Pharmacokinetics, Tolerability, and Fructosamine-Lowering Effect of a Novel, Controlled Release Formulation of α-Lipoic Acid

Joseph L. Evans, Ph.D.[1], Catherine J. Heymann, PA-C[2], Ira D. Goldfine, M.D.[3], and Laurence A. Gavin, M.D.[2,3]

1 Medical Research Institute, San Bruno, CA 94066
Present address: Diabetes Program, Telik, Inc. South San Francisco, CA 94080

2 Northern California Diabetes Institute, Seton Medical Center, Daly City, CA 94015

3 Diabetes Research Laboratory, Mount Zion Hospital and Department of Medicine, University of California, San Francisco, CA 94143

Manuscript Accepted for Publication (In press): Endocrine Practice (2001).

Address all correspondence to:

Laurence A. Gavin, M.D.
Northern California Diabetes Institute
Seton Medical Center
1800 Sullivan Avenue, Suite 408
Daly City, CA 94015

Phone: 650.994.9771
Fax: 650.994.0341
Email: lagavin@ix.netcom.com

Running Title*:* Controlled release lipoic acid reduces fructosamine

Abstract

Objective– (1) To determine the pharmacokinetics, safety, and tolerability of a novel, controlled release oral formulation of α-lipoic acid (LA), (2) To investigate whether sustaining the concentration of LA in plasma would have a beneficial effect on glycemic control in patients with type 2 diabetes.

Methods–(a) *Pharmacokinetic Study*: A single, 600 mg dose of either controlled release LA (CRLA) or quick release LA (QRLA) was administered orally to twelve normal human subjects. The plasma profile of LA was followed for twenty-four hours post-dose, and pharmacokinetic analyses performed. (b) *Safety and Tolerability Study*: Twenty-one patients with type 2 diabetes were given 900 mg CRLA daily for six weeks, followed by 1200 mg CRLA daily for an additional six weeks. Active treatment was followed by a three-week washout period. Throughout the study, patients continued on their pre-study anti-diabetic medications which included metformin (Glucophage®), sulfonylureas (Amaryl®, Glyburide®, Glucotrol®), acarbose (Precose®), troglitazone (Rezulin™), and insulin (either as monotherapy or in combination). CRLA was evaluated for safety and tolerability, and for effects on glycemic control.

Results–The T_{max} (time to maximum plasma concentration) of LA administered as CRLA was 1.25 h, and was approximately 2.5-fold longer compared to the T_{max} for QRLA (T_{max} = 0.5 h; $P < 0.02$). No significant side effects or changes in either liver or kidney function, or hematological profiles following the

administration of CRLA were observed. In fifteen patients, plasma fructosamine was reduced from 313 ± 48.6 μM (mean ± SD) to 283 ± 48.7 μM (30.1 ± 9.7 μM; $P < 0.05$) after twelve weeks of treatment with CRLA.

Conclusions–CRLA increased the plasma concentration of LA over time in healthy subjects, and was safe, well-tolerated and significantly reduced plasma fructosamine in patients with type 2 diabetes.

Keywords: antioxidant, controlled release, diabetes, fructosamine, glucose, lipoic, lipoic acid, pharmacokinetics

Introduction

α-Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to man (1-3). LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production (4;5). When administered exogenously, LA and its reduced form, dihydrolipoic acid (DHLA), act as multifunctional antioxidants (1;2). LA has been prescribed in Germany for over thirty years for the treatment of diabetes-induced neuropathy (6-8), and results from several recent controlled clinical studies indicate that this compound is safe, well-tolerated, and efficacious (8).

In addition to the beneficial effects of LA on diabetes-induced neuropathy, several clinical studies point to an improvement in insulin sensitivity and whole-body glucose metabolism in patients with Type 2 diabetes following continuous intravenous (*i.v.*) infusion of LA (9-11). It has been reported that *i.v.* infusion of LA markedly increases insulin-mediated glucose disposal (~30-50%) (9;10), whereas oral administration of LA has only marginal effects (<20%) (12;13). Furthermore, the currently available oral forms of LA have not been reported to reduce glucose, fructosamine, or HbA_{1c} levels in patients with diabetes (12-20). It is possible that this limitation of orally administered LA might be a function of its abbreviated duration in plasma (compared to *i.v.* LA), resulting from extensive first-pass metabolism (> 50%) and/or short plasma half-life (<0.5 h) (21). In this

regard, the superior ability of *i.v.* LA to improve insulin sensitivity might be due to the ability of *i.v.* adminstration to achieve a higher plasma concentration of LA, and/or to maintain it for a longer duration. A continuous infusion (over 20 minutes) of 200 mg LA resulted in a peak plasma level of approximately 8 μg/ml, and detectable levels were still observed six hours after the start of infusion (21). In contrast, oral administration of a 200 mg tablet resulted in a peak plasma level of approximately 0.66 μg/ml, which returned baseline < 3 hours after dosing (22).

In this preliminary, open-label study, we evaluated the pharmacokinetics, safety, and tolerability of a novel, controlled release oral formulation of α-lipoic acid (LA). This formulation was designed to maintain the plasma concentration of LA over time using controlled release drug delivery technology (polymeric cellulose resins). In addition, we also investigated whether this agent would result in a beneficial impact on glucose control in patients with Type 2 diabetes. We report here that this agent was safe, well-tolerated, and significantly reduced plasma fructosamine in patients with type 2 diabetes.

Materials and Methods

Subjects and Study Design: Pharmacokinetic Study. The pharmacokinetic profile of controlled release α-lipoic acid (CRLA) was evaluated in an open-label, single-dose, randomized, two-way crossover design. The study was sponsored by Medical Research Institute (San Bruno, CA; www.lipoic.com), and conducted by

Covance Clinical Research Unit at their Madison, WI study site. Twelve healthy male volunteers received a single dose of two 300 mg tablets of either CRLA (Medical Research Institute) or three 200 mg capsules of quick release LA (QRLA; Solgar, Leonia, NJ) after an eight-hour overnight fast (23). Subjects did not eat during the first four hours after dosing. Subjects were randomly assigned to sequence 1 (QRLA then CRLA) or to sequence 2 (CRLA then QRLA), with a washout of at least 3 days between treatments. Blood samples for the determination of plasma LA levels were collected via an indwelling catheter as follows: 0 hour (pre-dose); 5, 10, 15, 20, 30, 45 minutes; and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, and 24 hours post-dose. The concentration of LA in plasma was determined by a validated, high-performance liquid chromatography assay employing fluorescence detection (24). The lower limit of quantitation of LA was 15 ng/ml, and the upper limit was 500 ng/ml. Pharmacokinetic analyses of LA were computed using WinNonlin Professional software (version 3.0, Pharsight, Inc.). Plasma assays and statistical analyses were perfomed by Covance Laboratories, Inc. (Madison, WI).

Subjects and Study Design: Safety and Tolerability Study. The safety and tolerability of CRLA was assessed along with effects on glycemic control in an open-label, longitudinal design on 21 patients with Type 2 diabetes, who acted as their own control. The study was sponsored by Medical Research Institute, and conducted by Dr. Laurence A. Gavin within his private practice setting at Seton Medical Center (Daly City, CA). To be included in the study, patients were

required be diagnosed with type 2 diabetes (C-peptide > 1.2 ng/ml), under adequate control (HbA_{1c} > 7.5% and < 10.5%), and with a disease duration < 35 years. Patients with a history of cerebrovascular disease, congestive heart failure, advanced nephropathy, diastolic blood pressure > 100 mmHg, or BMI > 35 were ineligible for enrollment.

As this study was intended primarily to assess the safety and tolerability of a new formulation, patients were permitted to continue their pre-study anti-diabetic medications concurrently to facilitate patient recruitment. These medications included metformin (Glucophage®, Bristol-Myers Squibb, Princeton, NJ), sulfonylureas (Amaryl® and Glyburide®, Hoechst Marion Roussel, Kansas City, MO; Glucotrol®, Pfizer, New York, NY), acarbose (Precose®, Bayer, West Haven, CT), troglitazone (Rezulin™, Warner-Lambert, Morris Plains, NJ; withdrawn from market), and/or insulin. No dose change in these medications was made during the run-in period or during the course of the study.

The baseline clinical characteristics of the patients are shown in Table 1. The mean HbA_{1c} level (%) was 8.2 ± 1.5. Following a run-in period of two weeks, patients received 12 weeks of active treatment of CRLA. The agent was administered as 900 mg daily (2 x 300 mg tablets 30 minutes before breakfast and 1 x 300 tablet 30 minutes before dinner) for 6 weeks, followed by 1200 mg daily (2 x 300 mg tablets before breakfast and 1 x 300 tablet before both lunch and dinner) for 6 weeks. A three-week washout period followed active treatment.

Patients were monitored on a regular basis for glucose and lipid control, liver enzymes, along with other clinical markers including physical examination, vital signs, and adverse experience queries.

Six patients were not included in the final statistical analyses. These exclusions were made blinded to results. Four patients were excluded due to their recurring failure (≥ 3 instances) to adhere to their allocated diets. Diet was judged initially acceptable if it provided sufficient caloric intake to maintain body weight, and caloric distribution approximating the following: 50-60% carbohydrate, <30% fat, and 15-20% protein. Diets were evaluated at the beginning of the run-in phase, and monitored on a regular basis throughout the study. Failure to adhere was judged to have occurred if carbohydrate, fat, and/or total caloric intake grossly exceeded (>150%) a patient's usual weekly intake based on patient interviews. One patient was excluded due to premature withdrawal due to a recurring illness not considered related to study medication, and one patient was excluded from analyses due to repeated missed laboratory values. Glucose, HbA_{1C}, clinical chemistry and hematology assays, and lipid panels were performed in the clinical laboratory at Seton Medical Center. Fructosamine and C-peptide assays were performed at Specialty Laboratories, Inc. (Santa Monica, CA). Intra- and inter-assay coefficients of variation were ≤ 5%.

Ethics. The protocols for the pharmacokinetic study and the safety and tolerability study protocol were approved by the Institutional Review Boards of Covance and the Seton Medical Center, respectively. For both trials, each subject was informed about the purpose and risks of the study, and had given their written consent to participate. The studies were conducted in accordance with US Title 21 Code of Federal Regulations commonly known as Good Clinical Practices (GCPs), which are consistent with the Declaration of Helsinki. CRLA is a commercially available, non-prescription product (see below) regulated by the US Dietary Supplement Health and Education Act (DSHEA), and did not require Investigational New Drug (IND) approval prior to the initiation of these clinical studies.

Controlled Release α-Lipoic Acid (CRLA). LA used in the formulation of CRLA was purchased from Antibioticos SA (Rodano, Italy). This material is of the highest purity commercially available (> 99.0%), and produced in accordance with current Good Manufacturing Practices (cGMPs). CRLA tablets were formulated and manufactured for Medical Research Institute in the US in accordance with cGMPs. CRLA is currently manufactured and distributed (since 1999) in the US by Medical Research Institute under the trade name of Glucotize™. The proprietary nature of CRLA is protected under US Patents #6,191,162 and 6,197,340, and additional patents are pending.

Results

Clinical Trial 1: Pharmacokinetic Study in Healthy Individuals

The mean plasma concentration profile of LA following oral dosing is shown in Figure 1. The median T_{max} (time to maximum plasma concentration) for QRLA was 0.5 hours (range 0.25-1.5 h), which is indicative of rapid absorption with respect to LA. In comparison, the median T_{max} for CRLA was 1.25 hours (range 0.5-4.5 h), representing a 2.5 fold increase ($P < 0.02$; ANOVA). For C_{max} (maximum observed plasma concentration), mean values (± SD) of 6675 ± 3703 ng/ml and 1793 ± 742 and were determined for the QRLA and CRLA treatments, respectively ($P < 0.002$; ANOVA). The mean ratio of C_{max} for CRLA treatment to QRLA treatment was 27%, and is reflective of the decrease in C_{max} typically observed in controlled release formulations. The maximum plasma concentration of 1793 ng/ml achieved by a single-dose administration of 600 mg of CRLA corresponds to approximately 10 μM. This plasma concentration persisted for approximately 2.5 hours after dosing (Figure 1). For AUC_{0-24} (area under the plasma concentration-time curve from hours 0 to 24), mean values of 4466 ±1157 and 2621 ± 385 and ng • h/ml were determined for the QRLA and CRLA treatments, respectively ($P < 0.0001$; ANOVA). The mean ratio of AUC_{0-24} for CRLA treatment to QRLA treatment was ~60%, and suggests a reduction in overall bioavailability of the CRLA formulation compared to QRLA. The mean terminal elimination half-life ($T_{½}$; time required for concentration in plasma to decline to one-half initial concentration, or rate of elimination) was 0.5 ± 0.61

hours for QRLA and 0.4 ± 0.22 hours for CRLA ($P < 0.39$). These values were not significantly different, presumably due to high inter-subject variability following treatment with QRLA.

Clinical Trial 2: Safety and Tolerability Study in Individuals with Type 2 Diabetes

There were no significant side effects reported following the administration of CRLA to patients with type 2 diabetes. Two patients reported a slight metallic taste following the dose increase to 1200 mg/day, but this effect was transient and did not require either individual to withdraw from the study. There were no significant changes in liver enzymes, liver or kidney function, or hematological profiles (data not shown). Thus, CRLA was well tolerated and safe at daily doses of 900 mg for six weeks followed by 1200 mg for six weeks.

CRLA exhibited a significant effect with regard to the reduction of plasma fructosamine. At baseline, the mean plasma fructosamine was 313 ± 48.6 μM (SEM; n = 15), and after six weeks of treatment was 307 ± 43.0 μM ($P < 0.465$; Figure 2). At this point, the dose of CRLA was increased to 1200 mg/day. After three weeks on the higher dose, the mean plasma fructosamine was reduced to 275 ± 42.6 μM ($P < 0.033$; Figure 2). At the completion of active treatment (twelve weeks), the mean plasma fructosamine was 283 ± 48.7 μM ($P < 0.05$; Figure 2), corresponding to an overall mean decrease from baseline of 30.1 ± 9.7 μM. After a three-week washout, the mean plasma fructosamine rose to 304 ± 56.8 μM ($P < 0.454$; Figure 2). No significant changes were observed in either

fasting plasma glucose or HbA_{1c}. At baseline, fasting plasma glucose and HbA_{1c} were 157 ± 34 mg/dl and 8.2 ± 1.5 % (mean ± SD), respectively. At the completion of active treatment (twelve weeks), fasting plasma glucose and HbA_{1c} were 168 ± 36.5 mg/dl ($P < 0.37$) and 8.2 ± 0.84 % ($P < 0.94$), respectively. A trend toward a reduction in C-peptide was observed. At baseline, the mean plasma C-peptide was 5.0 ± 3.8 ng/ml and after twelve weeks of treatment fell to 4.2 ± 2.8 ng/ml (Table 1). The overall mean decease from baseline was 0.84 ± 0.72 ng/ml ($p < 0.26$). No significant changes were observed in triglycerides, total, high-density, or low-density lipoprotein cholesterol, body weight, or body mass index following treatment (Table 1).

Discussion

This is the first report of the development, use, and clinical assessment of a controlled release formulation of LA. This approach was initiated and pursued to test the hypothesis that limitations of the current oral QRLA with respect to effects on insulin sensitivity and metabolic control (compared to *i.v.* infusion) might be a function of the abbreviated duration for which LA is maintained in plasma.

Using controlled release drug delivery technology, the T_{max} of LA was increased approximately 2.5-fold (1.25 hours for CRLA vs. 0.5 hours for QRLA), reflecting the slower release of LA from the formulation matrix. Importantly, the

plasma concentration of LA remained level for several hours in the controlled release formulation, whereas it fell more rapidly when delivered in quick release capsules. The therapeutic implication of maintaining LA in plasma for a longer duration than can be achieved with typical oral QRLA is suggested by the clinical benefit of LA on whole-body insulin sensitivity when administered by *i.v.* infusion (9-11).

CRLA exhibited decreased a C_{max} compared to QRLA. This is also a formulation effect, since controlled release formulations are designed to reduce C_{max} (25). The reason for the observed decrease in overall bioavailability of the CRLA (judged by lower a AUC) compared to QRLA is unknown. It is possible that there was a difference in the rate or extent of absorption of the two formulations. It cannot be determined from this study if the controlled release matrix constituents affected the absorption of LA. Another possibility is that the slower release of the CRLA promoted more extensive first-pass hepatic metabolism. The $T_{1/2}$ value was not significantly different between the two formulations. This suggests that the increased duration of CRLA was due to controlled plasma delivery as opposed to a decrease in the actual rate of elimination. The $T_{1/2}$ of the QRLA capsules used here is in good agreement with that reported for enteric-coated tablets (21).

At doses of 900 mg/day for six weeks followed by 1200 mg/day for six weeks, CRLA was well tolerated, and did not produce any significant changes in

liver enzymes, liver or kidney function, or hematological profiles. No serious side effects were observed. These results are in good agreement with the long history of safety and tolerability of LA, whether administered by *i.v.* infusion or orally (8). It cannot be determined from this study whether CRLA interacted with other medications, although no subject required an adjustment in dose of their concurrent medication. To assess the potential for drug-drug interaction between CRLA and other anti-diabetic medications, more systematic studies would be required. A recent study has found that co-administration of single oral doses of QRLA and glibenclamide, or QRLA and acarbose did not result in drug-drug interactions (26).

With respect to glycemic control, CRLA produced a reduction of plasma fructosamine, an effect that was statistically significant at weeks nine and twelve. This corresponds to weeks three and six following dose escalation to 1200 mg CRLA per day. At the completion of active treatment, the decrease in fructosamine from baseline was 30 μm, corresponding to an approximate 10% overall reduction. Following a three-week washout period, fructosamine increased towards the baseline value. This finding provides preliminary support for our hypothesis that maintaining the level of LA in plasma over time might result in an overall improvement in glycemic control.

The decrease in fructosamine was observed in the absence of a reduction in fasting plasma glucose. The reason for this is unknown, and will have to be

addressed in future studies in which post-prandial glucose levels are also taken. The decrease in fructosamine was also observed in the absence of a reduction in HbA_{1c}. This might be attributable to the abbreviated duration of treatment at the effective 1200 mg dose (6 weeks total exposure), and/or statistical power too limited to detect a significant change, especially in light of the degree of variability of HbA_{1c} at baseline. A larger double-blind, placebo-controlled study of longer duration would be required to address this question. In conclusion, in this preliminary open-label study, CRLA increased the plasma concentration of LA over time in healthy subjects, and was safe, well-tolerated and significantly reduced plasma fructosamine in patients with type 2 diabetes. Although encouraging, these preliminary results need to be confirmed in a larger, double-blind, placebo-controlled study in which HbA_{1c} is the primary endpoint. If this goal is achieved, CRLA may emerge as a new, adjunctive, anti-diabetic treatment agent.

Acknowledgements

Dr. L. A. Gavin was supported by funding from Medical Research Institute (San Bruno, CA). Dr. I. D. Goldfine was supported in part by the Jay Gershow Fund. We are grateful to Dr. Peter Havel (University of CA, Davis) for his helpful comments, suggestions, and critical review of the manuscript during its preparation. Statistical analyses of the pharmacokinetic data were expertly performed by Dr. Guhan Balan (Covance, Inc.), and statistical analyses of the safety and metabolic data were expertly performed by Dr. Yu-Kun Chiang (San Jose, CA).

Abbreviations: ANOVA, analysis of variance**;** AUC**,** area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; CRLA, controlled release α-lipoic acid; DHLA, dihydrolipoic acid; HbA_{1c}, glycated hemoglobin; LA, α-lipoic acid; QRLA, quick release α-lipoic acid; T_{max}, time to maximum plasma concentration; $T_{1/2}$, terminal phase elimination half-life

References

1. **Packer L, Witt EH, Tritschler HJ** 1995 alpha-Lipoic acid as a biological antioxidant. Free Radic Biol Med 19:227-250

2. **Packer L, Witt EH, Tritschler HJ** 1998 Antioxidant properties and clinical applications of alpha-lipoic acid and dihydrolipoic acid. In: Cadenas E, Packer L (eds) Handbook of antioxidants.Dekker, New York545-591

3. **Fuchs J, Packer, L, Zimmer, G eds.** *Lipoic Acid in Health and Disease*: 1st ed. New York: Marcel Dekker. 1997.

4. **Reed LJ, DeBusk BG, Gunsalus IC, Hornberger JrCS** 1951 Crystalline α-lipoic acid: a catalytic agent associated with pyruvate dehydrogenase. Science 114:93-94

5. **Biewenga GP, Haenen GR, Bast A** 1997 The pharmacology of the antioxidant lipoic acid. Gen Pharmacol 29:315-331

6. **Biewenga G, Haenen GR, Bast A** 1997 The role of lipoic acid in the treatment of diabetic polyneuropathy. Drug Metab Rev 29:1025-1054

7. **Ziegler D, Gries FA** 1997 Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. Diabetes 46 Suppl 2:S62-S66

8. **Ziegler D, Reljanovic M, Mehnert H, Gries FA** 1999 Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. Exp Clin Endocrinol Diabetes 107:421-430

9. **Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, Jung WI, Augustin HJ, Dietze GJ** 1995 Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneimittel-Forschung 45:872-874

10. **Jacob S, Henriksen EJ, Tritschler HJ, Augustin HJ, Dietze GJ** 1996 Improvement of insulin-stimulated glucose-disposal in type 2 diabetes after repeated parenteral administration of thioctic acid. Exp Clin Endocrinol Diabetes 104:284-288

11. **Evans JL, Goldfine ID** 2000 α-Lipoic acid: a multi-functional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. Diabetes Technol Therap 2:401-413

12. **Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, Rett K** 1999 Oral administration of RAC-alpha-

lipoic acid modulates insulin sensitivity in patients with type 2 diabetes mellitus: a placebo-controlled pilot trial. Free Radic Biol Med 27:309-314

13. **Konrad T, Vicini P, Kusterer K, Hoflich A, Assadkhani A, Bohles HJ, Sewell A, Tritschler HJ, Cobelli C, Usadel KH** 1999 Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. Diabetes Care 22:280-287

14. **Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Moller W, Tritschler HJ, Mehnert H** 1999 Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radic Res 31:171-179

15. **Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, Kerum G, Malessa R** 1999 Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetes Care 22:1296-1301

16. **Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G** 1997 Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). Deutsche Kardiale Autonome Neuropathie. Diabetes Care 20:369-373

17. **Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte K, Nehrdich D, Tritschler HJ, Mehnert H, Ziegler D** 1999 Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. Diabet Med 16:1040-1043

18. **Borcea V, Nourooz-Zadeh J, Wolff SP, Klevesath M, Hofmann M, Urich H, Wahl P, Ziegler R, Tritschler H, Halliwell B, Nawroth PP** 1999 alpha-Lipoic acid decreases oxidative stress even in diabetic patients with poor glycemic control and albuminuria. Free Radic Biol Med 26:1495-1500

19. **Androne L, Gavan NA, Veresiu IA, Orasan R** 2000 In vivo effect of lipoic acid on lipid peroxidation in patients with diabetic neuropathy. In Vivo 14:327-330

20. **Haak E, Usadel KH, Kusterer K, Amini P, Frommeyer R, Tritschler HJ, Haak T** 2000 Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. Exp Clin Endocrinol Diabetes 108:168-174

21. **Hermann R, Niebch G, Borbe HO, Fieger-Buschges H, Ruus P, Nowak H, Riethmuller-Winzen H, Peukert M, Blume H** 1996 Enantioselective

pharmacokinetics and bioavailability of different racemic alpha-lipoic formulations in healthy volunteers. Eur J Pharm Sci 4:167-174

22. **Teichert J, Kern J, Tritschler HJ, Ulrich H, Preiss R** 1998 Investigations on the pharmacokinetics of alpha-lipoic acid in healthy volunteers. Int J Clin Pharmacol Ther 36:625-628

23. **Gleiter CH, Schug BS, Hermann R, Elze M, Blume HH, Gundert-Remy U** 1996 Influence of food intake on the bioavailability of thioctic acid enantiomers. Eur J Clin Pharmacol 50:513-514

24. **Niebch G, Buchele B, Blome J, Grieb S, Brandt G, Kampa P, Raffel HH, Locher M, Borbe HO, Nubert I, Fleischhauer I** 1997 Enantioselective high-performance liquid chromatography assay of (+)R- and (-)S-alpha-lipoic acid in human plasma. Chirality 9:32-36

25. **Fix J** Oral drug delivery. In: Mathiowitz E, ed. *Encyclopedia of Controlled Drug Delivery* (Vol. 2): 1st ed. New York: Wiley, 1999: 698-728

26. **Gleiter CH, Schreeb KH, Freudenthaler S, Thomas M, Elze M, Fieger-Buschges H, Potthast H, Schneider E, Schug BS, Blume HH, Hermann R** 1999 Lack of interaction between thioctic acid, glibenclamide and acarbose. Br J Clin Pharmacol 48:819-825

27. **Breithaupt-Grogler K, Niebch G, Schneider E, Erb K, Hermann R, Blume HH, Schug BS, Belz GG** 1999 Dose-proportionality of oral thioctic acid - coincidence of assessments via pooled plasma and individual data. Eur J Pharm Sci 8:57-65

Figure Legends

Figure 1. α-Lipoic acid concentration in plasma following single oral dose. Mean plasma concentration of quick release LA (QRLA) and controlled release LA (CRLA) in twelve healthy subjects after a single oral dose of 600 mg. For each formulation, plasma lipoic acid levels returned to baseline levels by 6 hours. Several data points that correspond to plasma values < 10 ng/ml are not shown in this plot. No error bars are shown for clarity, and since the statistical evaluation of these data is indicated in the text (*See Results: Clinical Trail 1*).

Figure 2. Effect of controlled release α-lipoic acid (CRLA) on plasma fructosamine in patients with Type 2 diabetes. Plasma fructosamine concentrations (mean ± SD; n = 15) during twelve-week active treatment and three-week washout phase. Initial dose of CRLA was 900 mg/day; dose was increased to 1200 mg/day after week six. *P* values are from paired *t*-test *vs.* baseline. Statistical significance was accepted at $P < 0.05$.

Table 1. Clinical Characteristics of Study Subjects at Baseline, During, and After Treatment

Characteristics	Baseline	Week 6	Week 12	Week 15 (Washout)	Δ Week 12 *vs.* Baseline (*P*-value)
n	21	--	--	--	--
Age (years)	61 ± 11.1	--	--	--	--
Male, n (%)	9 (42.9%)	--	--	--	--
Diabetes Duration (years)	11 ± 8.1	--	--	--	--
Height (in)	67 ± 4.7	--	--	--	--
Weight (lb)	195 ± 37.2	199 ± 40.0	193 ± 32.2	197 ± 35.6	-2.4 ± 12.7 (0.60)
Body Mass Index (kg/m^2)	31.1 ± 4.7	31.2 ± 4.9	30.2 ± 4.6	30.9 ± 4.8	-0.9 ± 2.8 (0.35)
HbA_{1c} (%)	8.2 ± 1.5	8.4 ± 0.6	8.2 ± 0.8	8.0 ± 0.7	0.03 ± 0.4 (0.94)
Fructosamine (μM)	313 ± 48.6	307 ± 43.0	283 ± 48.7*	304 ± 56.8	-30.1 ± 9.7 (0.05)
Fasting glucose (mg/dl)	157 ± 34.0	174 ± 41.4	168 ± 36.5	150 ± 46.9	10.4 ± 11.3 (0.37)
Fasting C-peptide (ng/ml)	5.0 ± 3.8	4.6 ± 2.7	4.2 ± 2.8	5.0 ± 3.2	-0.84 ± 0.7 (0.26)
Triglycerides (mg/dl)	222 ± 109	213 ± 123	218 ± 124	240 ± 164	-4.4 ± 20.5 (0.84)
Cholesterol (mg/dl)	180 ± 42.6	185 ± 29.5	187 ± 33.9	190 ± 35.7	6.4 ± 7.7 (0.42)
HDL Cholesterol (mg/dl)	43.4 ± 9.2	43.2 ± 10.8	41.9 ± 8.2	46.3 ± 11.6	-1.57 ± 1.7 (0.38)
LDL Cholesterol (mg/dl)	94.5 ± 38.5	103 ± 30.1	105 ± 34.3	101 ± 40	10.9 ± 5.7 (0.08)
VLDL Cholesterol (mg/dl)	41 ± 18.2	34.3 ± 14.0	38.8 ± 17.3	38.7 ± 21.4	-2.23 ± 4.2 (0.60)
Blood Pressure (mm Hg)					
Systolic	123 ± 11.1	122 ± 16.0	128 ± 14.7	134 ± 19.7	4.27 ± 3.6 (0.26)
Diastolic	74.1 ± 7.3	68.0 ± 9.5	72.3 ± 10.3	73.5 ± 10.0	-1.86 ± 3.0 (0.55)

* $P < 0.05$ (paired *t*-test *vs.* baseline). Values represent mean ± SD except for Δ Week 12 *vs.* Baseline, which is mean ± SEM.

Figures

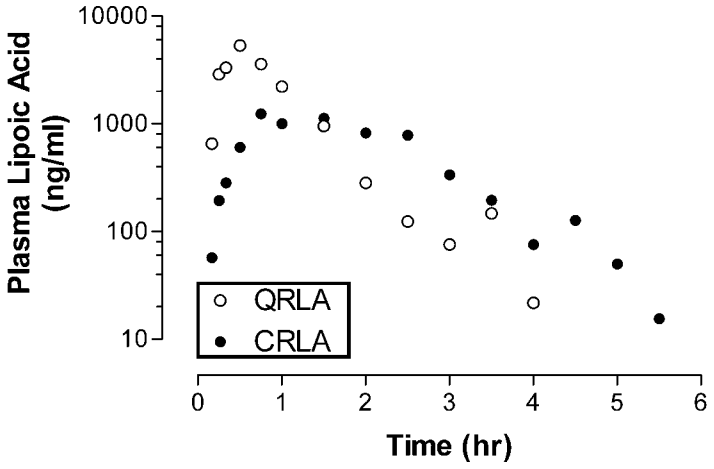

Figure 1

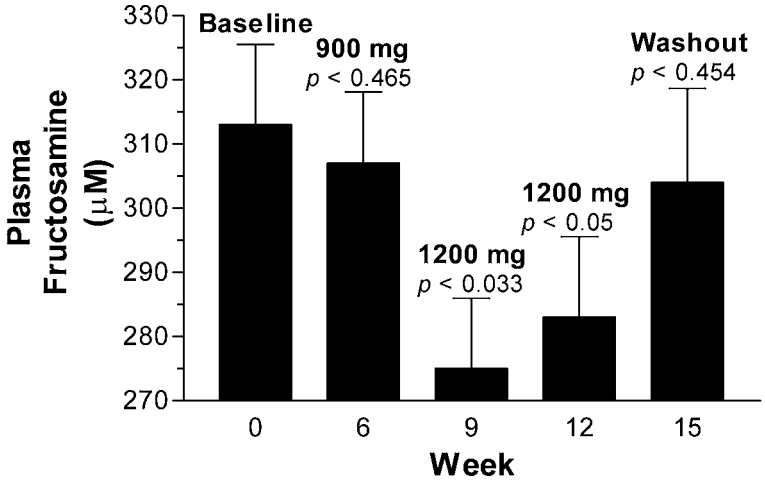

Figure 2