Evaluating the Efficacy of DiaMetrix™ in a Randomized, Double-Blind Placebo Controlled Human Clinical Trial

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ABSTRACT

Background: People with diabetes are at high risk of cardiac complications, which are exacerbated by elevated blood pressure and dysfunctional sugar and fat metabolism. The aim of this study was to evaluate effects of an herbal supplement, DiaMetrix, on blood glucose levels, triglycerides, cholesterol, and blood pressure in subjects with chronic uncontrolled blood glucose.

Methods: We did a randomized prospective double-blinded study in 100 subjects (47 men and 53 women) with fasting blood glucose levels between 160 and 240 mg/dL. The participants were randomly assigned to oral DiaMetrix at 6 tablets daily (n=50) or placebo (n=50) for 90 days. The endpoints included fasting blood glucose, body mass, oral glucose tolerance test, total cholesterol, HDL, triglycerides, glycosylated hemoglobin and blood pressure.

Results: All study participants completed the study. DiaMetrix reduced HbA1c, blood glucose (fasting and after challenge), triglycerides, systolic and diastolic blood pressure, total cholesterol, and body mass over time. Mean fasting glucose was significantly decreased in subjects taking DiaMetrix at 30, 60 and 90 days after baseline relative to those taking placebo. HbA1c mean change from baseline to 90 days was significantly decreased in subjects taking DiaMetrix. The DiaMetrix mean serum glucose was significantly decreased relative to placebo at 30, 120 and 180 minutes after the challenge. Triglycerides mean changes from baseline were significantly decreased by

DiaMetrix at 30, 60 and 90 days. For total cholesterol, DiaMetrix mean change from baseline to 90 days was significantly decreased relative to placebo. High and low density lipoproteins were not significantly affected. Systolic and diastolic blood pressure was significantly decreased at 60-90 days, and mean body mass was significantly decreased relative to placebo at 90 days.

Conclusions: This study demonstrated a reduction in the mean fasting blood sugar, blood pressure and body mass in subjects randomized to DiaMetrix. These findings of suggest that DiaMetrix, an over-the counter preparation, deserves further evaluation of its activity in larger clinical studies.

Introduction

Based on the data from the 2007 National Diabetes Fact Sheet published by the American Diabetes Association, 23.6 million children and adults in the United States (7.8% of the population) have diabetes and 1.6 million new cases of diabetes are diagnosed in people aged 20 years and older each year (*1*). In 2003-2004, there were an estimated 5.7 million people with undiagnosed diabetes and 57 million in a pre-diabetes state in the United States (*2*). In the latter, blood glucose levels known as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) are in the range of 100-125 mg/dL, while higher levels are associated type 2 diabetes mellitus, now increasingly recognized as an autoimmune-inflammatory disease (*2*). Notably, people with pre-diabetes are at increased risk of developing type 2 diabetes, a condition characterized by impaired insulin secretion from pancreatic Langerhans islands cells, increased hepatic glucose production and in consequence high blood glucose levels, and decreased use of glucose in muscle tissue. These defects are mainly responsible for the development and progression of type 2 diabetes (*3*). Furthermore, insulin resistance is associated with decreased rates of glycolysis, glycogenesis, lipogenesis, and protein synthesis. People with type 2 diabetes are also at high risk of fatal and non-fatal vascular events. In 2003–2004, 75% of adults with self-reported diabetes had elevated blood pressure of $\geq$ 130/80 mm Hg or used prescription medications for hypertension. Intensive control of glycemia decreases some vascular complications such as retinopathy and nephropathy (*4*).

DiaMetrix™ is an herbal dietary supplement composed of vitamin C (ascorbic acid), biotin USP, chromium (chelate), vanadium (chelate), garcinia cambogia extract (50% hydroxycitric acid), gymnema sylvestre extract (25%), cinnamon extract (4:1), bitter melon extract (10:1), betaine HCL, banaba extract (1% corosolic acid), fennugreek, dicalcium phosphate, cellulose, croscarmellose sodium, stearic acid, silicon dioxide, magnesium stearate, and hydroxypropyl methylcellulose.

Another recently completed study compared the activity of DiaMetrix to that of three anti-diabetic drugs; Metformin, Actos (pioglitazone hydrochloride), and Byetta (exenatide) in an obese diabetic mouse model using BKS.Cg-m+/+Lepr^{db}/BomTac female mice fed either normal diet or high fat diet (HFD) +/- drugs. DiaMetrix's protection against organ damage was comparable to that of Byetta and better than Actos and Metformin in the animals on normal diet. The mean values of most inflammatory plasma biomarkers were elevated in high fat diet relative to normal diet. Biomarker means varied significantly by treatment group and diet. On normal diet, DiaMetrix decreased levels of a number of pro-inflammatory cytokines, chemokines and growth factors such as eotaxin, MCP-1, MCP-3, M-CSF, and increased anti-inflammatory cytokine IL-4 relative to untreated. DiaMetrix treatment decreased G-CSF, GM-CSF, and TGFβ relative to untreated in high fat animals. Pyruvate kinase and AGE increased, while insulin was decreased in animals treated with DiaMetrix relative to untreated on normal diet. DiaMetrix demonstrated superior anti-inflammatory activity relative to the commonly used anti-diabetic drugs against a background of genetic obesity, supporting

the contention that DiaMetrix may be an effective intervention for type-2 diabetes (Hampshire *et al*., submitted).

The goal of this clinical study was to assess the efficacy of DiaMetrix treatment in diabetic subjects with fasting blood glucose levels between 160 and 240 mg/dL and to evaluate effects of oral DiaMetrix on clinical endpoints used in the routine evaluation of diabetic subjects. Safety data was not collected.

METHODS

Subjects

SyntraTech contracted the clinical study with a contract research organization, Fenestra Research Laboratories (Fenestra), Las Vegas, NV. Fenestra also conducted the tests as described below. In 2006-2007, Fenestra recruited 47 men and 53 women ages 23 to 50 (33 Black, 32 Caucasian, 25 Asian and 10 Hispanic) using participants recruited from a large diverse population of people living in or near the Las Vegas, NV area, with chronic uncontrolled blood glucose (people with fasting blood glucose levels between 160 mg/dL and 240 mg/dL with a mean of 197 mg/dL).

Excluded were subjects with a history of head trauma, serious diseases or illness diagnosed at this time, known moderate to severe renal insufficiency, recent history (<6 months prior to Visit 1) of myocardial infarction. Also excluded were those who regularly used oxygen therapy, those with known active tuberculosis, with treated basal

cell carcinoma, history of cancer within the last 5 years, thoracotomy with pulmonary resection within 1 year prior to the trial, those in a pulmonary rehabilitation program or who completed a pulmonary rehabilitation program in the 6 weeks prior to the screening visit (Visit 1), taking prescribed diuretic medications, cardiac stimulants, or any other prescribed or non-prescribed medication that might alter testing results, those taking opiate analgesics prescribed or otherwise obtained for any treatment reason including migraine treatment, or for recreation and history of drug addiction or alcohol addiction within six (5) months of this study period, females who were pregnant, lactating, or nursing or who may become pregnant during the course of the study, and those diagnosed as HIV-positive, diagnosed with AIDS, or with any neuromuscular condition including CP, MS, ALS, or Huntington's Chorea. Also excluded were people with uncontrolled hypertension (e.g. BP>140/90), or any condition not previously named that, in the opinion of Fenestra investigators or intake staff, would jeopardize safety or affect the validity of the results collected in this study.

The study included females or males 18 years of age or older, who signed a written informed consent. To be eligible for inclusion, potential subjects were required to document blood sugar imbalance for a minimum of the previous consecutive 6 months of the screening visit at a frequency of at least twenty (20) times each month based on daily glucometer readings. Eligible participants were randomized into two groups of 50 participants. The study was double blinded.

Compliance to inclusion and exclusion criteria was monitored and maintained through bi-weekly phone calls with Fenestra personnel and in-person office visits. All participants were instructed to contact their regular healthcare professional if they had any unusual or uncomfortable symptoms during the course of this study. All participants were instructed to make no changes to their daily activity or consumption of food or liquid relating to the amount, volume, or type consumed.

Procedures

Participants in both treatment groups, DiaMetrix and placebo (vegetarian tablet, magnesium citrate, silicon dioxide), were instructed to take two tablets three times daily, or three tablets two times daily if only two meals, approximately 15 minutes before meals. Participants were instructed to take product only if they ate a meal. Participants who met all inclusion criteria and none of the exclusion criteria at the first visit (day 0) and gave signed informed consent were then provided either the placebo or DiaMetrix™ along with instructions describing daily dosing to follow for the duration of the study. Baseline measurements were made at day 1 (visit 2). Following screening (day 0), randomization, and signed informed consent, participants entered a 1-week baseline period. In that time, participants were asked to refrain from taking any unnecessary over-the-counter or prescription medications, or natural products that they were not already taking for the remainder of the study. Ibuprofen, acetaminophen, and aspirin were allowed. At the third and fourth visits (days 14 and 30) evaluations were performed following standard procedures and the inclusion and exclusion criteria were

again reviewed with each participant on an individual basis. The fifth visit took place on day 60 and the sixth and final visit on day 90.

At the screen and prior to randomization, 14 of the participants reported mild headaches and "not feeling well". All 100 study participants were attempting to control their glucose levels with diet and exercise. Diet and exercise were not monitored during the study, but all participants were instructed to make no changes in their diet, activities, or water intake during the duration of the study at the screening and at subsequent visits.

Tests

The tests briefly described below were performed by Fenestra using standard clinical procedures.

Fasting Blood Glucose: Approximately 7 mL of venous blood was collected from each participant at each blood draw and fasting blood glucose was measured.

Body Mass: Body mass (lbs) was recorded on all participants at all 6 visits using a monthly calibrated weight scale.

Glucose Challenge: Each participant's fasting blood glucose (FBG) level was measured at baseline (day 2). For the oral glucose tolerance test (OGTT), all participants were given a test tablet (half of the participants were given active product and half of the

participants were given placebo), followed by a standard 75 g carbohydrate load drink. Blood plasma readings were taken at 30 minute, 120 minute, and 180 minute intervals.

Total Cholesterol: Participant's blood was taken after a 12-14 hour fasting period. Participants were asked to abstain from alcohol for at least 24 hours before 5-19 ml of arterial blood was drawn.

Lipoproteins: LDL levels were calculated by subtracting HDL readings plus one fifth of the triglycerides from the total cholesterol. LDL=Total cholesterol-(HDL+Triglycerides/5).

Triglycerides: The blood test was performed on fasting (12-14 hour) participants. Participants were asked to abstain from any alcohol for 24 hours before the test. Five to 10 mL of venous blood was drawn from each participant at each test interval.

Blood Pressure: Blood pressure was taken by medical professionals with a minimum of 20 years experience using a sphygmomanometer and stethoscope. Blood pressure measurements were taken an average of three times after a minimum rest of at least 15 minutes.

Hemoglobin A1c (HbA1c, Glycohemoglobin, Glycated hemoglobin, Glycosylated hemoglobin): Blood was drawn on Day 1 and Day 90. An arterial blood sample was obtained by inserting a needle into an artery of the participant's arm and a standard HbA1c vial of blood was collected by a healthcare professional.

Statistical methods

Continuously distributed outcomes were summarized with the mean ± one standard deviation. Treatment groups (DiaMetrix, Placebo) were contrasted on the mean of continuously distributed outcomes using repeated measures linear models of the

outcome in terms of time, treatment group, and the time by treatment group interaction with an autoregressive order 1 autocorrelation matrix. All statistical testing was 2-sided with a significance level of 5%. R Version 2.11.1 (R Foundation) was used throughout; tables were created using SAS Version 9.2 for Windows (SAS Institute, Cary, NC).

RESULTS

All participants completed the study; there were no missing data.

Demographic Characteristics: Treatment groups were similar with regard to the proportion male [DiaMetrix 22 (44%), Placebo 25 (50%)] and mean age (DiaMetrix 43.5±12.7, Placebo 45.8±10.8, p=0.32) and the percentage of subjects of the white race was significantly decreased among those randomized to DiaMetrix (DiaMetrix 24 (48%), Placebo 37 (74%), p=0.01); see Table 1.

Fasting Serum Glucose: Treatment group fasting glucose means (ng/dL), shown in Table 2 and Figure 2, were similar at baseline (DiaMetrix 196.6±17.5, Placebo 196.9±17.4, p=0.93) whereas the DiaMetrix mean (14 days: DiaMetrix 96.6±10.3, Placebo 205.5±30.7, p<0.001; 30 days: DiaMetrix 96.5±11.0, Placebo 204.9±21.6, p<0.001; 60 days: DiaMetrix 94.8±10.1, Placebo 209.4±22.5, p<0.001; 90 days: DiaMetrix 89.4±9.2, Placebo 205.2±20.2, p<0.001) and mean changes from baseline (DiaMetrix -107.2±14.5, Placebo 8.3±14.8, p<0.001) were significantly decreased at 90 days.

HbA1c (%): Treatment group HbA1c (%) means (Table 2) were similar at baseline (DiaMetrix 7.7±0.5, Placebo 7.7±0.5; p=0.93) whereas the mean at 90 days (DiaMetrix

4.7±0.3, Placebo 8±0.6, p<0.001) and the mean change from baseline to 90 days (DiaMetrix -3.0±0.5, Placebo 0.3±0.4, p<0.001) were significantly decreased in subjects taking DiaMetrix. At 90 days, no subject who received DiaMetrix had an HbA1c above 5%. In contrast, at 90 days no subject who received Placebo had an HbA1c below 6.9%.

Glucose Challenge Test (ng/dL): The DiaMetrix mean serum glucose (Table 2) was significantly decreased relative to placebo at 30, 120 and 180 minutes after the challenge (30 minutes: DiaMetrix 110.1±24.1, Placebo 205.1±18.5, p<0.001; 120 minutes: DiaMetrix 110.0±23.0, Placebo 221.9±14.6, p<0.001; 180 minutes: DiaMetrix 109.5±23.3, Placebo 225.8±12.6, p<0.001).

Triglycerides: Treatment group triglycerides means (mg/dl), see Table 2 and Figure 1, were similar at baseline (DiaMetrix 255.2±48.1, Placebo 254.5±46.5, p=0.95) whereas the DiaMetrix mean (30 days: DiaMetrix 234.6±50.2, Placebo 259.3±45.4, p=0.01; 60 days: DiaMetrix 213.9±44.4, Placebo 269.6±48.1, p<0.001; 90 days: DiaMetrix 203.2±42.4, Placebo 271.3±48.3, p<0.001) and mean changes from baseline (90 days: DiaMetrix -52.0±23.7, Placebo 16.8±28.6, p<0.001) were significantly decreased at 90 days.

Total Cholesterol: The DiaMetrix mean Cholesterol (µg/dL), see Table 2, was significantly increased at baseline relative to placebo (DiaMetrix: 338.5±96.9, Placebo: 301.3±89.4, p=0.01). The treatment group Cholesterol means did not differ significantly at 90 days (90 days: DiaMetrix 240.0±32.8, Placebo 261.2±29.2, p=0.13) whereas the DiaMetrix mean change from baseline was significantly decreased relative to placebo

(changes from baseline to 90 days: DiaMetrix -98.5±110.0, Placebo -40.1±99.6, p=0.004).

High Density Lipoproteins (HDL): The DiaMetrix mean HLDL (µg/dL), see Table 2, did not differ significantly from the placebo mean at baseline (DiaMetrix: 56.8±29.8, Placebo: 57.3±29.8, p=0.93) or at 90 days (90 days: DiaMetrix 47.7±9.3, Placebo 52.6±10.5, p=0.28; changes from baseline to 90 days: DiaMetrix -9.0±33.6, Placebo -4.7±35.0, p=0.45).

Low Density Lipoproteins (LDL): The DiaMetrix mean LDL (mg/dL), shown in Table 2, was significantly increased at baseline relative to placebo (DiaMetrix: 230.7±106.9, Placebo: 193.2±87.2, p=0.01) whereas the treatment group LDL means and mean changes in LDL did not differ significantly at 90 days (90 days: DiaMetrix 151.7±33.5, Placebo 154.4±30.3, p=0.86; changes from baseline to 90 days: DiaMetrix -79.0±120.8, Placebo -38±94.9, p=0.11).

Ratio Of Total Cholesterol To High Density Lipoproteins: The DiaMetrix mean ratio of total cholesterol to high density lipoproteins (Table 2) did not differ significantly from the placebo mean at baseline (DiaMetrix: 8.5±5.9, Placebo: 7.2±5.1, p=0.10) or at 90 days (90 days: DiaMetrix 5.3±1.5, Placebo 5.1±1.1, p=0.88).

Ratio Of Low Density Lipoproteins To High Density Lipoproteins: The DiaMetrix mean ratio of total cholesterol to high density lipoproteins (Table 2) did not differ significantly from the placebo mean at baseline (DiaMetrix: 6.2±5.2, Placebo: 4.9±4.3, p=0.06) or at 90 days (90 days: DiaMetrix 3.4±1.3, Placebo 3.1±0.9, p=0.65).

Systolic Blood Pressure: The DiaMetrix systolic blood pressure mean (Table 2) was significantly increased relative to placebo at baseline (Baseline: DiaMetrix 171.3±19.9, Placebo 155.2±25.1, p<0.001), whereas the treatment group means were not significantly different at 30 and 60 days (30 days: DiaMetrix 157.9±25.9, Placebo 154.2±21.4, p=0.37; 60 days: DiaMetrix 149.7±16.3, Placebo 155.4±19.4, p=0.16) and the DiaMetrix mean was significantly decreased at 90 days (90 days: DiaMetrix 142.9±14.6, Placebo 155.2±18.9, p=0.003). Analyses on changes from baseline showed significantly decreased mean changes from baseline to 90 (p<0.001) days in subjects randomized to DiaMetrix.

Diastolic Blood Pressure: Treatment group diastolic blood pressure means (mm Hg), see Table 2 and Figure 3, were similar at baseline and at 30 days (Baseline: DiaMetrix 75.2±9.9, Placebo 76.0±8.7, p=0.55; 30 days: DiaMetrix 74.5±6.4, Placebo 75.5±6.9, p=0.44), whereas the DiaMetrix mean was significantly decrease at 60 and 90 days (60 days: DiaMetrix 71.9±4.3, Placebo 76.7±5.7, p=0.001; 90 days: DiaMetrix 70.3±3.2, Placebo 76.6±5.2, p<0.001). The mean change from baseline to 90 days was significantly decreased in subjects randomized to DiaMetrix (p<0.001).

Body Mass: The DiaMetrix mean body mass (lb), see Table 2, was not significantly different from the placebo mean at baseline (DiaMetrix: 211.4±54.7, Placebo: 211.6±53.6, p=0.99). The treatment group weight means did not differ significantly at 90 days (90 days: DiaMetrix 202.1±54.0, Placebo 211.6±52.8, p=0.38) whereas the DiaMetrix mean change from baseline was significantly decreased relative to placebo (changes from baseline to 90 days: DiaMetrix -9.3±3.1, Placebo 0.0±2.9, p<0.001).

Discussion

This study in subjects with pre-diabetes and diabetes demonstrated statistically significant effects of DiaMetrix on fasting glucose level and the glucose challenge test, HbA1c, and blood pressure. Total cholesterol was decreased but LDL and HDL were not significantly affected. With respect to body mass, DiaMetrix treatment group mean change from baseline was significantly decreased relative to placebo.

Based on the magnitude of clinical responses, DiaMetrix compared favorably to standard therapeutics used in treatment of diabetes. Metformin is one of the oldest anti-diabetes drugs and was claimed to "lower the blood sugar to minimum physiological limit" in treated patients. Based on its favorable toxicity profile it was widely used but was approved by the U.S. Food and Drug Administration for type 2 diabetes in 1994 (6). Median HbA1c was 7.4% in the Metformin group compared with 8.0% in the conventional group, and intensive glucose control with Metformin decreased the risk of diabetes related endpoints in overweight diabetic patients, and was associated with less weight gain (6). Pioglitazone (Actos), a drug in the thiazolidinedione family, selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and modulates the transcription of

insulin-responsive genes involved in the control of glucose and lipid metabolism (7). Actos significantly decreased fasting plasma glucose level from 11.0+/-2.0 mmol/liter to 8.9+/-1.1 mmol/liter with a significant improvement in the hemoglobin HbA1c level from 9.2+/-1.8% to 8.3+/-1.5% (*11*). Rosiglitazone, another thiazolidinedione oral antidiabetic agent, has been shown to significantly reduce HbA1c and fasting plasma glucose under different dosing regimens (8). Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. It displays biological properties similar to human glucagon-like peptide-1 through regulation of glucose metabolism and insulin secretion but its mechanism of action is still under study [2]. A 52-week treatment with exenatide reduced HBA1C by −0.8 ± 0.1% (9).

At present, the management of type 2 diabetes focuses on glucose control through lowering of blood glucose and by extension HbA1c and other advanced glycation end products (*3*). In our opinion, these clinical endpoints are symptoms of disease, not disease mechanisms. Persistent high blood sugar in people is a problem; however, even with perfect glucose control people still suffer from significant organ pathologies, morbidity and mortality. Drugs that are designed to control blood sugar have many liabilities such as induction of hypoglycemia. Thus the commonly accepted emphasis on controlling blood sugar as a sole endpoint may be somewhat misguided in that blood sugar level is only one of the multiple facets of diabetes. We feel that more emphasis should be placed on control of the immune dysfunction that is a major biochemical driver of the pathology of diabetes. Therefore, understanding how drugs impact

inflammatory biomarker profiles will be extremely important in understanding and treating diabetes. We propose that the optimal therapeutic strategy for diabetes should address not only blood sugar control, but also be directed to control of immune system imbalance in a effort to delay disease progression (*3*).

Given that type 2 diabetes is fundamentally an inflammatory disease (*2*), in our recent *in vivo* study in a model of human type 2 diabetes in obese mice, we selected a broad range of endpoints to evaluate mechanism of action of DiaMetrix. In addition to commonly tested metabolites (glucose, advanced glycation end product, insulin, cholesterol, triglycerides), we included pyruvate kinase, hexokinase II, and citrate as potentially relevant endpoints along with a large panel of cytokines, chemokines, endocrine markers and growth factors and have shown that of DiaMetrix significantly downregulated several pro-inflammatory chemokines, cytokines, and growth factors and upregulated levels of the anti-inflammatory cytokine IL-4. We speculate that DiaMetrix may break the self reinforcing inflammatory cycle and thus slow down the natural course of the disease (Hampshire *et al*., submitted).

In conclusion, this study demonstrated a reduction in the mean fasting blood sugar, blood pressure and body mass in subjects randomized to DiaMetrix. These findings suggest that DiaMetrix, an over-the counter preparation, deserves further evaluation of its activity in larger clinical studies.

Competing interests

KRH, SM, and RM are owners of SyntraTech.

EI, RTS, JM, and CL are consultants for SyntraTech.

Authors' contributions

KRH, SM, and RM funded the study and analysis of the clinical data.

JM and CL performed statistical analysis of the clinical data.

EI, JM and RTS reviewed the results and wrote the manuscript.

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DiaMetrix Human Study (14 October 2010)

Table 1. Demographics

	Syntra-5 (N=50)	Placebo (N=50)	Total	P-Value
Male [N (%)]	22 (44)	25 (50)	47 (47)	0.69[1]
White [N (%)]	24 (48)	37 (74)	61 (61)	0.01[1]
Age (Mean ± SD)	43.48±12.68	45.82±10.77	44.65±12	0.32[2]

[1]Pearson's Chi Square Test
[2]F Test for treatment

DiaMetrix Human Study (14 October 2010)

Table 2. Blood Chemistry

Outcome (Mean ± SD)	Time	DiaMetrix - (N=50)	Placebo (N=50)	Total	P-Value
High Density Lipoprotein (?g/?L)	Baseline	56.8±29.8	57.3±29.8	57±30	0.93[1]
	Day 90	47.7±9.3	52.6±10.5	50.1±10	0.28[2]
	Change from Baseline to Day 90	-9±33.6	-4.7±35	-6.9±34	0.45[2]
Low Density Lipoprotein (?g/?L)	Baseline	230.7±106.9	193.2±87.2	212±99	0.01[1]
	Day 90	151.7±33.5	154.4±30.3	153±32	0.86[2]
	Change from Baseline to Day 90	-79±120.8	-38.8±94.9	-58.9±110	0.11[2]
Ratio of Low Density Lipoprotein to High Density Lipoproteins	Baseline	6.2±5.2	4.9±4.3	5.6±5	0.06[1]
	Day 90	3.4±1.3	3.1±0.9	3.2±1	0.65[2]
Systolic Blood Pressure (mm Hg)	Baseline	171.3±19.9	155.2±25.1	163.2±24	< 0.001[1]
	Day 30	157.9±25.9	154.2±21.4	156±24	0.37[2]
	Day 60	149.7±16.3	155.4±19.4	152.6±18	0.16[2]
	Day 90	142.9±14.6	155.2±18.9	149±18	0.003[2]
	Change from Baseline to Day 90	-28.4±17.1	0±10.5	-14.2±20	< 0.001[2]
Diastolic Blood Pressure (mm Hg)	Baseline	75.2±9.9	76±8.7	75.6±9	0.55[1]
	Day 30	74.5±6.4	75.5±6.9	75±7	0.44[2]
	Day 60	71.9±4.3	76.7±5.7	74.3±6	0.001[2]
	Day 90	70.3±3.2	76.6±5.2	73.5±5	< 0.001[2]
	Change from Baseline to Day 90	-4.9±9	0.7±6.5	-2.1±8	< 0.001[2]
Weight (lbs)	Baseline	211.4±54.7	211.6±53.6	211.5±54	0.99[1]
	Day 90	202.1±54	211.6±52.8	206.8±53	0.38[2]
	Change from Baseline to Day 90	-9.3±3.1	0±2.9	-4.6±6	< 0.001[2]

[1]F Test for treatment
[2]F Test for treatment based on a repeated measures ANOVA in terms of treatment, time and treatment by time and an AR(1) correlation structure (treatment by time interaction: p-value < 0.001).

DiaMetrix Human Study (14 October 2010)

Table 2. Blood Chemistry

Outcome (Mean ± SD)	Time	DiaMetrix (N=50)	Placebo (N=50)	Total	P-Value
Fasting Serum Glucose (mg/dL)	Baseline	196.6±17.5	196.9±17.4	196.8±17	0.93[1]
	Day 14	96.6±10.3	205.5±30.7	151.1±59	< 0.001[2]
	Day 30	96.5±11	204.9±21.6	150.7±57	< 0.001[2]
	Day 60	94.8±10.1	209.4±22.5	152.1±60	< 0.001[2]
	Day 90	89.4±9.2	205.2±20.2	147.3±60	< 0.001[2]
	Change from Baseline to Day 90	-107.2±14.5	8.3±14.8	-49.5±60	< 0.001[2]
A1c (%)	Baseline	7.7±0.5	7.7±0.5	7.7±0.01	0.93[1]
	Day 90	4.7±0.3	8±0.6	6.3±2	< 0.001[2]
	Change from Baseline to Day 90	-3±0.5	0.3±0.4	-1.4±2	< 0.001[2]
Serum Glucose (mg/dL)	Minute 30	110.1±24.1	205.1±18.5	157.6±52	< 0.001[1]
	Minute 120	110±23	221.9±14.6	165.9±59	< 0.001[2]
	Minute 180	109.5±23.3	225.8±12.6	167.6±61	< 0.001[2]
Triglycerides (mg/dL)	Baseline	255.2±48.1	254.5±46.5	254.9±47	0.95[1]
	Day 30	234.6±50.2	259.3±45.4	247±49	0.01[2]
	Day 60	213.9±44.4	269.6±48.1	241.7±54	< 0.001[2]
	Day 90	203.2±42.4	271.3±48.3	237.2±57	< 0.001[2]
	Change from Baseline to Day 90	-52±23.7	16.8±28.6	-17.6±43	< 0.001[2]
Cholesterol (?g/?L)	Baseline	338.5±96.9	301.3±89.4	319.9±95	0.01[1]
	Day 90	240±32.8	261.2±29.2	250.6±33	0.13[2]
	Change from Baseline to Day 90	-98.5±110	-40.1±99.6	-69.3±108	0.004[2]
Ratio of Cholesterols to High Density Lipoproteins	Baseline	8.5±5.9	7.2±5.1	7.8±6	0.10[1]
	Day 90	5.3±1.5	5.1±1.1	5.2±1	0.88[2]

[1]F Test for treatment
[2]F Test for treatment based on a repeated measures ANOVA in terms of treatment, time and treatment by time and an AR(1) correlation structure (treatment by time interaction: p-value < 0.001).

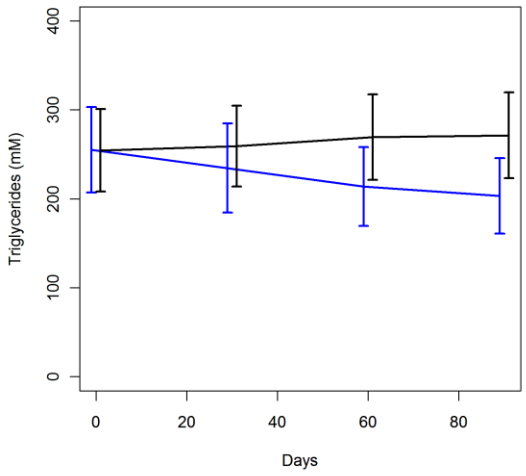

Figure 1 Mean triglycerides (mM) by treatment group (Blue: DiaMetrix, Black: Placebo); whiskers extend to the mean ±1 standard deviation. The treatment by time interaction was significant ($p < 0.001$); treatment group contrasts on the mean were significant at 30 ($p=0.01$), 60 ($p<0.001$) and 90 days ($p<0.001$) based on a repeated measures linear model with an autoregressive order 1 covariance assumption.

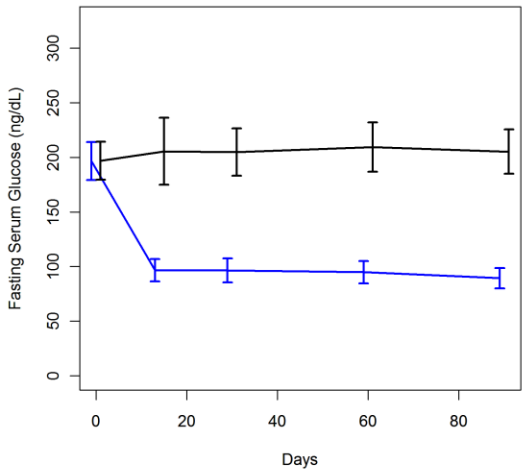

Figure 2 Mean fasting serum glucose(ng/dl) by treatment group (Blue: DiaMetrix, Black: Placebo); whiskers extend to the mean±1 standard deviation. The treatment by time interaction was significant ($p<0.001$); treatment group contrasts on the mean were significant at 14 ($p<0.001$), 30 ($p<0.001$), 60 ($p<0.001$) and 90 days ($p<0.001$) based on a repeated measures linear model with an autoregressive order 1 covariance assumption.

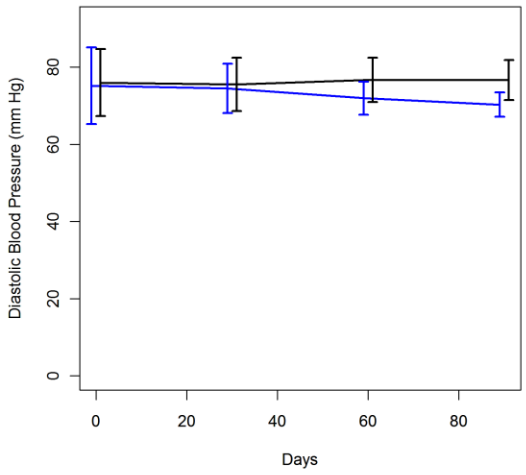

Figure 3 Mean diastolic blood pressure (mmHg) by treatment group (Blue: DiaMetrix, Black: Placebo); whiskers extend to the mean±1 standard deviation. The treatment by time interaction was significant ($p<0.001$); treatment group contrasts on the mean were significant at 60 ($p<0.001$) and 90 days ($p<0.001$) based on a repeated measures linear model with an autoregressive order 1 covariance assumption.