

PAPER

A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects

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BACKGROUND: Treatment of obese subjects with topiramate has recently been associated with significant weight loss in a 6-month dose-ranging study.

OBJECTIVE: To investigate the long-term efficacy and safety of topiramate in obese subjects.

DESIGN: Randomised, double-blind, placebo-controlled study investigating three doses of topiramate: 96, 192, and 256 mg/day. All subjects also participated in a nonpharmacological weight-loss programme.

SUBJECTS: The study included 1289 subjects 18–75 y with a body mass index ≥ 30 kg/m² and < 50 kg/m² in the absence of comorbidities, or ≥ 27 kg/m² and < 50 kg/m² in the presence of controlled hypertension and/or dyslipidaemia.

DURATION: The original study design was for a 6-week, single-blind, placebo run-in phase followed by an 8-week titration phase and 2 y of maintenance at the assigned dose. Sponsor ended study early in order to develop a new controlled-release formulation with the potential to enhance tolerability and simplify dosing in this patient population. Therefore, none of the subjects completed the full 2 y of treatment. Efficacy results are based on subjects who were enrolled early enough to have had an opportunity to complete 1 y at their assigned dose (modified intent-to-treat population, MITT) before learning of the decision to terminate the study. Safety results are based on all subjects who took at least one dose of study medication.

RESULTS: The safety population consisted of 1282 subjects, and the MITT efficacy population was 854 subjects. At 60 weeks, subjects in the placebo group lost 1.7% of their baseline body weight, while subjects in the topiramate 96, 192, and 256 mg/day treatment groups lost 7.0, 9.1, and 9.7%, respectively ($P < 0.001$, MITT, last observation carried forward). Weight loss $\geq 5\%$ of baseline weight was achieved by 18% of subjects in the placebo arm vs 54, 61, and 67% of subjects receiving topiramate 96, 192, and 256 mg/day, respectively; weight loss $\geq 10\%$ was achieved by 6 vs 29, 40, and 44%, respectively ($P < 0.001$). Weight loss was accompanied by significant improvements in blood pressure (systolic/diastolic changes of +0.4/+1.0, -3.1/-1.3, -5.7/-3.4, and -4.6/-2.4 mmHg were observed for placebo, topiramate 96 mg/day, 192 mg/day, and 256 mg/day, respectively, $P < 0.001$) and glucose and insulin. The most common adverse events more frequently observed in topiramate-treated subjects occurred mostly during the titration phase and were related to the central or peripheral nervous system and included paresthesia, difficulty with concentration/attention, depression, difficulty with memory, language problems, nervousness, and psychomotor slowing.

CONCLUSION: Topiramate treatment of obese subjects over the course of 1 y resulted in clinically significant weight loss. Improvements were also observed in blood pressure and glucose tolerance.

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Introduction

Obesity, a serious and growing problem worldwide,^{1–4} contributes greatly to morbidity and mortality^{5–7} and significantly increases the risk of chronic and potentially disabling conditions such as diabetes,⁸ hypertension,^{9,10} dyslipidaemia,⁹ coronary artery disease,¹¹ ischaemic

stroke,¹² and osteoarthritis.¹³ Furthermore, loss of weight by obese individuals has been shown to reduce the risk of type 2 diabetes,^{14,15} to lower blood pressure,^{16,17} and to improve lipid profiles.¹⁷ Lifestyle interventions aimed at reducing energy intake and increasing physical activity are usually the initial recommendations for weight loss, but results are often disappointing.^{14,15}

Topiramate is a sulfamate-substituted monosaccharide currently approved in more than 75 countries worldwide for the treatment of selective seizure disorders.¹⁸ In clinical trials of topiramate for seizure disorders, weight loss has been noted.¹⁸ Additionally, weight loss associated with topiramate has also been observed in several rodent models of obesity.¹⁹ A 6-month dose-ranging study in obese human subjects²⁰ investigated topiramate at doses of 64, 96, 192, and 384 mg/day (in divided twice-daily dosing). All doses produced significantly greater weight loss than placebo, but weight loss in the 192 mg/day group was similar to the 384 mg/day group.

The present study aimed to investigate the efficacy and safety of topiramate doses of 96, 192, and 256 mg/day over a 2-y period. However, the topiramate immediate release (IR) clinical programme in obesity and diabetes was discontinued in order to develop a new controlled-release formulation with the potential to enhance tolerability and simplify dosing in this patient population. This report includes efficacy results for weight loss and several secondary outcomes (blood pressure, lipids, and glycaemic control parameters) for subjects who enrolled early enough to have had the opportunity to complete 1y of maintenance therapy before the decision was made to terminate the study early—the modified intent-to-treat (MITT) population. Safety results are presented for all subjects who received at least one dose of study medication and received at least one on-treatment safety evaluation.

Subjects and methods

Subject eligibility

Subjects were eligible for this study if they were between the ages of 18 and 75 y and had a body mass index (BMI) ≥ 30 and $< 50 \text{ kg/m}^2$ in the absence of comorbidities. For subjects with controlled hypertension or dyslipidaemia, the minimum BMI for study entry was $\geq 27 \text{ kg/m}^2$. Medications for those conditions had to have been stable for at least 2 months prior to enrollment. Subjects with diabetes were excluded with the exception of those with type 2 diabetes diagnosed at enrollment, if they did not require antidiabetic medication. Exclusion criteria included recent changes in weight, uncontrolled thyroid disease, history of eating disorders, malignancy within the past 5 years, enteropathy, previous weight-loss surgery, significant cardiovascular disease, uncontrolled hypertension, history of hepatic disease or renal impairment, significant central nervous system (CNS)-related or psychiatric disorders, and current long term use of psychotropic medications. Female subjects of child-bearing potential were required to use an approved method of contraception. Participants were recruited from 29 sites in Europe and South Africa. The study was carried out from 25 July 2000 to 28 June 2002. It was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice and was approved by Ethical Committees at all sites. All subjects gave written informed consent.

Study design

This was a four-arm, parallel-group, randomised, double-blind, placebo-controlled multicentre trial. The study design consisted of five phases: a 6-week placebo weight-loss run-in phase, an 8-week titration phase, a 104-week (2-y) maintenance phase, a 2-week taper phase, and a 4-week follow-up phase (Figure 1). However, sponsor's decision to end the

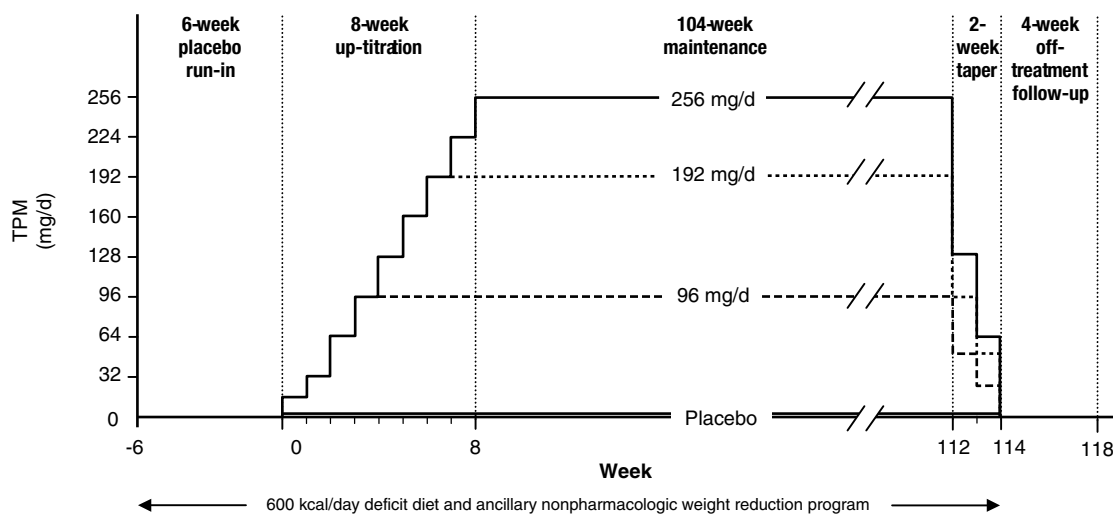


Figure 1 Trial design.

study early in order to develop a new controlled-release formulation of topiramate led to early termination of the study before any subject had the opportunity to complete the full 2-y maintenance phase. The longest duration of treatment received by any subject was 83 weeks. Consequently, subjects received the final maintenance-phase examination at their next scheduled visit and then entered the taper and follow-up phase. The study termination decision accounts for the majority of subject withdrawals from this study. Other withdrawals occurred because of lack of efficacy, adverse events, patients lost to follow-up, and 'other reasons' (eg, lack of compliance with medication intake or diet) (Figure 2).

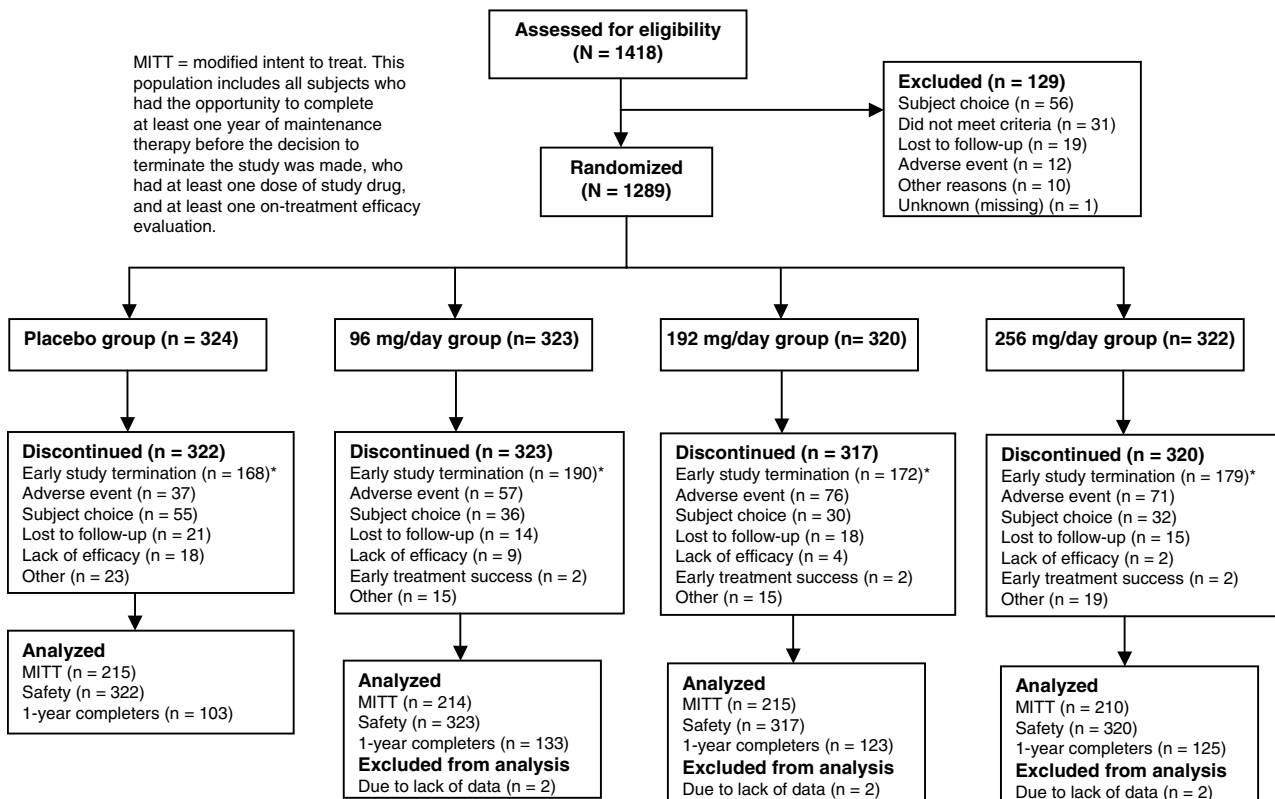
Nonpharmacological intervention

Beginning with enrollment (before the 6-week run-in phase) and ending with the last follow-up visit, all subjects were to follow a standardised, commercially available, nonpharmacological weight management programme known as PATHWAYS TO CHANGE[®] (Johnson and Johnson Health Care Systems, Inc., Piscataway, NJ, USA). This programme,

administered on a one-to-one basis by trained counsellors, focuses on lifestyle management in the areas of nutrition, exercise, and psychosocial structuring. At each subject visit, the counsellor administered a different lifestyle lesson, which was consistent for that visit at all sites. The lessons provided subjects with a variety of diet and exercise information. In addition, user-friendly, interactive support materials were provided. Each visit lasted approximately 15 min. Subjects were prescribed an individualised 600-kcal deficit diet (based on estimates of total energy expenditure²¹) with a maximum of 30% fat. The allowed dietary intake was recalculated at 6-month intervals to account for weight loss.

Enrollment and run-in phase

At the initial visit, subjects were assessed with a medical examination including history, physical examination, anthropometric measurements (weight, height, and waist and hip circumference), an oral glucose tolerance test, and a 12-lead electrocardiogram (ECG). In addition, blood and urine samples were collected for laboratory analysis. Enrolled subjects then entered the 6-week, single-blind,



*Early study termination was the decision of the sponsor.

Figure 2 Subject disposition.

placebo run-in phase. Subjects who lost more than 6% of initial body weight during this period or were considered noncompliant with medication (on the basis of tablet count) or with nonpharmacological therapy were not randomised.

Randomisation, titration, and maintenance phase

Subjects who remained eligible at the end of the placebo run-in phase were then randomised to topiramate 96, 192, or 256 mg/day or placebo. Topiramate was administered in two divided doses. Investigators were blinded to the assigned treatment and to any subsequent changes in dose. Gradual titration has been shown to improve tolerability of topiramate, therefore, a titration schedule was incorporated into the study design. All subjects randomised to receive topiramate at any dose were started at 16 mg/day for week 1 and were then titrated upward over a total period of up to 8 weeks. The dose was increased by 16 mg/day to 32 mg/day for the second week. From week 3 onwards, the dose was increased by 32 mg/day weekly until the assigned dose was reached. Thus, subjects randomised to topiramate 96 mg/day reached their assigned dose at the beginning of week 4, those randomised to 192 mg/day at the beginning of week 7, and those randomised to 256 mg/day at the beginning of week 9 (Figure 1). During the maintenance phase, subjects were followed at 4-week intervals for both efficacy and safety.

Taper and follow-up phase

Topiramate has not been associated with adverse events specifically related to drug withdrawal; however, it was considered good clinical practice to gradually withdraw subjects following long-term administration of a CNS-active agent. Therefore, at the end of the maintenance phase, topiramate was tapered over a period of 2 weeks. The weekly dose decrease was as close to 50% as allowed by the available tablet strengths. The final study visit occurred 4 weeks after last study medication intake.

Dosage adjustment related to adverse events

If a subject experienced an intolerable adverse event, the investigator was encouraged to omit one or two doses of drug, then rechallenge the subject. If the investigator felt that rechallenge was medically inadvisable, or if intolerance continued after rechallenge, the subject was assigned to the next lower randomised dose of topiramate. Subjects on 96 mg/day, however, were to be reassigned to 64 mg/day (a nonrandomised dose), and those on placebo reassigned to placebo. All dose reductions were carried out in a double-blinded fashion. If subjects continued to experience intolerance after a single dosage reduction, they were discontinued from the study.

Early completers

Subjects who achieved maximum weight loss as defined by the following criteria were considered early completers and were withdrawn: either a BMI <25 kg/m² on two consecutive occasions and the second BMI assessment lower than the first (withdrawal at investigator's discretion) or BMI <22 kg/m² on two consecutive assessments (withdrawal mandatory).

Evaluations and statistical analysis

The planned sample size of 260 subjects per treatment arm was selected in order to have a sufficiently large safety database and to have sufficient subjects with long-term safety data (up to 2y); this resulted in statistical power that exceeded 90% to detect a difference of the desired 5% in mean percentage change in body weight between the active and placebo groups in both the ITT and MITT populations.

MITT population

The primary efficacy analysis population was predefined as a MITT population before the study results were unblinded. This modification was necessary because it was believed that after an announcement of the premature termination of the study, it would not be possible to guarantee that subsequent data collected would not be subject to potential bias. The MITT analysis used only data obtained prior to the close-down announcement and only from subjects who had the opportunity to complete the predefined 60 weeks of treatment for the primary end point of this study before the closedown announcement.

The predefined primary efficacy end point was the percent weight change between baseline and week 60 (1y of maintenance). The last-observation-carried-forward (LOCF) approach for imputing the missing values was used. To adjust for multiple comparisons, the step-down multiple testing framework for comparing treatments with a control of Dunnett and Tamhane was used.²² For the primary efficacy measure, the two-sided significance level was 0.05. The primary efficacy end point was analysed using analysis of covariance (ANCOVA) with treatment, centre, and treatment-by-centre as factors. The respective baselines, together with gender and weight loss during the placebo run-in phase, were treated as covariates.

Secondary end points discussed in this publication include changes in body weight, anthropometric measurements, blood pressure, lipid profile, and blood glucose levels. Safety end points included reported adverse events and safety-related changes seen on haematology, blood chemistry, and urinalysis panels, as well as on physical examination and ECG.

The oral glucose testing results at baseline and week 60 were analysed to see if there was a treatment effect as described below. The odds of being in the normal glucose tolerance category vs abnormal glucose tolerance (impaired glucose tolerance and type 2 diabetes) were calculated at

baseline and week 60. The odds ratios of being normal at week 60 vs at baseline were calculated for the placebo group and the topiramate-treated groups separately. The equality of the two odds ratios was tested using a logit model.

Results

A total of 1289 subjects were randomised. This was in excess of the planned sample size in order to expand the population exposed to long-term treatment for safety evaluation. Subject disposition throughout the study is illustrated in Figure 2. Selected demographic and baseline data for the safety population are shown in Table 1. A total of 854 subjects were randomised early enough to have had the opportunity to receive at least 1 y of maintenance medication (60 weeks total: 8-week titration phase and 52-week maintenance phase) before announcement of study termination. There was a total of 709 withdrawals from the randomised population due to the sponsor's early termination decision: 168, 190, 172, and 179 in the placebo, topiramate 96, 192, and 256 mg/day groups, respectively. There were no notable imbalances in demographic and other baseline parameters in either the safety or MITT populations.

Weight loss during placebo run-in period

The mean percentage change in weight (during the placebo run-in period from enrollment to randomisation) was -1.0 , -1.3 , -1.3 , and -1.1% for placebo and topiramate 96, 192, and 256 mg/day treatment groups, respectively.

Change in body weight

From randomisation (after the run-in phase) to week 60, the mean decrease in body weight for subjects in the three topiramate treatment groups was 7.0, 9.1, and 9.7% for 96, 192, and 256 mg/day, respectively, compared with 1.7% in placebo-treated subjects (adjusted for multiplicity $P < 0.001$ vs placebo) (MITT population, LOCF analysis) (Figure 3).

LOCF analyses of secondary end points associated with weight loss at week 60 for the MITT population are shown in Table 2. A significantly greater proportion of topiramate-treated subjects lost at least 5% of their baseline body weight than those receiving placebo (18, 54, 61, and 67% for placebo, 96, 192, and 256 mg/day groups, respectively). Statistically significant differences were observed between the 192 and 96 mg/day groups, but not between the 256 and

Table 1 Selected demographic and baseline data for safety population

	Placebo (n = 322)	Topiramate			Total (n = 1282)
		96 mg/day n = (323)	192 mg/day (n = 317)	256 mg/day (n = 320)	
Age (y)					
Mean (s.d.)	44.1 (10.84)	44.1 (10.78)	45.1 (10.81)	44.8 (10.70)	44.5 (10.78)
Sex: n (%)					
Male	55 (17)	62 (19)	56 (18)	62 (19)	235 (18)
Female	267 (83)	261 (81)	261 (82)	258 (81)	1047 (82)
Race: n (%)					
White	308 (96)	310 (96)	306 (97)	313 (98)	1237 (96)
Black	9 (3)	8 (2)	7 (2)	6 (2)	30 (2)
Asian	5 (2)	3 (1)	3 (1)	1 (<1)	12 (1)
Other	0	2 (1)	1 (<1)	0	3 (<1)
Height (cm)					
Mean (s.d.)	167.2 (8.26)	167.9 (8.19)	167.0 (8.09)	167.2 (8.60)	167.3 (8.28)
Weight (kg)					
Mean (s.d.)	104.0 (16.589)	105.3 (17.956)	103.3 (17.627)	106.3 (18.777)	104.8 (17.769)
BMI (kg/m²)					
Mean (s.d.)	37.2 (5.009)	37.3 (5.343)	37.0 (4.881)	37.9 (5.389)	37.3 (5.167)
Waist circumference (cm)					
Mean (s.d.)	110.0 (12.621)	110.7 (13.069)	109.5 (13.364)	112.1 (13.616)	110.6 (13.191)
Antihypertensive drug use					
n (%)	66 (20)	73 (23)	65 (21)	80 (25)	284 (22)
Lipid-lowering drug use					
n (%)	14 (4)	9 (3)	17 (5)	13 (4)	53 (4)

BMI = body mass index; s.d. = standard deviation.

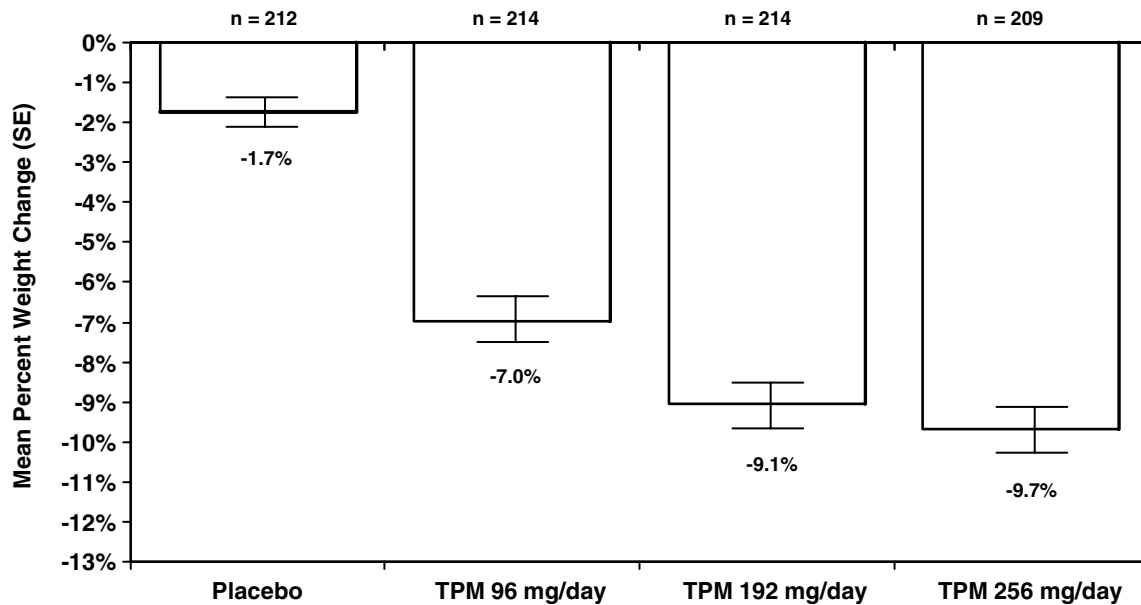


Figure 3 The 1-y (60 weeks of treatment) mean percentage change from baseline body weight (MITT, LOCF).

Table 2 Secondary weight-related efficacy end points (MITT population, LOCF)

	Placebo	Topiramate (mg/day)		
		96	192	256
BMI (kg/m ²) change from baseline to 60 weeks	-0.6	-2.6*	-3.3***	-3.6****
Weight loss (kg)				
From baseline to week 60	1.7	7.3*	9.3***	10.0****
From enrollment to week 60	2.7	8.6*	10.6***	11.1****
% Subjects ≥5% weight loss at week 60	18	54*	61****	67****
% Subjects ≥10% weight loss at week 60	6	29*	40****	44****
Δ Waist circumference (cm) at week 60	-2.4	-6.3*	-8.6***	-8.8****

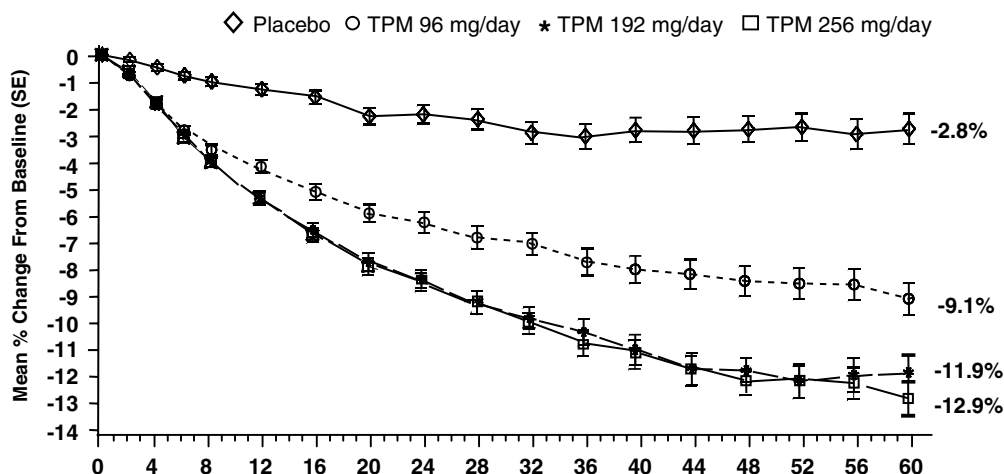
* $P \leq 0.001$ vs placebo; ** $P \leq 0.01$ vs 96 mg/day; *** $P > 0.05$ (NS) vs 192 mg/day; **** $P > 0.05$ (NS) vs 96 mg/day; ***** $P \leq 0.05$ vs 96 mg/day.

192 mg/day groups. The mean percent change in weight over time for the MITT population is shown in Figure 4. Placebo subjects lost weight up to approximately week 32, then reached a plateau and started regaining weight after week 60. In contrast, subjects in all topiramate groups continued gradually losing weight through week 60; this was maintained in the small number of subjects who reached week 76; the diminishing number at this time point was caused mainly by the sponsor's premature termination of the study. Owing to these declining subject numbers, caution is advised in the interpretation of the weight-loss data after week 60. The 96 mg/day topiramate group demonstrated less weight loss than the 192 and the 256 mg/day groups. There was no additional weight loss observed on 256 mg/day compared to 192 mg/day. Two subjects in each active treatment arm were defined as early completers. The majority of these subjects had been in the double-blind phase for more than 1 y.

Blood pressure

In this predominantly normotensive population, topiramate-treated subjects had clinically relevant and statistically significant reductions in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with placebo treatment (SBP/DBP changes of +0.4/+1.0, -3.1/-1.3, -5.7/-3.4, and -4.6/-2.4 mmHg were observed for placebo, topiramate 96 mg/day, topiramate 192 mg/day, and topiramate 256 mg/day, respectively, $P < 0.001$ vs placebo). These decreases were most marked in subjects who had elevated blood pressure at baseline (Table 3).

At baseline, 40, 48, 39, and 56 subjects in the placebo, topiramate 96, 192, and 256 mg/d groups, respectively, were taking antihypertensive medication (MITT population). Eight, six, two, and nine subjects increased their background antihypertensive medications, and one, four, nine, and four decreased their dose on placebo and topiramate 96, 192, and 256 mg/day, respectively. In all,



	Baseline	Week 32	Week 60
Placebo	n = 215	n = 139	n = 102
96 mg/day	n = 214	n = 162	n = 133
192 mg/day	n = 215	n = 152	n = 122
256 mg/day	n = 210	n = 153	n = 124

Figure 4 Mean percentage change over time from baseline body weight. MITT population with averages for each time point based on all nonmissing observations. Diminishing 'n's over time are mainly accounted for by the premature termination of the study by the sponsor; reasons for withdrawal are listed in Figure 2.

Table 3 Mean change in blood pressure from baseline to 60 weeks (MITT population, LOCF)

	Topiramate (mg/day)			
	Placebo	96	192	256
<i>N</i>	212	214	214	209
Baseline SBP (mmHg)	126.4	124.8	127.1	127.2
SBP change (mmHg)	0.4	-3.1*	-5.7*	-4.6*
Baseline DBP (mmHg)	78.8	78.0	79.9	79.7
DBP change (mmHg)	1.0	-1.3*	-3.4*	-2.4*
<i>Subjects with baseline SBP ≥ 140 mmHg</i>				
<i>N</i>	39	32	44	49
Mean baseline SBP (mmHg)	149.0	149.9	149.4	147.3
SBP change (mmHg)	-7.1	-11.1	-14.8**	-11.8**
<i>Subjects with baseline DBP ≥ 90 mmHg</i>				
<i>N</i>	28	30	34	37
Mean baseline DBP (mmHg)	94.4	93.2	94.2	93.3
DBP change (mmHg)	-4.9	-6.9	-11.6***	-7.3

DBP=diastolic blood pressure; SBP=systolic blood pressure. * $P \leq 0.001$ vs placebo; ** $P \leq 0.05$ vs placebo; *** $P \leq 0.01$ vs placebo.

93% of subjects in the placebo, topiramate 96, and 192 mg/day groups had no change in antihypertensive medication during the trial. In the topiramate 256 mg/day group, 89% had no change in antihypertensive medication.

Lipids

This was a predominantly normolipidaemic population and lipid changes are therefore shown in Table 4 for patients with abnormal baseline levels. At baseline, in the MITT population, 10, six, eight, and nine subjects in the placebo, topiramate 96, 192, and 256 mg/day groups, respectively, were taking lipid-lowering agents. Six, two, one, and zero patients on placebo, topiramate 96, 192, and 256 mg/day changed their background dosage, respectively.

Oral glucose tolerance test

In this predominantly nondiabetic population, improvements in glucose and insulin were observed during a 2-h oral glucose tolerance test (OGTT) given at baseline and at week 60 (Table 5).

A proportion of subjects in each treatment group was identified as having impaired glucose tolerance or type 2 diabetes. Shifts in oral glucose tolerance status from baseline to week 60 are summarised in Table 6 and were analysed by comparing odds ratios of having normal glucose tolerance at week 60 relative to baseline between placebo-treated and pooled topiramate-treated subjects.

The odds ratio of having normal glucose tolerance at week 60 (72/[17+5]) compared to baseline (70/[19+5]) in the placebo group is 1.12. For topiramate-treated subjects, however, the odds ratio of having normal glucose tolerance at week 60 (308/[19+8]) compared to baseline (273/

Table 4 Mean percent change to 60 weeks in fasting lipids for subjects with abnormal lipid values at baseline (MITT population, observed)

Parameter	Placebo	Topiramate (mg/day)		
		96	192	256
Total cholesterol (mmol/l)				
N	54	68	73	60
Baseline mean	6.2	6.1	6.0	6.0
Mean percent change (%)	2.2	-2.1*	1.7	0.3
LDL cholesterol (mmol/l)				
N	52	62	65	51
Baseline mean	4.1	4.2	4.0	4.1
Mean percent change (%)	5.1	-3.8*	2.0	-1.1*
HDL cholesterol (mmol/l)				
N	17	27	23	26
Baseline mean	0.9	0.9	0.9	0.8
Mean percent change (%)	21.3	19.2	21.5	21.5
Triglycerides (mmol/l)				
N	36	43	32	41
Baseline mean	2.6	2.4	2.4	2.6
Mean percent change (%)	-21.2	-27.4	-21.4	-24.3

Abnormal baseline lipid values defined as total cholesterol ≥ 5.2 mmol/l; LDL cholesterol ≥ 3.4 mmol/l; HDL cholesterol < 1.0 mmol/l; and triglycerides ≥ 1.7 mmol/l. * $P \leq 0.05$ vs placebo.

Table 5 Mean change in fasting and 2-h plasma glucose, and plasma insulin from baseline to 60 weeks (MITT population, observed)

Parameter	Placebo	Topiramate (mg/day)		
		96	192	256
Fasting plasma glucose (mmol/l)				
N	94	122	112	112
Baseline mean	5.6	5.8	5.7	5.7
Mean change	0.1	-0.2*	-0.2*	-0.2*
2-h glucose (mmol/l)				
N	94	118	108	109
Baseline mean	6.6	6.4	6.5	6.3
Mean change	-0.2	-0.8**	-0.8**	-0.7**
Fasting insulin (μU/ml)				
N	94	115	106	109
Baseline mean	14.0	16.3	16.4	13.9
Mean change	0.8	-2.3	-5.3**	-1.5
2-h insulin (μU/ml)				
N	89	107	100	105
Baseline mean	64.7	65.5	68.5	50.2
Mean change	-4.3	-22.2**	-21.9***	-8.1***

* $P < 0.001$ vs placebo; ** $P \leq 0.01$ vs placebo; *** $P \leq 0.05$ vs placebo.

[47 + 15]) is 2.59, which is statistically significantly higher than the placebo group ($P < 0.001$) (Table 6).

Safety results

Adverse events occurring in more than 5% of study subjects (see Table 7) were mostly related to the central or

Table 6 Shift in glucose tolerance status from baseline to 60 weeks (MITT population, observed)

Baseline	Total	Week 60					
		NGT		IGT		Type 2 diabetes	
	N	n	%	n	%	n	%
Placebo							
NGT	70	64	91	6	9	0	0
IGT	19	7	37	9	47	3	16
Type 2 diabetes	5	1	20	2	40	2	40
Total	94	72	77	17	18	5	5
Total TPM^a							
NGT	273	265	97	6	2	2	1
IGT	47	38	81	6	13	3	6
Type 2 diabetes	15	5	33	7	47	3	20
Total	335	308	92	19	6	8	2

NGT = normal glucose tolerance; IGT = impaired glucose tolerance. ^aThe proportions of subjects at baseline and week 60 were similar for all doses.

peripheral nervous system, which is consistent with the known profile of the drug.¹⁸ Most CNS-related adverse events had an initial onset early in treatment, predominantly during the titration phase, and were mostly rated as mild to moderate in severity and resolved under continued study drug treatment or after stopping study drug. The proportion of subjects who had dose reductions because of adverse events was 6% in the placebo group and 15, 25, and 24%, in the topiramate 96, 192, and 256 mg/day arms, respectively.

Approximately, 55% of subjects were withdrawn due to the study's early termination by the sponsor (Figure 2). The most common adverse events leading to withdrawal are shown in Table 8. Serious adverse events were observed in 9% of placebo subjects and in 11% of topiramate-treated subjects. Four subjects in the active treatment arms had a serious adverse event of suicidal ideation and two subjects reported a suicide attempt as a serious adverse event (one in the 96 mg/day group and the other in the 256 mg/day group). Five cases were rated by the investigator as possibly or probably related to study drug; the other case was deemed not related. No completed suicides were observed. Five of the six subjects recovered without sequelae after the study drug was discontinued. One subject (in the 192 mg/day group) reported residual depressive symptomatology. Depression without suicidal ideation was observed in one placebo subject and depressive psychosis emerged in another. Two additional subjects reported suicidal ideation as nonserious adverse events under topiramate treatment; both events resolved upon discontinuation of study drug. The majority of instances of suicidal ideation or attempt were associated with concurrent depression. A relationship to dose or to duration of treatment could not be identified. Interpretation is further confounded by the fact that two subjects had a personal history of psychiatric disorders (depression, panic

Table 7 Most common treatment-emergent adverse events in safety population—*n* (%)

Body system/preferred term	Placebo (n = 322)	Topiramate			Total TPM (n = 960)
		96 mg/day (n = 323)	192 mg/day (n = 317)	256 mg/day (n = 320)	
Any adverse event	286 (89)	307 (95)*	306 (97)**	305 (95)*	918 (96)
<i>Central and peripheral nervous system disorders</i>					
Paraesthesia	30 (9)	174 (54)**	191 (60)**	184 (58)**	549 (57)
Dizziness	37 (11)	32 (10)	38 (12)	44 (14)	114 (12)
Language problems	2 (1)	16 (5)**	22 (7)**	22 (7)**	60 (6)
<i>Respiratory system disorders</i>					
Upper respiratory tract infection	121 (38)	137 (42)	120 (38)	129 (40)	386 (40)
Coughing	20 (6)	30 (9)	21 (7)	32 (10)	83 (9)
Sinusitis	17 (5)	15 (5)	25 (8)	21 (7)	61 (6)
<i>Psychiatric disorders</i>					
Anorexia	15 (5)	39 (12)**	45 (14)**	44 (14)**	128 (13)
Difficulty with concentration/attention	10 (3)	33 (10)**	40 (13)**	37 (12)**	110 (11)
Depression	25 (8)	24 (7)	38 (12)	40 (13)**	102 (11)
Difficulty with memory	22 (7)	28 (9)	26 (8)	41 (13)**	95 (10)
Mood problems	13 (4)	17 (5)	21 (7)	29 (9)**	67 (7)
Insomnia	19 (6)	17 (5)	28 (9)	17 (5)	62 (6)
Somnolence	13 (4)	11 (3)	23 (7)	20 (6)	54 (6)
Nervousness	6 (2)	14 (4)	18 (6)**	20 (6)*	52 (5)
Psychomotor slowing	2 (1)	12 (4)**	13 (4)*	20 (6)**	45 (5)
<i>Body as a whole – general disorders</i>					
Fatigue	63 (20)	65 (20)	72 (23)	80 (25)	217 (23)
<i>Gastrointestinal system disorders</i>					
Diarrhoea	29 (9)	34 (11)	25 (8)	43 (13)	102 (11)
Abdominal pain	26 (8)	25 (8)	37 (12)	31 (10)	93 (10)
Constipation	18 (6)	27 (8)	24 (8)	26 (8)	77 (8)
Mouth dry	10 (3)	20 (6)	34 (11)**	17 (5)	71 (7)
<i>Special senses other, disorders</i>					
Taste perversion	4 (1)	26 (8)**	50 (16)**	41 (13)**	117 (12)
<i>Vision disorders</i>					
Vision abnormal	7 (2)	10 (3)	19 (6)**	24 (8)*	53 (6)

Adverse events that were reported by at least 5% of the subjects in the ‘total topiramate’ treatment group and at a greater incidence than placebo. Subjects with multiple occurrences of the same adverse event are counted only once for that particular preferred term or body system. Only individual topiramate treatment groups were compared with the placebo group. * $P \leq 0.01$ vs placebo, Fisher exact test (two-sided); ** $P \leq 0.001$ vs placebo, Fisher exact test (two-sided); *** $P \leq 0.05$ vs placebo, Fisher exact test (two-sided).

Table 8 Common adverse events leading to withdrawal in the safety population—*n* (%)

	Placebo	Topiramate (mg/day)			All topiramate
		96	192	256	
All AEs leading to withdrawal	37 (11)	58 (18)*	76 (24)**	71 (22)**	205 (21)
Paraesthesia	0	14 (4)**	15 (5)**	16 (5)**	45 (5)
Depression	7 (2)	8 (2)	18 (6)*	12 (4)	38 (4)
Difficulty with concentration/attention	3 (1)	12 (4)*	9 (3)	14 (4)**	35 (4)
Difficulty with memory	3 (1)	5 (2)	5 (2)	13 (4)*	23 (2)
Fatigue	6 (2)	5 (2)	9 (3)	6 (2)	20 (2)
Mood problems	0	3 (1)	7 (2)**	9 (3)**	19 (2)

In at least 2% topiramate-treated subjects. * $P \leq 0.05$ vs placebo, Fisher exact test (two-sided); ** $P \leq 0.001$ vs placebo, Fisher exact test (two-sided); *** $P \leq 0.01$ vs placebo, Fisher exact test (two-sided).

attacks) and three subjects were on concomitant drugs that may be associated with psychiatric side effects (metoprolol, atenolol, fosinopril). Additionally, at-risk patients may

potentially have entered the study as these subjects were to be excluded on the basis of medical history alone, and not through specific screening tools.

Other serious adverse events deemed by the investigator to be at least possibly related to study drug included difficulty with concentration (two cases), psychosis (two cases), increase in hepatic enzymes (four cases), and renal calculus (four cases). One subject in the 96-mg/day group and one in the 256 mg/day group experienced psychosis; both recovered without sequelae after stopping study drug intake. Three subjects in the 96 mg/day dosing arm and one subject in the 192 mg/day group reported serious adverse events related to increases in hepatic enzymes. All four cases had potential alternative aetiologies (concomitant use of atorvastatin, fatty liver with pre-existing elevation of liver enzymes, cholestasis combined with fatty liver and pancreatic cancer). Two subjects in the placebo group and 15 subjects in the pooled topiramate-treated groups experienced a renal stone, four of which were rated as a serious adverse event because of hospitalisation. In the majority of cases, the stones were passed spontaneously. Over two-thirds of subjects with a renal stone continued on study drug. Dose-related decreases in bicarbonate were observed, consistent with the carbonic anhydrase inhibitory activity of topiramate. There was one death during the course of the study. A 56-y-old male subject receiving topiramate 96 mg/day, who had a history of hypertension and was a previous smoker, experienced two heart attacks after initiation of treatment; the second proved fatal. The investigator considered the relationship of this event to study medication doubtful.

Discussion

In this study, treatment of obese subjects with topiramate resulted in sustained and clinically relevant weight loss over the course of 1 y. This weight loss was accompanied by significant reductions in both systolic and diastolic blood pressure and improvements in glucose tolerance.

The only medications currently approved for long-term treatment of obesity are sibutramine and orlistat.^{23–28} In contrast to studies with other weight loss agents,^{24,25,29} data from the current study indicate that weight loss with topiramate is more pronounced and ongoing to week 60. Although few subjects were in the study beyond 60 weeks, weight loss was maintained in this small group of subjects. Ongoing weight loss until week 60 is an important finding that warrants further investigation in longer-term trials. These data also support the conclusion of a previous 6-month topiramate study that maximum efficacy may be reached at a topiramate dose of 192 mg/day, with little gain from escalation to higher doses.²⁰ A dose of 96 mg/day retains considerable efficacy, but less than that seen with doses of 192 mg/day. Further support for topiramate's efficacy is provided by the observation that more than half of the subjects in all active treatment groups lost at least 5% of their initial body weight.

A significant decrease in both systolic and diastolic blood pressure and an improvement in glucose tolerance were also

observed; the relationship of these findings to weight loss needs further investigation.

Two subjects reported adverse events of suicide attempt and six subjects reported adverse events of suicide ideation. None of these events was a completed suicide. No dose relationship could be identified and it is unclear whether or not the cases in the present study are related to topiramate intake. It is of note that at higher doses, there is a small increased incidence of depressive symptoms. It is unclear whether these represent true major depressive episodes or changes in mood. In addition, this study was in a predominantly female obese population, recognised to have an increased prevalence of depression and attempted suicide.³⁰

The mechanism by which topiramate induces weight loss has not completely been elucidated. In a variety of animal models,^{31–33} topiramate reduced both appetite and interfered with the efficiency of energy utilization. The effect on efficiency of energy utilization may reflect topiramate's ability to stimulate lipoprotein lipase activity in brown adipose tissue and skeletal muscle,^{19,33} thus potentially increasing thermogenesis and substrate oxidation. Topiramate also increases expression of uncoupling proteins 2 and 3 in adipose tissue and skeletal muscle, thus directly decreasing efficiency of energy utilization.³²

Topiramate's enhancement of gamma-aminobutyric acid (GABA)-mediated chloride fluxes,³⁴ blockade of kainate-induced fluxes,³⁵ and state-dependent blockade of Na⁺ channels³⁶ appear relevant to its antiseizure activity, but bear no obvious relationship to appetite or weight loss. Topiramate is also a weak inhibitor of carbonic anhydrase, especially isoenzymes II and IV,³⁷ which presumably accounts for its frequent induction of paraesthesia.

A majority of the subjects treated with topiramate experienced paraesthesia. Most, however, tolerated this effect well—only 5% withdrew as a result. This was nevertheless the most common reason for withdrawal in either group. Other commonly observed adverse events were related to the CNS, and 17% of subjects under topiramate treatment withdrew from the study for this reason, *vs* 7% in the placebo group. Assessment of the true withdrawal rates for adverse events is impaired by the large number of subjects withdrawn by the sponsor because of early termination, although the data presented for this study is in keeping with a previously published completed study of topiramate.²⁰

The main limitation of this study was the early study termination by the sponsor, which necessitated an MITT analysis. Although this approach, which was defined prior to the database lock, was intended to eliminate potential bias, the analysis methodology is relatively novel. Another potential limitation is the common occurrence of paresthesia on topiramate *vs* placebo, which may have led to some patients and investigators to assume that the patient was on active drug. If this occurred in the same subjects that were losing weight, this effect could have been further confounding. It is worth noting, however, that a small percentage of

subjects on placebo also reported paresthesia, and additionally, many subjects randomised to placebo lost weight, as evidenced by the average percent decrease over time in that group.

In conclusion, this study supports a previous publication²⁰ indicating that lower doses of topiramate deliver clinically relevant weight loss in the long-term treatment of obese subjects. Importantly, weight loss was ongoing until week 60, with maintenance of body weight to the longest follow-up at 76 weeks. The most common treatment-emergent adverse events are those related to the central and peripheral nervous system and psychiatric disorders. Further clinical studies will be needed to more fully investigate the efficacy and safety of topiramate in the long-term treatment of obese patients.

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