

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Topiramate Controlled-Release in the Treatment of Obese, Type 2 Diabetic Patients[†]

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Running Title: Topiramate in obese diabetic patients

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[†] This report describes an investigational use of topiramate. Topiramate is not approved in any country for the treatment of obesity or diabetes.

ABSTRACT

OBJECTIVE: This is a randomized, placebo-controlled study of the weight loss efficacy and safety of a controlled-release (CR) formulation of topiramate in overweight and obese patients with type 2 diabetes, treated with diet and exercise alone, or in combination with metformin.

RESEARCH DESIGN AND METHODS: Patients with type 2 diabetes, BMI ≥ 27 , with HbA_{1c} $>6.5\%$ and $<11.0\%$, treated with diet and exercise alone or in combination with metformin monotherapy were enrolled. Patients were randomized to placebo or topiramate CR titrated up to 175 mg/d. Treatment consisted of a 7-week titration phase followed by a 9-week maintenance phase.

RESULTS: A total of 111 subjects were randomized and analyzed. By the end of week 16, patients in the placebo and topiramate groups lost 2.5 kg and 6.0 kg, which represented 2.3% and 5.8%, respectively, of their baseline body weight ($P < 0.001$ vs placebo). HbA_{1c} improved from a baseline of 7.4% in the placebo and 7.6% in the topiramate groups to 7.1% and 6.7% respectively, representing a 0.4%, and 0.9% reduction from baseline ($P < 0.001$ vs. placebo). Topiramate also significantly reduced blood pressure and urinary albumin excretion. Adverse events were predominantly neuropsychiatric, or central and peripheral nervous system-related.

CONCLUSION: Topiramate CR treatment produced significant weight loss and meaningful improvements in HbA_{1c} and blood pressure in obese patients with type 2 diabetes mellitus treated with diet and exercise or in combination with metformin. However, the CNS and psychiatric adverse event profile of topiramate CR makes it unsuitable for the treatment of obesity and diabetes.

The study has been registered at www.ClinicalTrials.gov, identifier NCT00231647.

Obesity and weight gain are major factors for type 2 diabetes (1,2), and nearly 90% of the population with type 2 diabetes is considered overweight or obese (**Error! Reference source not found.**). Weight reduction can significantly improve multiple parameters of metabolic control (4).

Topiramate has been approved in many countries for the treatment of seizure disorders and the prophylaxis of migraine headaches (5). Weight loss was incidentally but consistently observed in most of the studies in these neurologic indications, despite no specific dietary interventions. Recently reported placebo-controlled trials performed in nondiabetic and diabetic populations have shown that treatment with topiramate (immediate release formulation dosed twice daily) can induce significant weight loss (6-11). The controlled release (CR) formulation of topiramate that utilizes an osmotic pump technology was developed to deliver once daily dosing with improved tolerability (12).

This study aimed to evaluate the efficacy and safety of topiramate CR as a pharmacological adjunct in patients with type 2 diabetes treated with diet and exercise, alone or in combination with metformin.

RESEARCH DESIGN AND METHODS

The study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC (Raritan, NJ) and. The study was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice and approved by Ethics Committees at all sites. All patients provided full written informed consent prior to enrollment.

Patients

This study was performed at 22 outpatient clinical centers in the United States which enrolled obese patients with type 2 diabetes, treated with diet and exercise alone or in combination with metformin. Eligible patients had BMI between 27 and 50 kg/m², HbA_{1c} 6.5%-11.0%, and fasting plasma glucose 7.0-13.3 mmol/L. Patients were excluded if they had uncontrolled hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >100 mmHg), diabetic microvascular complications, severe recurrent hypoglycemic episodes, any condition likely to affect body weight, clinically significant hepatic or renal disease, personal or family history of kidney stones, history of neuropsychiatric disorder or CNS condition, including neuropsychiatric disorders diagnosed at screening using an abbreviated 11-item Diagnostic Interview Schedule (DIS) (13). In addition, Patients using medication expected to influence weight, glycemic control, or using psychotropic medication were also excluded. Patients receiving any anti-diabetic medication, other than a stable dose of metformin, were excluded. Patients with changes in lipid or anti-hypertensive medications within 2 months of the study were also excluded.

Study design

This study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. There was a 1-week screening phase, and eligible patients were randomized to placebo or topiramate treatment and entered a 7-week titration phase followed by a 9 week maintenance phase, a 2-week taper, and a 2-week follow-up phase. Randomization used an interactive voice

response system, with a computer-generated randomization schedule. Patients were stratified by concomitant metformin monotherapy and study center. Treatment assignment was blinded to the investigators, study site staff and patients.

Nonpharmacologic treatment. Patients were instructed to follow a nonpharmacologic lifestyle intervention program (Pathways to Change[®], Johnson & Johnson Healthcare Systems, Inc., Piscataway, NJ) for the duration of the study, including the follow-up period. The program consisted of an individualized 600 kcal deficit diabetic diet, a behavioral modification program, and a physical activity program.

Pharmacologic treatment. Eligible patients were randomized to placebo or topiramate CR 175 mg/d. Patients randomized to topiramate had their dosage titrated upward by 25 mg/d each week over a 7-week period and then continued on the 175 mg/d dose during the maintenance phase. On study completion or early withdrawal, study drug was tapered over 2 weeks, and a final assessment was performed after a 2-week off-drug follow-up period. After the first week of the study, a single reduction to the next lower dose in a double-blind manner was allowed if patients experienced intolerable adverse events. Patients on topiramate doses of 100 mg/d or higher were down-titrated to 75 mg/d. Patients on topiramate doses of 75 and 50 mg/d were down-titrated to 50 and 25 mg/d, respectively, and patients on topiramate 25 mg/d were withdrawn from the study. Placebo dose adjustments were done similarly.

Assessments. Weight was measured using calibrated scales. Blood pressure was measured with a wall-mounted sphygmomanometer and

assessed as the mean of 3 sitting measurements taken after 5 minutes' rest. Other measurements included lipid profile, C-reactive protein and adiponectin. Oral glucose tolerance tests (75 g) were administered at baseline and at the end of the maintenance phase (Week 16) with blood samples taken at 30 and 120 minutes for the measurement of plasma glucose, insulin, and C-peptide levels. A homeostatic model assessment (HOMA) was utilized to derive estimates of beta-cell function and insulin sensitivity (14). Urinary albumin/creatinine ratio was measured from a random single void urine collection. Adverse events were reported either spontaneously or in response to general, non-direct questions. Blood glucose monitors and diaries were distributed for recording of hypoglycemic episodes. During the the study, an abbreviated 6-item DIS was administered at every visit to screen for newly emergent depression and/or suicidal ideation.

Patient withdrawal. Patients were withdrawn from the study if they met predefined criteria for persistent hyperglycemia, unexplained severe hypoglycemia, frequent mild or moderate hypoglycemia or persistent asymptomatic hypoglycemia. Also, patients whose responses to the DIS suggested a diagnosis of depression or suicidal thoughts were withdrawn and referred for mental health consultation.

Statistical analysis. The sample size was selected to achieve at least 95% power to detect a 2.7% difference between the mean percentage weight loss in the placebo and the topiramate CR treated arm. These calculations used a SD of 3.8%, which was estimated from the results of studies on immediate release formation of TPM [topiramate] (10,11).

The primacy efficacy analysis set was predefined as a modified intention to treat (MITT) analysis set, which consisted of all randomized subjects who received at least one dose of study drug and provided at least one post-baseline efficacy evaluation. The primary endpoint was mean percent change in body weight from baseline to Week 16 using the last-observation-carried-forward (LOCF) approach, which was analyzed by using analysis of covariance with treatment and diabetes treatment as factors and with baseline weight as covariate. Response rates were analyzed using the Cochran-Mantel-Haenszel test stratified by baseline diabetes treatment. Missing values were imputed on the basis of LOCF.

RESULTS

Patient Baseline Characteristics and Disposition

The study began recruitment on February 4, 2004 and the last patient completed the study on December 16, 2004. The clinical centers screened 345 patients for participation in the study, of which 113 were randomized, and 111 included in the analysis. Two patients were excluded from the analysis: one did not take any study drug post-randomization, and the other withdrew from the study after taking one dose of study drug due to possible anemia, prior to any measurements having been made. Overall, 81% of placebo patients (n=46) and 72% of topiramate patients (n=39) completed the study. Among patients treated with topiramate who completed the study, final dosing was 175 mg (n=34), 150 mg (n=1), 75 mg (n=3), and 50 mg (n=1).

Among the patients who withdrew from the study, the reasons for withdrawal included: adverse event (placebo 7%,

topiramate 9%), patient choice (placebo 4%, topiramate 7%), lost to follow up (placebo 2%, topiramate 6%), and unknown (placebo 7%, topiramate 6%). Among patients treated with topiramate who did not complete the study, final dosing was 175 mg (n=7), 150 mg (n=1), 100 mg (n=2), 75 mg (n=2), and 50 mg (n=4).

Baseline characteristics and demographics of the patients are shown in Table 1. The two treatment groups were similar except that the placebo group had a higher proportion of men. The proportions of patients receiving concomitant antihypertensive or lipid-lowering agents were 59% and 29%, respectively. Over 95% of patients did not have any change in these concomitant medications or doses over the study period.

Efficacy

Weight. Topiramate significantly reduced body weight during the 16 weeks of treatment (Table 2). By the end of week 16, patients in the placebo and topiramate groups had lost 2.5 kg and 6.0 kg, which represented 2.3% and 5.8%, respectively, of their baseline body weight ($P < 0.001$ vs placebo), or a placebo-subtracted weight loss of 3.5%. The treatment groups began to diverge in weight by week 2 of titration (Figure 1A). Similar differences in weight loss between TPM and PLAC were observed when completers were analyzed. The proportion of patients who lost $\geq 5\%$ of baseline body weight at week 16 in the placebo and topiramate groups were 19% and 50%, respectively ($P \leq 0.001$ vs placebo), and the proportion of patients who lost $\geq 10\%$ of baseline body weight were 2% and 20%, respectively ($P = 0.002$ vs placebo). Consistent with the effects of

topiramate on body weight, there were greater reductions in BMI, and waist and hip circumferences in the topiramate-treated patients. The waist circumference was reduced by 2.3 cm and 4.2 cm in the placebo and topiramate groups, respectively (P=0.078 vs placebo). The hip circumference was reduced by 1.0 cm and 3.2 cm in the placebo and topiramate groups, respectively (P=0.012 vs placebo).

Glycemic Control. Fasting plasma levels was reduced by 0.6 mmol/L and 1.6 mmol/L from a baseline of 9.3 mmol/L and 9.2 mmol/L in the placebo and topiramate groups, respectively (P=0.002 vs. placebo). HbA_{1c} improved from a baseline of 7.4% in the placebo and 7.6% in the topiramate groups to 7.1% and 6.7%, respectively, representing a between-treatment group difference of 0.5% (P<0.001) in the change from baseline. The treatment groups began to separate in HbA_{1c} by week 4 of titration (Figure 1B).

The proportion of patients having an absolute HbA_{1c} reduction of at least 0.7% at week 16 in the placebo and topiramate groups were 25% and 48%, respectively (P=0.009 vs placebo), and the proportion of patients having an HbA_{1c} reduction of at least 1.0% were 21% and 35%, respectively (P=0.100 vs placebo). The proportion of patients having achieved HbA_{1c} <7.0% at week 16 in the placebo and topiramate groups were 46% and 69%, respectively (P=0.014 vs placebo).

Compared with placebo, patients on topiramate also demonstrated a significantly greater improvement in fasting plasma glucose and 2-hour glucose following an OGTT. Consistent with these changes, there were significant increases in 2-hour insulin and C-peptide values in the topiramate group, compared with the placebo group. Calculations based on

HOMA revealed no significant differences between the two treatment groups in basal pancreatic beta-cell function or insulin resistance.

Other Endpoints

A significant improvement was observed in systolic and diastolic blood pressure in the topiramate group compared with placebo (Table 2). Topiramate treatment was also associated with a significant reduction in the urinary albumin/creatinine ratio (Table 2).

A comprehensive lipid profile performed at baseline and week 16 revealed reductions in total, LDL and HDL cholesterol and triglycerides with topiramate treatment. These changes were not statistically significant except for HDL cholesterol. However, there were no differences in the total to HDL-cholesterol ratio and LDL to HDL-cholesterol ratio. There was a nonsignificant reduction in C-reactive protein and an increase in adiponectin (P =0.058) with topiramate treatment.

Safety

Table 3 lists common adverse events that occurred in at least 5% of topiramate-treated patients and at a greater incidence versus placebo. These adverse events were generally related to the CNS or peripheral nervous system or were psychiatric in nature. The onset of CNS and Psychiatric adverse events occurred primarily during the 7-week titration phase in the topiramate-treated subjects. Of the 23 topiramate-treated subjects with CNS adverse events, 2 subjects had adverse events that persisted at the end of the study. For the 18 topiramate-treated subjects with psychiatric adverse events, 4 subjects had adverse events that persisted. There was only one serious adverse event in the topiramate group, a case of renal

calculus considered possibly drug-related by the investigator. There were no deaths in the study.

The overall incidence for withdrawal due to adverse events was 7% (4 patients) in the placebo group and 9% (5 patients) in the topiramate group. In the placebo group, 2 patients withdrew due to depression and 2 due to hyperglycemia or worsening of diabetes control. In the topiramate group, 5 patients withdrew due to adverse events. Three of these patients had adverse events that were considered drug-related, one patient had renal calculus, one had depression, and one patient had fatigue, dizziness and confusion. The other 2 patients had non-drug-related adverse events of anxiety and dizziness as judged by the investigator. One (2%) patient in the placebo group and 7 (13%) patients in the topiramate group had dose reduction or interruption of treatment due to intolerable adverse events.

Three patients in each treatment group reported hypoglycemic symptoms, but only 1 patient in the placebo group had hypoglycemia confirmed by a low blood glucose value (40 mg/dL). The other patients reported hypoglycemic symptoms only.

Consistent with the carbonic anhydrase inhibitory effect of topiramate, asymptomatic decrease in bicarbonate was observed. The changes from baseline were 1.1, and -1.1 mmol/L for the placebo and topiramate groups, respectively. All patients had normal bicarbonate levels at the final visit. No other significant changes in laboratory analytes were observed.

DISCUSSION

This randomized trial demonstrated the efficacy of topiramate,

in a controlled-release formulation, as adjunctive therapy in obese persons with type 2 diabetes treated with diet and exercise alone, or in combination with metformin. Treatment with topiramate induced rapid and meaningful weight reduction and improvement in glycemic control compared with placebo. These results are consistent with previously reported results in obese patients with type 2 diabetes treated with topiramate (10, 11) or other weight-loss inducing agents (15,16).

The mechanism of action by which topiramate causes weight loss is not known. Animal studies suggest that central action may potentially reduce appetite and/or food intake (17,18). Studies in rodent models suggest that topiramate may also affect energy utilization, possibly due to stimulation of lipoprotein lipase in adipose tissue and skeletal muscle (19).

It is not known whether topiramate's effects on glycemic control parameters are independent of its weight loss effect. The HOMA analyses were inconclusive but there was a significantly higher level of insulin secretion 2 hours post OGTT with improved glucose responses.

Apart from effects on body weight and HbA_{1c}, treatment with topiramate led to significant reductions in systolic and diastolic blood pressure compared with placebo. The degree of blood pressure reduction is similar to that observed in the trials of antihypertensive agents. A reduction in urinary albumin excretion was also observed, most likely related to improvements in blood pressure and glycemic control. The observed changes in these surrogate markers suggest a potential for improvement in the cardiovascular risk profile for this

population of obese diabetic patients. However, the effect of topiramate on lipids is neutral. There is a small reduction in HDL-cholesterol, with the ratios of total-cholesterol and LDL-cholesterol to HDL cholesterol not being different between the two treatment groups. The large variation in lipid measurements among subjects, as well as the small sample size, makes interpretation difficult. Although C-reactive protein level was reduced with topiramate treatment, the difference from placebo was not significant.

The timing and frequency of CNS and psychiatric adverse events reported were similar to those previously reported in obese nondiabetic and diabetic patients (6-11) and also similar to those reported in the topiramate label. There were substantially more CNS and psychiatric adverse events in patients treated with topiramate. These results, therefore, indicate that a controlled release formulation does not provide tolerability advantages over immediate release formulation.

In summary, treatment with the CR formulation of topiramate was demonstrated to effectively reduce body weight along with meaningful improvements in HbA_{1c} levels and 2-hour post OGTT insulin secretion in addition to significant lowering of blood pressure and urinary albumin excretion in obese patients with type 2 diabetes treated with diet and exercise alone or with metformin monotherapy. However, the CNS and psychiatric adverse event profile of topiramate CR makes it unsuitable for the treatment of obesity and diabetes.

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Table 1—Patient characteristics at baseline (modified intent-to-treat)

| | Placebo (n = 57) | Topiramate CR 175 mg/d (n = 54) | Total (n = 111) |
|---------------------------------|---------------------|---------------------------------------|--------------------|
| Age (years) | 53.5 (11.1) | 51.8 (11.5) | 52.7 (11.3) |
| Male (%) | 42 | 22 | 32 |
| White (%) | 79 | 70 | 75 |
| Body weight (kg) | 110.2 (19.4) | 106.0 (17.2) | 108.1 (18.4) |
| BMI (kg/m ²) | 37.7 (5.7) | 38.1 (5.3) | 37.9 (5.5) |
| FPG (mmol/L) | 9.3 (2.0) | 9.2 (2.0) | 9.3 (2.0) |
| HbA _{1c} (%) | 7.5 (0.82) | 7.6 (0.93) | 7.5 (0.87) |
| Baseline diabetes treatment (%) | | | |
| Diet only | 30 | 22 | 26 |
| Diet and metformin | 70 | 78 | 74 |

Table 2—Mean changes from baseline (modified intent-to-treat, last observation carried forward) in primary and key secondary endpoints.

| | Placebo | | | Mean Change from Baseline | TPM CR 175 mg/d | | | Mean Change from Baseline | P-value for Between- Treatment Group Difference |
|---------------------------------|---------|------------|------------|------------------------------------|-----------------|------------|------------|------------------------------------|---|
| | n | Baseline | Week 16 | | n | Baseline | Week 16 | | |
| Body Weight (kg) | 5 5 | 109.7±19.6 | 107.3±19.7 | -2.5±3.1 | 54 | 106.0±17.2 | 100.0±18.1 | -6.0±5.2 | <0.001 |
| % change from baseline | | | | -2.3±2.9 | | | | -5.8±4.8 | <0.001 |
| Anthropomorphic Measurements | | | | | | | | | |
| BMI (kg/m ²) | 5 5 | 37.7±5.8 | 36.9±5.9 | -0.8±1.1 | 54 | 38.1±5.3 | 36.0±5.9 | -2.1±1.8 | <0.001 |
| Waist Circumference (cm) | 5 2 | 114.7±11.9 | 112.5±11.6 | -2.3±4.7 | 47 | 115.4±11.4 | 111.2±12.7 | -4.2±5.7 | 0.078 |
| Hip Circumference (cm) | 5 2 | 123.0±13.1 | 122.0±13.1 | -1.0±4.7 | 47 | 122.2±12.1 | 119.0±12.7 | -3.2±4.5 | 0.012 |
| Glycemic Control Parameters | | | | | | | | | |
| HbA _{1c} (%) | 5 5 | 7.4±0.83 | 7.1±0.89 | -0.4±0.80 | 52 | 7.6±0.92 | 6.7±0.85 | -0.9±0.77 | <0.001 |
| Fasting plasma glucose (mmol/L) | 5 5 | 9.3±2.1 | 8.7±1.8 | -0.6±1.8 | 52 | 9.2±2.1 | 7.6±2.2 | -1.6±2.0 | 0.002 |

HOMA

| | | | | | | | | | |
|-----------------------------------|----|-----------|-----------|-----------|----|-----------|-----------|----------|-------|
| Pancreatic beta-cell function (%) | 50 | 43.7±36.0 | 43.6±26.6 | -0.1±27.9 | 45 | 54.7±69.4 | 54.8±75.7 | 0.0±71.5 | 0.665 |
| Insulin resistance | 50 | 4.8±4.6 | 4.0±2.3 | -0.8±4.3 | 45 | 5.7±4.3 | 4.6±4.1 | -1.1±3.6 | 0.583 |

Table 2 (cont'd)—Mean changes from baseline (modified intent-to-treat, last observation carried forward) in primary and key secondary endpoints.

| | Placebo | | | Mean Change from Baseline | TPM CR 175 mg/d | | | Mean Change from Baseline | P-value for Between- Treatment Group Difference |
|--|-------------|------------|------------|---------------------------------|-----------------|------------|------------|------------------------------------|---|
| | n | Baseline | Week 16 | | n | Baseline | Week 16 | | |
| OGTT | | | | | | | | | |
| Fasting plasma glucose (mmol/L) | 4 4 | 9.2±1.9 | 8.6±1.8 | -0.6±1.8 | 39 | 9.3±2.1 | 7.4±2.3 | -1.9±1.8 | 0.001 |
| 2-hr plasma glucose (mmol/L) | 4 8 | 16.4±3.8 | 15.3±3.7 | -1.1±2.9 | 42 | 15.7±3.2 | 13.1±4.1 | -2.6±4.1 | 0.018 |
| Baseline plasma insulin (μIU/mL) | 5 2 | 11.3±9.7 | 10.3±5.1 | -1.1±8.4 | 45 | 13.6±10.1 | 12.7±10.1 | -1.0±6.62 | 0.279 |
| 2-hr plasma insulin (μIU/mL) | 4 7 | 34.6±27.4 | 34.1±23.3 | -0.5±18.2 | 41 | 45.1±48.5 | 54.5±43.6 | 9.5±40.0 | 0.009 |
| Mean Blood Pressure | | | | | | | | | |
| Systolic (mmHg) | 5 5 6 | 127.9±15.1 | 123.7±14.3 | -4.2±12.9 | 54 | 127.2±12.5 | 117.1±11.8 | -10.2±12.8 | 0.004 |
| Diastolic (mmHg) | 5 5 | 78.4±8.9 | 76.8±10.6 | -1.6±8.7 | 54 | 79.1±7.1 | 73.8±8.5 | -5.3±8.5 | 0.032 |
| Urinary albumin/ creatinine ratio (mg/mg creatinine) | 4 3 7 | 0.031±0.04 | 0.029±0.05 | - 0.002±0.038 | 39 6 | 0.046±0.08 | 0.018±0.02 | - 0.028±0.07 | 0.033 |

Table 2 (cont'd)—Mean changes from baseline (modified intent-to-treat, last observation carried forward) in primary and key secondary endpoints.

| | Placebo | | | Mean Change from Baseline | TPM CR 175 mg/d | | | Mean Change from Baseline | P-value for Between- Treatment Group Difference |
|--|---------|-----------|-----------|---------------------------------|-----------------|-----------|-----------|------------------------------------|---|
| | n | Baseline | Week 16 | | n | Baseline | Week 16 | | |
| Lipid Profile[†] | | | | | | | | | |
| Total cholesterol (mmol/L) | 5 3 | 5.37±1.01 | 5.28±1.03 | -1.4±11.6 [†] | 46 | 5.53±1.31 | 5.16±1.22 | -5.9±12.2 [†] | 0.109 |
| LDL cholesterol (mmol/L) | 5 3 | 3.27±0.89 | 3.34±0.90 | 3.4±19.1 [†] | 46 | 3.40±1.04 | 3.29±0.98 | -1.7±16.1 [†] | 0.250 |
| HDL cholesterol (mmol/L) | 5 3 | 1.25±0.33 | 1.28±0.31 | 3.5±13.2 [†] | 46 | 1.18±0.31 | 1.15±0.28 | -1.6±11.3 [†] | 0.016 |
| Triglycerides (mmol/L) | 5 2 | 1.73±0.67 | 1.76±0.72 | 6.4±40.0 [†] | 46 | 2.02±1.22 | 1.72±1.09 | -7.3±34.6 [†] | 0.246 |
| Total cholesterol/ HDL cholesterol ratio | 5 3 | 4.54±1.30 | 4.29±1.04 | -0.25±0.68 | 46 | 4.93±1.63 | 4.66±1.34 | -0.28±0.89 | 0.410 |
| LDL cholesterol/ HDL cholesterol ratio | 5 3 | 2.79±1.03 | 2.73±0.84 | -0.06±0.53 | 46 | 3.06±1.25 | 2.99±1.06 | -0.06±0.68 | 0.413 |
| Other Endpoints | | | | | | | | | |
| Adiponectin (ng/mL) | 5 2 | 5068±2729 | 5514±3641 | 446±1655 | 45 | 4644±2464 | 5741±3146 | 1098±1862 | 0.058 |
| C-Reactive Protein (mg/L) | 5 3 | 7.1 ±6.7 | 7.1 ±7.5 | 0.0 ±3.9 | 46 | 7.7 ±6.1 | 6.7 ±7.6 | -1.1 ±6.3 | 0.522 |

Data are mean ± standard deviation. [†] Changes in lipid parameters are listed as mean percent change from baseline.

Table 3— Adverse events (safety population)

| | Placebo n = 57 | Topiramate CR 175 mg/d n = 54 |
|---|-------------------|-------------------------------------|
| Number (%) of patients with 1 or more: | | |
| Adverse events | 42 (74) | 49 (91) |
| Serious adverse events | 2 (4) | 1 (2) |
| Adverse event which resulted in discontinuation | 4 (7) | 5 (9) |
| Common treatment-emergent adverse events (AEs) occurring in at least 5% of topiramate-treated patients and at a greater incidence than in placebo-treated patients, n (%) | | |
| Gastro-intestinal system disorders | 21 (37) | 19 (35) |
| Constipation | 4 (7) | 7 (13) |
| Dyspepsia | 3 (5) | 4 (7) |
| Gastroenteritis | 2 (4) | 3 (6) |
| Body as a whole - general disorders | 18 (32) | 17 (31) |
| Fatigue | 2 (4) | 6 (11) |
| Pain | 3 (5) | 3 (6) |
| Central and peripheral nervous system disorders | 12 (21) | 23 (43) |
| Paresthesia | 0 | 15 (28) |
| Dizziness | 2 (4) | 8 (15) |
| Neuropathy | 1 (2) | 3 (6) |
| Hypoesthesia | 0 | 3 (6) |
| Respiratory system disorders | 15 (26) | 13 (24) |
| Upper respiratory tract infection | 8 (14) | 9 (17) |

| | | |
|------------------------|---------|----------|
| Sinusitis | 1 (2) | 4 (7) |
| Psychiatric disorders | 6 (11) | 18 (33) |
| Anxiety | 2 (4) | 4 (7) |
| Difficulty with memory | 0 | 4 (7) |
| Insomnia | 1 (2) | 3 (6) |
| Somnolence | 0 | 4 (7) |
| Appetite increased | 0 | 3 (6) |

Figure 1. Mean percent change in (A) body weight and (B) HbA_{1c} from baseline over time. Topiramate treatment is represented by (●) and placebo treatment represented by (○).

