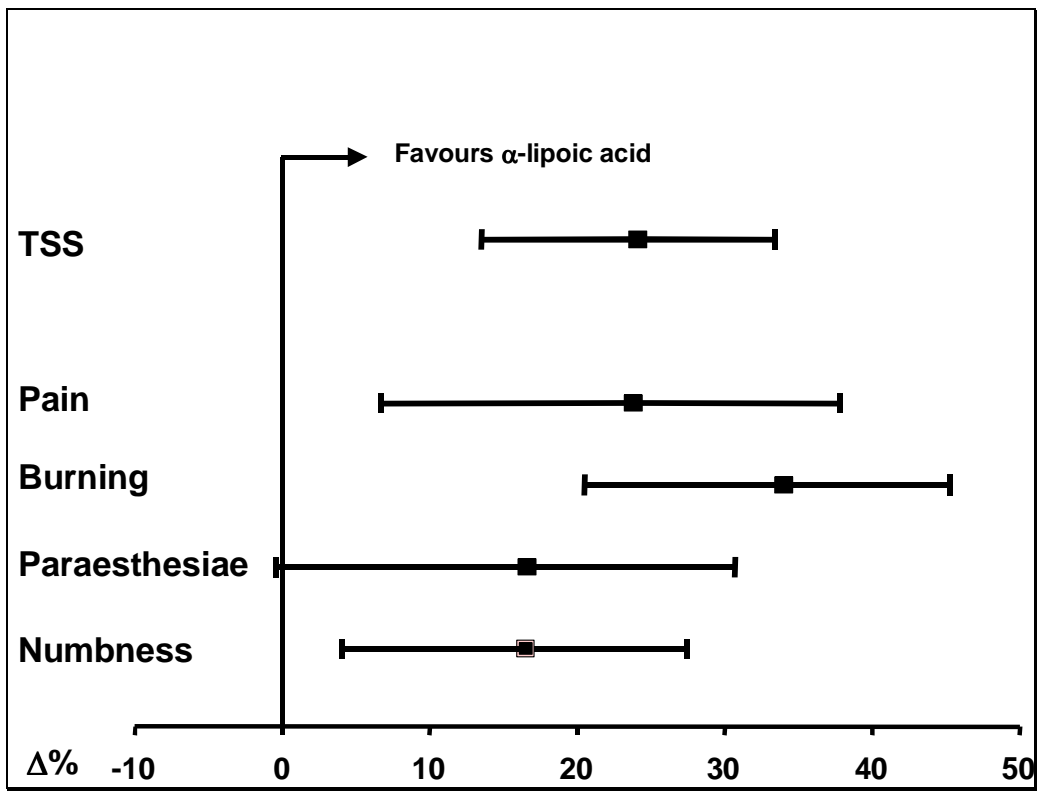
Displayed are point estimates for $\Delta\% = 1 - \text{ratio of the geometric means}$ with 95% CI; CI > 0 favours α -lipoic acid.
LV: last value

Fig. 3: Response rates for the Total Symptom Score (TSS) in the groups treated with α -lipoic acid (■) and placebo (□) at 3 weeks in the four individual trials and the pooled data.



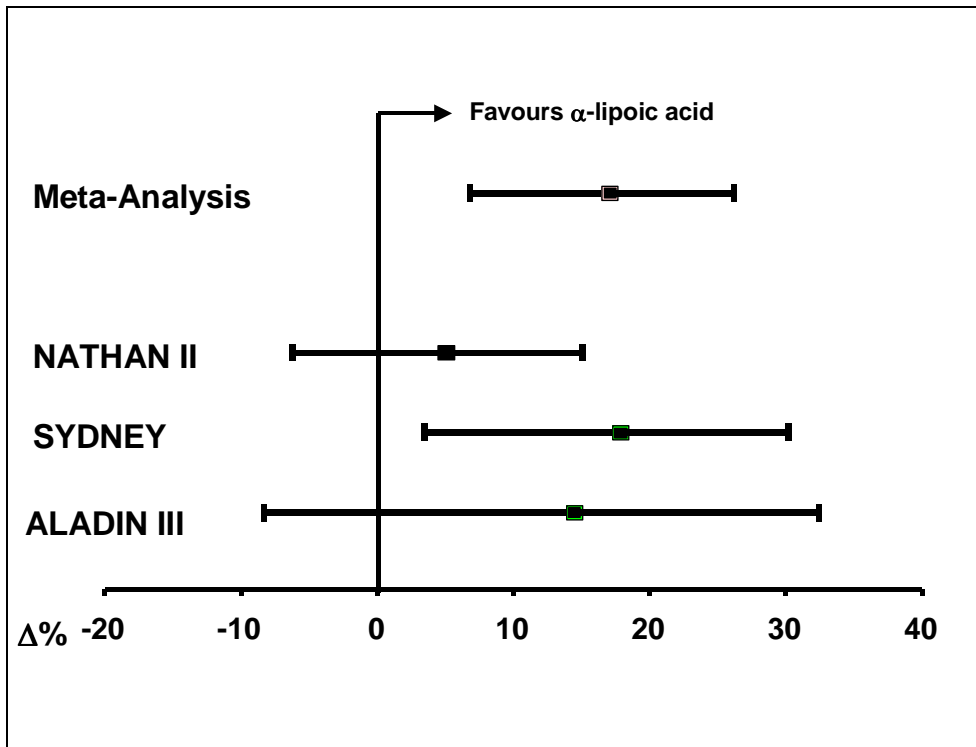
*p<0.05 for α -lipoic acid vs placebo

Fig. 4: Relative differences between α -lipoic acid and placebo at 3 weeks vs baseline in the TSS and the four individual neuropathic symptoms in the pooled groups.



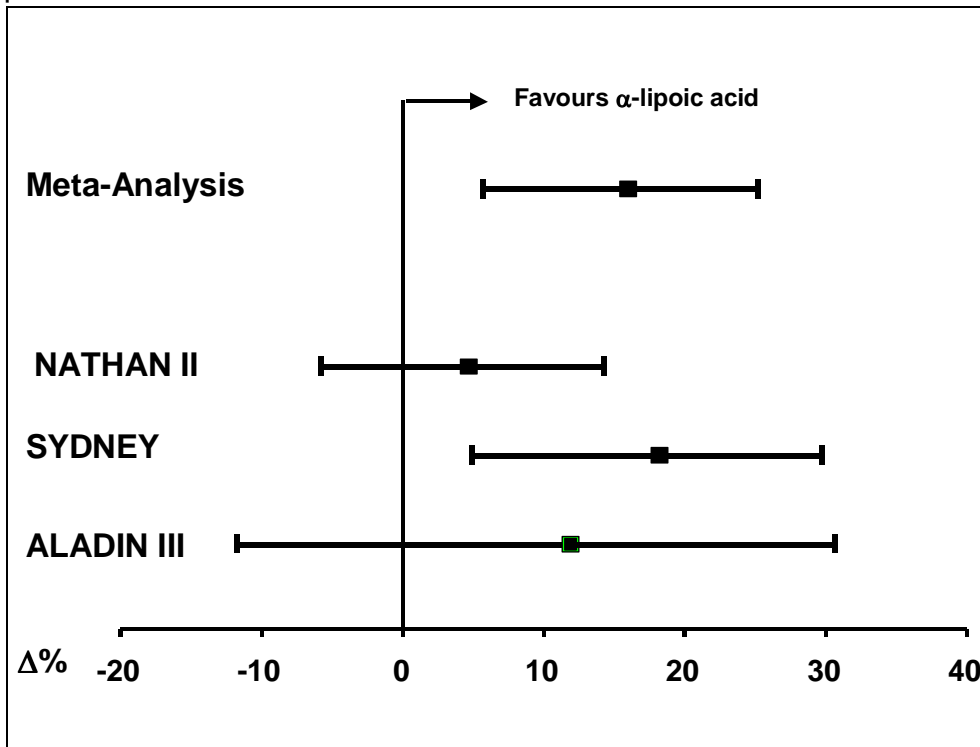
Displayed are point estimates for $\Delta\% = 1 - \text{ratio of the geometric means}$ with 95% CI; CI > 0 favours α -lipoic acid.

Fig. 5: Relative differences in the Neuropathy Impairment Score (NIS) between α -lipoic acid and placebo at 3 weeks vs baseline shown for the pooled data and three individual trials.



Displayed are point estimates for $\Delta\% = 1 - \text{ratio of the geometric means}$ with 95% CI; CI > 0 favours α -lipoic acid.

Fig. 6: Relative differences in the Neuropathy Impairment Score of the lower limbs (NIS-LL) between α -lipoic acid and placebo at 3 weeks vs baseline shown for the pooled data and three individual trials.



Displayed are point estimates for $\Delta\% = 1 - \text{ratio of the geometric means}$ with 95% CI; CI > 0 favours α -lipoic acid.