Prevention of Type 2 Diabetes in Subjects With Prediabetes and Metabolic Syndrome Treated With Phentermine and Topiramate Extended Release

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OBJECTIVE

To evaluate over 108 weeks the effect of phentermine and topiramate extended release (PHEN/TPM ER) treatment on progression to type 2 diabetes and/or cardiometabolic disease in subjects with prediabetes and/or metabolic syndrome (MetS) at baseline.

RESEARCH DESIGN AND METHODS

Subanalysis of a phase 3, randomized, placebo-controlled, double-blind study of overweight/obese subjects (BMI ≥27 to ≤45 kg/m^2) with two or more comorbidities. Subjects were randomized to placebo, PHEN 7.5 mg/TPM ER 46 mg (7.5/46), or PHEN 15 mg/TPM ER 92 mg (15/92) plus lifestyle modifications for 108 weeks. Percent weight loss in the intent-to-treat population using multiple imputation (ITT-MI), annualized incidence rate of progression to type 2 diabetes, and changes in glycemia, lipid parameters, blood pressure, and waist circumference were evaluated.

RESULTS

At baseline, 475 subjects met the criteria for prediabetes and/or MetS. After 108 weeks, subjects with prediabetes and/or MetS in the placebo, 7.5/46, and 15/92 groups experienced mean percent weight loss of 2.5, 10.9, and 12.1%, respectively (ITT-MI; $P < 0.0001$ vs. placebo), associated with reductions of 70.5 and 78.7% in the annualized incidence rate of type 2 diabetes for those receiving 7.5/46 and 15/92, respectively (ITT, $P < 0.05$), versus placebo. The ability of PHEN/TPM ER to prevent diabetes was related to degree of weight lost and was accompanied by significant improvements in cardiometabolic parameters. PHEN/TPM ER was well tolerated by this subgroup over 2 years.

CONCLUSIONS

PHEN/TPM ER plus lifestyle modification produced significant weight loss and markedly reduced progression to type 2 diabetes in overweight/obese patients with prediabetes and/or MetS, accompanied by improvements in multiple cardiometabolic disease risk factors.

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The increased prevalence of type 2 diabetes, together with its burden of patient suffering and societal costs, underscores the importance of finding effective strategies for both treatment and prevention of this disease (1,2). Two clinical constructs for identifying individuals at high risk of developing type 2 diabetes are prediabetes and metabolic syndrome (MetS). Prediabetes is a state of dysglycemia defined by impaired fasting glucose (IFG) and/or impaired glucose tolerance (1,3). It is estimated that 79 million Americans aged 20 years or older have prediabetes (2), with 25% of them progressing to type 2 diabetes within 3–5 years (3,4). Type 2 diabetes is associated with abdominal obesity and insulin resistance (diagnostic criteria were established by the Advanced Treatment Panel III of the National Cholesterol Education Program); MetS is a cluster of risk factors for cardiovascular disease (5–8). Individuals with MetS are at a fivefold increased risk of developing type 2 diabetes (5). Because IFG is one of the constituent traits used to identify MetS, overlap with criteria for prediabetes exists, and the risk of progression to type 2 diabetes is further increased in individuals who satisfy both sets of criteria (9). Thus, effective treatment of these at-risk individuals is imperative for the prevention of type 2 diabetes.

Sustained loss of 5–10% of body weight in obese and overweight patients has proven to be effective in preventing progression from prediabetes (3,10–13) and MetS (10,14) to type 2 diabetes. It also ameliorates the cardiometabolic disease process, as shown by an increase in insulin sensitivity and a reduction in cardiovascular disease risk factors (12,13,15). However, achieving sustained weight loss at a clinically meaningful level sufficient to reduce risk remains a challenge for many patients (16,17). The primary approach to treating obesity and its related complications involves lifestyle modifications, including reductions in caloric intake (by 500–1,000 calories/day) combined with increases in physical activity (18). Bariatric surgery can also be an effective weight loss option for patients meeting specific criteria (19) and may reduce the incidence of type 2 diabetes (20–22), but the approach entails risks associated with surgery, nutritional deficiencies, and weight regain in some patients (23).

In patients for whom lifestyle changes alone are insufficient and bariatric surgery is not an option, pharmacotherapies may be considered. Phentermine and topiramate extended release (PHEN/TPM ER; Qsymia; VIVUS, Inc., Mountain View, CA) have been shown to induce significant weight loss when combined with lifestyle modification in overweight/obese adults (24–26). The CONQUER study assessed effectiveness of PHEN/TPM ER for weight loss in overweight/obese adults with two or more weight-related comorbidities over 56 weeks (clinicaltrials.gov, NCT00553787) (25) and was followed by SEQUEL, a 52-week blinded extension study (NCT00796367) (26). In order to assess the ability of PHEN/TPM ER to reduce progression to type 2 diabetes and improve cardiometabolic parameters in patients at high risk of developing type 2 diabetes, we analyzed the subpopulation of patients meeting the criteria at baseline for prediabetes and/or MetS who elected to enroll in SEQUEL.

RESEARCH DESIGN AND METHODS

SEQUEL was a 52-week extension of the 56-week, phase 3, randomized, double-blind, parallel-group, placebo-controlled CONQUER trial (25,26). The selection process for the 36 SEQUEL sites was based on high initial CONQUER enrollment and subject retention. Subject outcomes and randomization remained blinded during this process. All subjects who completed CONQUER on treatment at this subset of 36 sites were eligible to enroll in the SEQUEL extension study (26). All subjects entering SEQUEL maintained their original randomized treatment assignment from CONQUER (in a 2:1:2 ratio, stratified by sex and diabetes status) of once-daily oral placebo, PHEN 7.5 mg/TPM ER 46 mg, or PHEN 15 mg/TPM ER 92 mg (placebo, 7.5/46, and 15/92, respectively), plus lifestyle modification counseling based on the LEARN (lifestyle, exercise, attitudes, relationships, and nutrition) program (27), for an additional 52 weeks, resulting in 108 weeks of treatment. A computer-generated algorithm had been used to randomize subjects to study treatment at the beginning of the CONQUER study. Investigators and subjects remained blinded to treatment assignment. Study drug compliance (assessed by count of capsules returned by subject) and lifestyle counseling were addressed at each study visit, conducted every 4 weeks. At baseline (CONQUER week 0), subjects were overweight or obese adults (aged 18–70 years), with BMIs of 27–45 kg/m^2, and two or more of the following weight-related comorbidities: central adiposity, dyslipidemia, hypertension, or type 2 diabetes. Subjects were actively managed to standard of care for their comorbidities, including the option to add, discontinue, or dose-adjust medications. The trials were approved by each center's institutional review board and overseen by an independent data safety review board. All subjects provided written informed consent. The first subject was enrolled into this study on 6 December 2008, and the last subject completed the study on 8 June 2010.

The subgroup analyses presented in this article were performed on the subset of subjects with prediabetes and/or MetS at baseline who elected to enroll in the SEQUEL study. Subjects with a medical history of type 2 diabetes at baseline were excluded from this analysis. The criteria for prediabetes were as defined by the American Diabetes Association: IFG (fasting glucose levels 100–125 mg/dL [5.6–6.9 mmol/L]) or impaired glucose tolerance (blood glucose 140–199 mg/dL [7.8–11.0 mmol/L] 2 h after 75-g glucose load during an oral glucose tolerance test [OGTT]) (3). The diagnosis of MetS was made when three or more of the following five criteria were met: waist circumference ≥102 cm in men or ≥88 cm in women; triglycerides ≥150 mg/dL (1.7 mmol/L) or taking one or more lipid-lowering medications; HDL cholesterol (HDL-C) <40 mg/dL (1.0 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women or taking one or more lipid-lowering medications; systolic blood pressure ≥130 mmHg or

diastolic blood pressure ≥85 mmHg or taking one or more antihypertensive medications; and fasting glucose ≥100 mg/dL (5.6 mmol/L) or taking drug treatment for elevated glucose (5).

The primary end point was percent weight loss from baseline, which was assessed after 108 weeks (or early termination) in the SEQUEL study. Prespecified secondary end points were assessed at baseline, week 56, and week 108 (or early termination) and included annualized incidence rate of progression to type 2 diabetes and changes in glycemia, lipid parameters, blood pressure, and waist circumference (25,26). Remission of MetS (i.e., no longer meeting the diagnostic criteria as evidenced by satisfying only two or less of these criteria) at week 108 was also assessed. Finally, at week 56, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen, both of which are inflammatory markers associated with MetS, were measured, as was adiponectin, which is decreased in subjects with obesity and cardiometabolic disease (28).

For analyses of glucose and insulin as measured by OGTT (75-g loading dose), the change in each parameter from the preglucose loading dose sample to the sample obtained 2 h after the glucose loading dose at each applicable visit was calculated. OGTT was measured at baseline, week 4, week 56, and week 108. Fasting blood glucose was measured at baseline and weeks 4, 16, 28, 40, 56, 48, 96, and 108. Subjects were considered to have progressed to type 2 diabetes if their blood glucose was ≥126 mg/dL under fasting conditions during two or more consecutive measurements and/or ≥200 mg/dL at 2 h after an OGTT.

Statistical Analysis

In this subanalysis, primary and secondary end points were assessed in the intent-to-treat (ITT) population using ANCOVA with terms for treatment group and baseline value. To accommodate missing data, multiple imputation (MI) was applied to all end points where missing data were apparent using, specifically, a two-step imputation process with $m = 5$ imputations per step (29). In the first step, data were imputed to create a monotone missing data pattern by using a Markov chain Monte Carlo algorithm. In the second step, remaining missing data were imputed using Rubin regression method (30). The complete imputed data sets were then analyzed by ANCOVA as described above, and the results from analysis of the separate imputed data sets were pooled into single estimates and tested as described by Schafer (31).

The annualized incidence rate of type 2 diabetes was calculated as the number of newly diagnosed subjects divided by the number of subject-years of follow-up for each treatment group. The number of subject-years of follow-up was calculated as the sum of the number of days across all subjects from the randomization date in CONQUER to the onset date of type 2 diabetes or to the date of study completion or discontinuation (for subjects who did not develop type 2 diabetes) divided by 365.25. Absolute risk was calculated as the number of subjects progressing to type 2 diabetes divided by the number of subjects in each treatment group. The rates of progression to type 2 diabetes among the treatment groups were compared using a χ^2 test.

Analyses of the primary and secondary end points were also performed on the ITT sample with last observation carried forward (ITT-LOCF), consisting of all subjects who were randomized, took one or more doses of the study drug or placebo, and had one or more postbaseline body weight measurements; protocol-prespecified statistical assessments have been described elsewhere (25,26).

RESULTS

Of the 866 subjects who completed CONQUER at eligible SEQUEL sites, 675 (77.9%) elected to enroll in the SEQUEL extension study (Supplementary Fig. 1) (26). The SEQUEL cohort included 145 (21.5%) subjects with type 2 diabetes at baseline and 55 (8.1%) subjects who did not meet criteria for either prediabetes or MetS; these individuals were excluded from the current analysis, leaving 475 (70.4%) at-risk subjects as defined by either prediabetes or MetS criteria, including 316 with prediabetes, 451 with MetS, and 292 meeting criteria for both prediabetes and MetS. Baseline demographics and clinical characteristics for subjects with prediabetes and/or MetS were similar among the treatment arms (Table 1).

Weight Loss

Treatment with PHEN/TPM ER induced significantly greater weight loss versus placebo in subjects in the prediabetes and/or MetS cohort. After 108 weeks of treatment, this cohort lost 10.9 and 12.1% of their body weight in the 7.5/46 and 15/92 treatment arms, respectively, vs. 2.5% in those subjects receiving placebo (ITT-MI; $P < 0.0001$), with similar results in the ITT-LOCF analysis (Fig. 1). The degree of weight loss in the placebo and PHEN/TPM ER treatment arms was similar in subjects with prediabetes or MetS at baseline and in the overall SEQUEL population at week 108 (26). No subjects experienced a BMI <18.5 kg/m^2 at study end.

Progression to Type 2 Diabetes

Although subjects in all treatment arms with prediabetes and/or MetS were administered a moderate lifestyle intervention program, the cumulative incidence rates of type 2 diabetes (Fig. 2*A*) were markedly reduced in subjects randomized to PHEN/TPM ER when compared with placebo over 108 weeks. The annualized incidence rate of type 2 diabetes in this population was 6.1, 1.8, and 1.3 for placebo, 7.5/46, and 15/92 (reductions of 70.5% with 7.5/46 and 78.7% with 15/92; $P < 0.05$ vs. placebo; ITT). The absolute risk reduction of progression to type 2 diabetes was 11.4, 3.5, and 2.5% for placebo, 7.5/46 (95% CI 1.8–13.9% vs. placebo), and 15/92 (3.5–14.3% vs. placebo). In subjects meeting criteria for prediabetes, subjects receiving 7.5/46 had a 48.6% reduction in the annualized incidence rate of type 2 diabetes and those receiving 15/92 had an 88.6% reduction versus placebo (Fig. 2*B*). Furthermore, subjects with MetS receiving 7.5/46 had a 76.6% reduction and those receiving 15/92 had a 79.7% reduction (Fig. 2*B*).

The magnitude of effect for type 2 diabetes prevention was related to the degree of weight loss achieved at 108

Table 1—Baseline demographics and clinical characteristics of the cohort with prediabetes and/or MetS at baseline (ITT)*

Demographic or clinical characteristic	Placebo (*n* = 159)	PHEN/TPM 7.5/46 (*n* = 115)	PHEN/TPM 15/92 (*n* = 201)
Mean age, years (SD)	52.5 (9.7)	52.4 (10.9)	51.3 (10.5)
Women, *n* (%)	101 (63.5)	75 (65.2)	132 (65.7)
Race, *n* (%)			
Caucasian	139 (87.4)	102 (88.7)	169 (84.1)
Black	19 (11.9)	11 (9.6)	27 (13.4)
Other	2 (1.3)	3 (2.6)	7 (3.5)
Mean weight, kg (SD)	102.9 (19.0)	104.4 (18.3)	103.4 (17.8)
Mean BMI, kg/m^2 (SD)	36.1 (4.5)	36.2 (4.5)	36.3 (4.4)
Mean waist circumference, cm (SD)	113.7 (12.9)	113.4 (12.3)	113.1 (11.9)
Mean blood pressure (mmHg)			
Systolic (SD)	129.1 (14.4)	127.8 (12.0)	128.1 (13.0)
Diastolic (SD)	80.9 (9.5)	80.5 (9.2)	80.5 (8.4)
Mean heart rate, bpm (SD)	70.4 (10.9)	72.8 (9.9)	72.5 (10.3)
Mean total cholesterol, mg/dL (SD)	205.7 (41.9)	203.6 (35.6)	204.0 (40.4)
Mean LDL-C, mmol/L (SD)	3.3 (0.9)	3.2 (0.8)	3.2 (0.9)
Mean non–HDL-C, mmol/L (SD)	4.1 (1.1)	4.0 (0.9)	4.1 (1.0)
Mean HDL-C, mmol/L (SD)	1.2 (0.3)	1.3 (0.3)	1.2 (0.28)
Mean triglycerides, mmol/L (SD)	1.8 (0.7)	1.8 (0.8)	1.8 (0.8)
Mean fasting glucose, mmol/L (SD)	5.7 (0.7)	5.8 (0.7)	5.7 (0.8)
Mean glycated hemoglobin, % (SD) (mmol/mol [SD])	5.7 (0.5) (39 [5.5])	5.7 (0.4) (39 [4.4])	5.7 (0.5) (39 [5.5])
Fasting insulin, pmol/L (SD)	122.2 (80.6)	122.2 (90.3)	119.5 (67.4)
Mean hs-CRP, mg/L (SD)	5.4 (6.7)	6.6 (10.6)	6.2 (7.8)†
Subjects with antidiabetes medication use, *n* (%)	1 (0.6)	1 (0.9)	2 (1)
Subjects with antihypertensive medication use, *n* (%)	106 (66.7)	69 (60.0)	124 (61.7)
Subjects with lipid-lowering medication use, *n* (%)	64 (40.3)	49 (42.6)	81 (40.3)

LDL-C, LDL cholesterol. *Defined as subjects with prediabetes, MetS, or both at baseline. †There were missing values for hs-CRP for one subject in the 15/92 group.

weeks in the ITT-MI population (Fig. 2*C*). Greater weight loss was associated with a greater reduction in incidence of type 2 diabetes regardless of randomization group. Subjects achieving <5% weight loss had the highest annualized type 2 diabetes incidence rate: 6.3. The lowest incidence rate, 0.9, was observed with weight loss of ≥15%; an intermediate type 2 diabetes incidence rate of 1.3 was seen among those with ≥5 to <10% or ≥10 to <15% weight loss (ITT-MI; $P <$ 0.05 vs. <5% weight loss for all comparisons). In the ITT-LOCF analysis, annualized incidence rate of type 2 diabetes was 6.1 (SD 1.3), 1.8 (0.9), 0.6 (0.6), and 1.3 (0.8) for the <5, ≥5 to <10, ≥10 to <15, and ≥15% groups, respectively.

Effects on Cardiometabolic Disease Parameters

PHEN/TPM ER also significantly improved cardiometabolic disease risk factors versus placebo in subjects with prediabetes and/or MetS. When compared with placebo, fasting glucose, fasting insulin, 2-h post-OGTT glucose, fasting triglycerides, and HDL-C were all improved in the PHEN/TPM ER groups over 108 weeks (ITT-MI) (Fig. 3). Reductions in systolic blood pressure (mmHg) of –3.9 (SE 0.98), –5.0 (1.14), and –5.1 (0.91) and reductions in diastolic blood pressure of –3.7 (0.73), –3.6 (0.82), and –3.8 (0.61) were observed with placebo, 7.5/46, and 15/92, respectively (not significant vs. placebo; ITT-MI) (Supplementary Table 1). Subjects treated with PHEN/TPM ER also had reduced waist circumference, HbA_{1c}, and homeostasis model assessment of insulin resistance and increased whole body insulin sensitivity index versus placebo at week 108 (ITT-MI) (Supplementary Table 1). Similar results were seen in the ITT-LOCF analysis (Supplementary Table 2).

Among those with MetS at baseline, by week 108, a significantly greater percentage of subjects treated with 7.5/46 (22.4%) and 15/92 (27.6%) achieved remission of MetS compared with placebo (9.2%; $P = 0.0001$ vs. placebo). Also, at week 56 in subjects with prediabetes and/or MetS, PHEN/TPM ER was associated with lower hs-CRP values (–1.7, –2.7, and –2.2 mg/dL in placebo, 7.5/46, and 15/92, respectively; *P* = not significant vs. placebo; ITT-MI), lower fibrinogen levels (–10.1, –11.3, and –15.2 mg/dL in placebo, 7.5/46, and 15/92; *P* = not significant vs. placebo; ITT-MI), and increased adiponectin concentrations (0.4, 2.2, and 2.9 μg/mL in placebo, 7.5/46, and 15/92; $P < 0.0001$ vs. placebo; ITT-MI).

Adverse Events

Reported adverse events (AEs) in the prediabetes and/or MetS groups indicated that PHEN/TPM ER was generally well tolerated; more subjects receiving PHEN/TPM ER experienced paraesthesia, sinusitis, dry mouth,

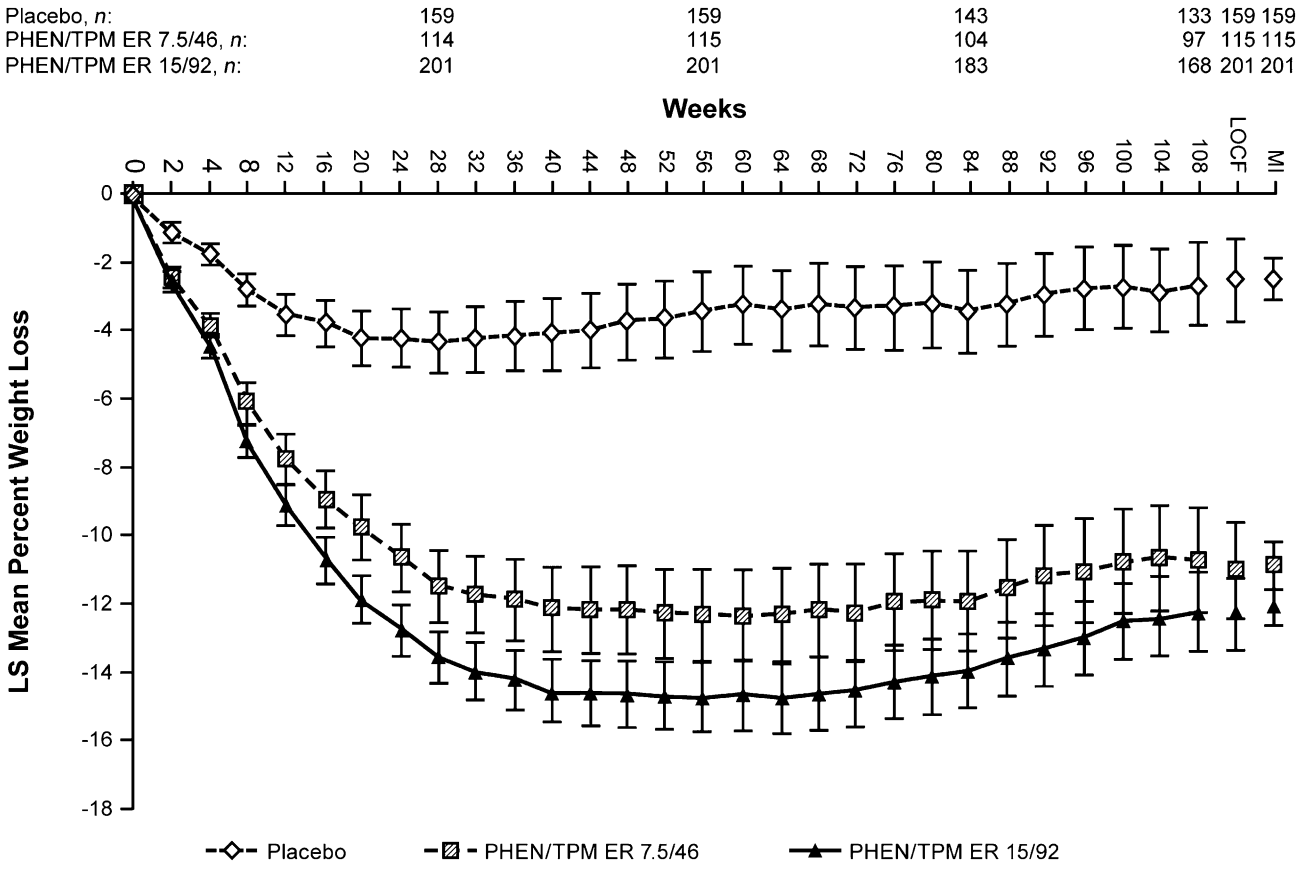

Figure 1—Percent weight loss from baseline to week 108 in the cohort with prediabetes and/or MetS at baseline. Least squares mean percent weight loss in the ITT population of subjects with prediabetes and/or MetS. $P < 0.0001$ vs. placebo for all time points assessed. LS, least squares.

constipation, headache, and dysgeusia than those receiving placebo (Supplementary Table 3). The types and severity of AEs seen in this subgroup analysis were similar to those seen in the overall SEQUEL populations and in other clinical trials investigating PHEN/TPM ER for the treatment of obesity (24–26).

Among subjects with prediabetes and/or MetS, two (1.3%), five (4.3%), and three (1.5%) subjects in the placebo, 7.5/46, and 15/92 groups, respectively, experienced palpitations, and zero, one (0.9%), and two (1.0%) subjects, respectively, experienced tachycardia.

In the placebo, 7.5/46, and 15/92 groups, respectively, discontinuation of study medication due to treatment-emergent AEs occurred in 3.1, 6.1, and 5.5%, and serious treatment-emergent AEs occurred in 5.0, 7.0, and 8.5% at week 108; only appendicitis occurred in ≥1% of subjects receiving any treatment dose (two subjects in the 15/92 group) (Supplementary Table 4). No deaths occurred during the SEQUEL study.

CONCLUSIONS

This subgroup analysis of patients participating in the CONQUER and SEQUEL studies allowed for assessment of the ability of PHEN/TPM ER to prevent progression to type 2 diabetes in at-risk patients during a 2-year period. In patients with prediabetes and/or MetS, PHEN/TPM ER was highly effective in inducing and sustaining weight loss and had a profound effect on prevention of type 2 diabetes, as measured by cumulative and annualized incidence rates. There was a 71 and 79% reduction in progression to type 2 diabetes among patients treated with 7.5/46 and 15/92 compared with placebo over 108 weeks. Additional studies are needed to determine whether weight loss associated with PHEN/TPM ER treatment will be maintained beyond 2 years or lead to sustained lower rates of progression to type 2 diabetes as compared with patients treated with placebo. However, most cases of type 2 diabetes in PHEN/TPM ER–treated patients occurred in the first year of the study, whereas cases continued to accumulate into the second year in the placebo group (Fig. 2*A*); thus, the difference in cumulative incidence between the PHEN/TPM ER and placebo groups, and the relative degree of type 2 diabetes prevention, may continue to increase over time.

The ability to prevent type 2 diabetes was greatly dependent on the magnitude of weight loss, independent of randomization group. The annualized incidence rate for type 2 diabetes was progressively reduced as weight loss increased, with the lowest value realized at ≥15% weight loss, suggesting that greater weight loss is associated with greater benefits. Previous studies of lifestyle intervention, such as the Diabetes Prevention Program (DPP) (13), have

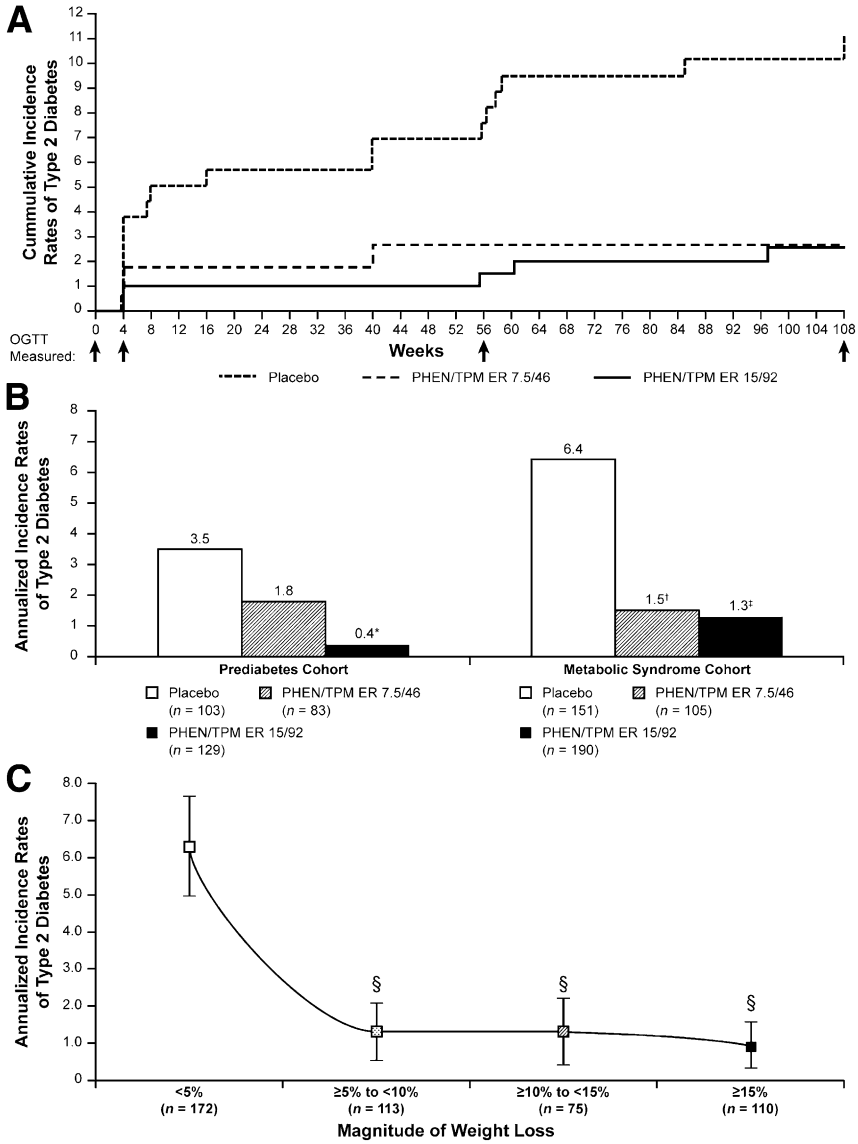

Figure 2—Incidence rates of type 2 diabetes from baseline to week 108 in SEQUEL study. *A*: Cumulative incidence rates of type 2 diabetes at study end (Kaplan-Meier) in the prediabetes and/or MetS cohort (ITT). *B*: Annualized incidence rates of type 2 diabetes at study end in the prediabetes cohort and the MetS cohort (ITT). *C*: Relationship between weight loss and type 2 diabetes incidence at study end in the prediabetes and/or MetS cohort (ITT-MI). Error bars represent 95% CI. Annualized incidence rate of type 2 diabetes was based on first occurrence of two consecutive fasting glucose ≥7.0 mmol/L, two consecutive OGTT ≥11.1 mmol/L, or taking antidiabetes medications at end point. **P* = 0.0125 vs. placebo; †*P* = 0.0093 vs. placebo; ‡*P* = 0.0007 vs. placebo; §*P* < 0.05 vs. <5% weight loss for all comparisons.

also indicated that the degree of weight loss was a predominant determinant of type 2 diabetes prevention (32), although the Finnish Diabetes (12,33) and Da Qing (11) studies demonstrated that both weight loss and exercise exerted independent effects. The DPP study, wherein patients achieved ~6% mean weight loss at 2 years and ~4% weight loss at 4 years in the lifestyle intervention arm, reported a progressive 16% reduction in type 2 diabetes risk with every kilogram of weight loss but without an indication that there was a threshold of weight loss for maximal type 2 diabetes prevention (13,32). The current study is in agreement with the DPP, demonstrating that greater weight loss leads to greater reductions in the rate of type 2 diabetes. All categories with ≥5% weight loss experienced greater reductions in cumulative type 2 diabetes incidence when compared with the weight loss category of <5%. Thus, although modest weight loss of ~5%, as recommended by the ADA (3), is beneficial, greater degrees of weight loss appear to lead to greater prevention of type 2 diabetes.

Although the current study was limited to 2 years, the DPP, Finnish Diabetes, and Da Qing studies all demonstrated that after changes in or discontinuation of active treatment, the incidence of new type 2 diabetes diagnoses remained reduced compared with placebo or usual care over longer periods of follow-up (11,34–36). Based on these data, we theorize that reduced rates of type 2 diabetes may continue to

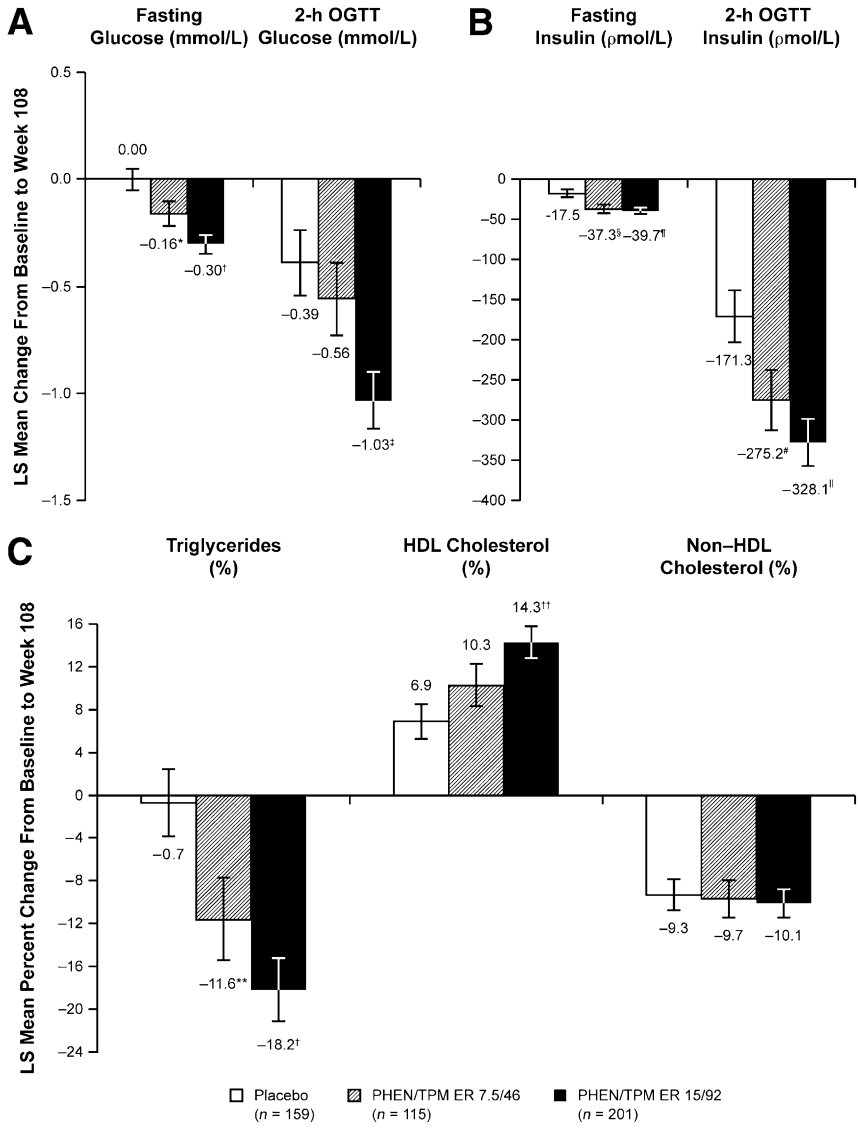

Figure 3—Glycemic and lipid parameters at week 108 in the cohort with prediabetes and/or MetS at baseline (ITT-MI). *A*: Least squares mean percent change from baseline in glucose in subjects in the prediabetes and/or MetS cohort. *B*: Least squares mean percent change from baseline in insulin in the prediabetes and/or MetS cohort. *C*: Least squares mean percent change from baseline in lipid parameters in the prediabetes and/or MetS cohort. Error bars represent 95% CI. **P* = 0.0474; †*P* < 0.0001; ‡*P* = 0.0028; §*P* = 0.0126; ¶*P* = 0.0012, #*P* = 0.0419; ‖*P* = 0.0004; ***P* = 0.0262; ††*P* = 0.0009 vs. placebo for all comparisons. LS, least squares.

be observed in the PHEN/TPM ER treatment arms compared with placebo, even after discontinuation of study drug. Of course, this is just speculation, but it does constitute a compelling consideration for future studies.

Importantly, weight loss and prevention of type 2 diabetes as a consequence of PHEN/TPM ER therapy were accompanied by an increase in insulin sensitivity, as manifested by reduced glucose and insulin values, and improvements in cardiometabolic risk factors (blood pressure, waist circumference, triglycerides, and HDL-C). Furthermore, systemic inflammation, as measured by hs-CRP and fibrinogen at week 56, was reduced, and levels of the insulin-sensitizing adipocytokine adiponectin, at week 56, were increased. Since insulin resistance, dyslipidemia, inflammation, and dysregulated secretion of adipocytokines are all hallmarks of cardiometabolic disease, these findings are indicative of the potential reversal of this pathophysiologic process (37,38).

It should be noted that in clinical trials assessing PHEN/TPM ER, all patients received advice on lifestyle modification, and the current benefits reflect the combination of PHEN/TPM ER and the lifestyle program (25,26). The LEARN program is similar to the DPP lifestyle intervention in that it strongly emphasizes behavior modification; however, the LEARN program has a less stringent calorie reduction requirement (decrease of 500 vs. 750–1,000 kcal in DPP) and encourages a progressive increase in exercise, rather than specifying a minimum amount of physical activity, as in DPP (27,39). Although the differences between lifestyle intervention alone (placebo

group) and PHEN/TPM ER with lifestyle intervention to promote weight loss and prevent type 2 diabetes were relatively small in the SEQUEL trial, treatment with PHEN/TPM ER should nevertheless be combined with lifestyle modification to realize the full clinical benefits demonstrated in this study. These findings have particular relevance to real-world treatment decisions, since maintaining clinically meaningful weight loss through lifestyle changes alone is challenging (16,17). The robust clinical benefits observed with an effective pharmacologic agent combined with lifestyle modification thus may confer a significant advantage to improve outcomes in patients at high risk of developing type 2 diabetes.

In general, PHEN/TPM ER was well tolerated, with no meaningful differences in safety in the prediabetes and/or MetS cohort during 108 weeks when compared with the overall SEQUEL population, and no differences between years 1 and 2 (26). Given the high risk of type 2 diabetes, which confers extensive patient suffering and high societal costs, the potential benefit-to-risk ratio of weight-loss treatment could be particularly favorable in patients with prediabetes and/or MetS.

This study had certain limitations. SEQUEL was limited to high-enrolling centers with high patient retention from CONQUER, so not all patients were eligible for the extension (26). Patients enrolled at sites eligible to participate in SEQUEL had slightly greater weight loss (~1% across treatment arms) at CONQUER end point than patients at non-SEQUEL sites. In addition, a higher percentage of PHEN/TPM ER–treated patients elected to continue in the study, so the original 2:1:2 randomization ratio was not maintained in the SEQUEL trial. The overall enrolled population for the SEQUEL clinical trial was larger than the subset of patients evaluated in this subanalysis; even so, baseline demography, efficacy, and safety were similar to the overall population, suggesting continuity across populations (25,26). Because patients with type 2 diabetes were excluded, there were some significant differences, mostly in glycemic parameters, between the cohort included in this analysis and those who were excluded (Supplementary Table 5). Also, because the study involved active management to standards of care, changes in concomitant medications for treatment of hypertension, dyslipidemia, and hyperglycemia are likely to have affected related study variables, often narrowing the gap between PHEN/TPM ER–treated patients and those taking placebo. However, active management was applied by treatment-blinded clinicians across placebo and PHEN/TPM ER treatment groups. Although these medication adjustments may affect some parameters, this also means that the study is largely representative of the type of care given in routine clinical practice, indicating that clinical benefits observed here may also be achieved in a real-world setting (3). In a separate analysis of the overall SEQUEL population, including those with type 2 diabetes, the weight loss associated with PHEN/TPM ER treatment induced improvement in cardiometabolic parameters even as use of medications to treat dysglycemia, hypertension, and dyslipidemia was reduced as compared with placebo (40). This suggests that weight loss associated with PHEN/TPM ER may lead to reduced medication burden for the treatment of weight-related comorbidities. Lastly, although 2 years is longer than any registration studies, it would be beneficial to have longer-term data to add to our understanding of the benefits and risks of prolonged PHEN/TPM ER use.

This study demonstrates that PHEN/TPM ER plus lifestyle modification was generally well tolerated and produced significant weight loss through 108 weeks in patients with prediabetes and/or MetS at baseline. The ability of PHEN/TPM ER to prevent progression to type 2 diabetes was profound, with both PHEN/TPM ER treatment groups exhibiting statistically significant reductions in incidence rate in these high-risk individuals with prediabetes and/or MetS, with greater weight loss leading to greater reductions in progression to type 2 diabetes. Concomitant improvements in glucose homeostasis, insulin sensitivity, and cardiometabolic disease biomarkers were also observed. These data indicate that adding PHEN/TPM ER to lifestyle modification may constitute a new and effective therapeutic approach in patients with obesity and cardiometabolic disease, even as an alternative to bariatric surgery, by virtue of the ability of PHEN/TPM ER to produce substantial weight loss and to reduce risk of progression to type 2 diabetes in patients at high risk.

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