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

Running title: PHEN/TPM ER and Type 2 Diabetes Prevention

Authors: W. Timothy Garvey, MD¹; Donna H. Ryan, MD²; Robert Henry, MD³; Nancy J.V. Bohannon, MD⁴; Hermann Toplak, MD⁵; Michael Schwiers, MS⁶; Barbara Troupin, MD⁷; Wesley W. Day, PhD⁷

Author Affiliations: ¹Department of Nutrition Sciences, University of Alabama at Birmingham and the Birmingham VA Medical Center, Birmingham, Alabama, USA; ²Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA; ³University of California San Diego School of Medicine and the San Diego VA Medical Center, San Diego, California, USA; ⁴Monteagle Medical Center, San Francisco, California, USA; ⁵Medical University of Graz, Graz, Austria; ⁶Medpace, Cincinnati, Ohio, USA; ⁷VIVUS, Inc., Mountain View, California, USA

Corresponding Author: W. Timothy Garvey, MD, Department of Nutrition Sciences, Webb 232, University of Alabama at Birmingham, 1720 Second Avenue South, Birmingham, AL 35294-3360 (205.996.7433; garveyt@uab.edu).
ABSTRACT [248/250]

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/m²) with ≥2 comorbidities. Subjects were randomized to placebo, PHEN 7.5mg/TPM ER 46mg (7.5/46), or PHEN 15mg/TPM ER 92mg (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, which 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.
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 (IGT) (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 5-fold 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 500–1000 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) has 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 ≥2 weight-related comorbidities over 56 weeks (ClinicalTrials.gov, NCT00553787) (25) and was followed by SEQUEL, a 52-week blinded extension study (ClinicalTrials.gov, 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 gender and diabetic 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 body mass indices of 27–45 kg/m², and ≥2 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 December 6, 2008, and the last subject completed the study on June 8, 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 IGT (blood glucose 140–199 mg/dL [7.8–11.0 mmol/L] 2 hours following 75-g glucose load during an oral glucose tolerance test [OGTT]) (3). The diagnosis of MetS was made when ≥3 of the following 5 criteria were met: waist circumference ≥102 cm in men or ≥88 cm in women; triglycerides ≥150 mg/dL (1.7 mmol/L) or taking ≥1 lipid-lowering medication; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (1.0 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women or taking ≥1 lipid-lowering medication; systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg or taking ≥1 antihypertensive medication; 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 ≤2 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 pre–glucose loading dose sample to the sample obtained 2 hours 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 ≥2 consecutive measurements and/or ≥200 mg/dL at 2 hours after an OGTT.

**Statistical analysis**

In this subanalysis, primary and secondary end points were assessed in the intent-to-treat (ITT) population using analysis of covariance (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 2-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’s regression method (30). The complete imputed datasets were then analyzed by ANCOVA as described above, and the results from analysis of the separate imputed datasets 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 chi-square test.

Analyses of the primary and secondary end points were also performed on the intent-to-treat sample with last observation carried forward (ITT-LOCF), consisting of all subjects who were randomized, took ≥1 dose of the study drug or placebo, and had ≥1 post-baseline body weight measurement; 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 (Appendix Figure 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, versus 2.5% in those subjects receiving placebo (ITT-MI; \( P < 0.0001 \)), with similar results in the ITT-LOCF analysis (Figure 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 less than 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 (Figure 2A) was 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; \( P < .05 \) 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 (95% CI: 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 (Figure 2B). Furthermore, subjects with MetS receiving 7.5/46 had a 76.6% reduction and those receiving 15/92 had a 79.7% reduction (Figure 2B).

The magnitude of effect for type 2 diabetes prevention was related to the degree of weight loss achieved at 108 weeks in the ITT-MI population (Figure 2C). 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 (SD: 0.9), 0.6 (SD: 0.6), and 1.3 (SD: 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-hour post-OGTT glucose, fasting triglycerides, and HDL-C were all improved in the PHEN/TPM ER groups over 108 weeks (ITT-MI; Figure
3). Reductions in SBP (mm Hg) of −3.9 (SE: 0.98), −5.0 (SE: 1.14), −5.1 (SE: 0.91) and reductions in DBP of −3.7 (SE: 0.73), −3.6 (SE: 0.82), and −3.8 (SE: 0.61), were observed with placebo, 7.5/46, and 15/92, respectively (not significant vs placebo; ITT-MI; Appendix Table 1). Subjects treated with PHEN/TPM ER also had reduced waist circumference, HbA$_{1c}$, and Homeostasis Model of Assessment-Insulin Resistance and increased Whole Body Insulin Sensitivity Index versus placebo at week 108 (ITT-MI; Appendix Table 1). Similar results were seen in the ITT-LOCF analysis (Appendix 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, constipation, headache, and dysgeusia.
than those receiving placebo (Appendix 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, 2 (1.3%), 5 (4.3%), and 3 (1.5%) subjects in the placebo, 7.5/46, and 15/92 groups, respectively, experienced palpitations, and 0, 1 (0.9%), and 2 (1.0%) of 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 (2 subjects in the 15/92 group; Appendix 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 (Figure 2A); 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 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 approximately 6% mean weight loss at 2 years and approximately 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, while modest weight loss of approximately 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 present 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 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 kcal vs 750-1000 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: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 (Appendix 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 seen 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, while 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 seen. 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.
ACKNOWLEDGMENTS

We would like to acknowledge and thank the CONQUER and SEQUEL patients, investigators, and study coordinators, the Medpace team (study CRO), the UAB Diabetes Research and Training Center (DK079626), The Lockwood Group (Sarah Odeh, BS, CMPP) for editorial assistance (funding for editorial assistance was provided by VIVUS, Inc.), and VIVUS, Inc., internal contributors. Dr W. Timothy Garvey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLAIMER INFORMATION

Dr Garvey has participated in clinical trials with Merck & Co., Inc., Weight Watchers, National Institutes of Health, the Veterans Administration, Amylin Pharmaceuticals, VIVUS, Inc., Abbott Laboratories, and Daiichi-Sankyo Inc. He has served as an advisor, consultant, and/or speaker for Alkermes, Daiichi-Sankyo Inc., LipoScience, VIVUS, Inc., Janssen Pharmaceuticals, Inc., and Tethys Bioscience. He is a scientific advisory board member at Daiichi-Sankyo Inc., Tethys Bioscience, LipoScience, and Alkermes, and he holds stock in Bristol-Myers Squibb, Isis/Genzyme, Merck & Co., Inc., Pfizer Inc., Eli Lilly and Company, and VIVUS, Inc. Dr Garvey has grants/grants pending with Merck & Co., Inc., Amylin Pharmaceuticals, and Weight Watchers. He has received payment for lectures, including service on speakers’ bureaus, from Merck & Co., Inc. Dr Garvey has received payment from VIVUS, Inc., for consulting fee/honorarium and support for travel to meetings for the current study or for other purposes.
Dr Ryan has received payment from VIVUS, Inc., for consulting fee/honorarium and support for travel to meetings for the current study or for other purposes. She is a board member for Nutrisystem and Alere Wellbeing, and a consultant for VIVUS, Inc., Novo Nordisk Inc., Eisai Pharmaceuticals, Dainippon Sumitoma Pharma, and Scientific Intake. She holds stock in Scientific Intake. Dr Ryan has received honoraria from Cleveland Clinic Foundation, Medical Exchange International, CME Incite, Academy of Nutrition and Dietetics, American Society of Bariatric Physicians, Continuing Education Alliance, American Heart Association, Vindico™, Obesity Action Coalition, George Washington University, American Society of Bariatric Physicians, Minimally Invasive Surgery Symposium, Professional TV Network, National Institutes of Health, and the European Union Innovative Medicines Initiative.

Dr Henry has served as a consultant and/or an advisor for Amgen Inc., AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo Inc., Elcelyx Therapeutics Inc., Gilead Sciences, Inc., Intarcia Therapeutics, Inc., Isis Pharmaceuticals, Inc., Eli Lilly and Company, Johnson & Johnson, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk Inc., Roche/Genentech, Sanofi-Aventis, and VIVUS, Inc. Dr Henry has grants/grants pending for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Medtronic Inc., and Sanofi-Aventis.

Dr Bohannon’s institution has received payment from VIVUS, Inc., for a research grant and an investigators’ meeting. Dr Bohannon has grants from Calibra Medical, Intuity Medical, Halozyrne Therapeutics, Johnson & Johnson, Eli Lily and Company, Novartis,
Sanofi-Aventis, and Valeritus Medical Solutions. Dr Bohannon has received payment for lectures and consulting and advisory boards, including service on speakers’ bureaus, from VIVUS, Inc., Amylin Pharmaceuticals, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly and Company, Johnson & Johnson, Janssen, Merck & Co., Inc., Merck/Schering-Plough, Novartis, Quest Diagnostics, Santarus, Sanofi-Aventis, and Tethys Bioscience. She holds stock in VIVUS, Inc., Eli Lilly and Company, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer Inc., Santarus, and Sanofi-Aventis.

Dr Toplak has received consulting fees/honoraria from VIVUS, Inc., Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk Inc., Sanofi-Aventis, Takeda Pharmaceutical Company, Merck & Co., Inc., and Novartis. He has grants/grants pending with Merck & Co., Inc., Takeda Pharmaceuticals Company, and Novartis. He has received payment for lectures, including service on speakers’ bureaus, for Merck & Co., Inc., Takeda Pharmaceuticals Company, Novartis, Novo Nordisk Inc., and Sanofi-Aventis. He has received travel/accommodations/meeting expenses from VIVUS, Inc unrelated to this manuscript.

Mr Schwiers was employed as the lead statistician for Medpace, Inc., the study CRO, throughout the study design, execution, and analysis; he was paid for his statistical analysis of all data presented in the manuscript by VIVUS, Inc.

Dr Day and Dr Troupin are employees of VIVUS, Inc.
AUTHOR CONTRIBUTIONS

W. T. G. contributed to the study concept and design, acquisition, analysis, and interpretation of data and drafting and critical revision of the manuscript. D. H. R. contributed to the analysis and interpretation of data and critical revision of the manuscript. R. H. contributed to the analysis and interpretation of data and critical revision of the manuscript. N. J. V. B. contributed to the analysis and interpretation of data and critical revision of the manuscript. H. T. contributed to the analysis and interpretation of data and critical revision of the manuscript. M. S. contributed to the acquisition, analysis, interpretation, and statistical analysis of data and drafting and critical revision of the manuscript. B. T. contributed to the study concept and design, acquisition, analysis, and interpretation of data and drafting and critical revision of the manuscript. W. W. D. contributed to the study concept and design, acquisition, analysis, and interpretation of data and critical revision of the manuscript.
FUNDING

Funding for the study and for editorial assistance was provided by VIVUS, Inc. VIVUS, Inc., was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
References

1. Diabetes public health resource: 2007 national diabetes fact sheet. Atlanta, GA: Centers for Disease Control and Prevention. Available from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed October 17, 2012.

2. The facts about diabetes: a leading cause of death in the U.S. Bethesda, MD: National Diabetes Education Program. Available from http://ndep.nih.gov/diabetes-facts/index.aspx. Accessed May 14, 2012.

3. American Diabetes Association. Standards of medical care in diabetes--2012. Diabetes Care 2012;35(Suppl 1):S11-S63.

4. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30(3):753-759.

5. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120(16):1640-1645.

6. Bakris G, Stockert J, Molitch M, Zhou Q, Champion A, Bacher P, Sowers J; STAR Investigators. Risk factor assessment for new onset diabetes: literature review. Diabetes Obes Metab 2009;11(3):177-187.

7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-2497.

8. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112(17):2735-2752.

9. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM; San Antonio Heart Study. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. Diabetes Care 2003;26(11):3153-3159.

10. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365(9468):1415-1428.

11. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20(4):537-544.
12. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344(18):1343-1350.
13. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393-403.
14. Deedwania PC, Volkova N. Current treatment options for the metabolic syndrome. Curr Treat Options Cardiovasc Med 2005;7(1):61-74.
15. Karam JG, McFarlane SI. Update on the prevention of type 2 diabetes. Curr Diab Rep 2011;11(1):56-63.
16. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. Metabolism 1990;39(9):905-912.
17. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev 2005;18(2):CD005270.
18. National Heart, Lung, and Blood Institute. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 2000. Available from http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf. Accessed February 8, 2013.
19. Bariatric Surgical and Procedural Interventions in the Treatment of Obese Patients with Type 2 Diabetes: a position statement from the International Diabetes Federation Taskforce on Epidemiology and Prevention: International Diabetes Federation Consensus Panel; 2011. Available from http://www.bakeridi.edu.au/Assets/Files/IDF-Position-Statement-Bariatric-Surgery.pdf. Accessed February 8, 2013.
20. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database Syst Rev 2009;15(2):CD003641.
21. Hussain SS, Bloom SR. The pharmacological treatment and management of obesity. Postgrad Med 2011;123(1):34-44.
22. Carlsson LM, Peltonen M, Ahlin S, Anveden Å, Bouchard C, Carlsson B, Jacobson P, Lönnroth H, Maglio C, Näslund I, Pirazzi C, Romeo S, Sjöholm K, Sjöström E, Wedel H, Svensson PA, Sjöström L. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. N Engl J Med 2012;367(8):695-704.
23. Kofman MD, Lent MR, Swencionis C. Maladaptive eating patterns, quality of life, and weight outcomes following gastric bypass: results of an Internet survey. Obesity (Silver Spring) 2010;18(10):1938-1943.
24. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B, Day WW. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20(2):330-342.
25. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low-dose, controlled-release, phentermine plus topiramate combination
on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377(9774):1341-1352.

26. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95(2):297-308.

27. Brownell K. The LEARN Program for Weight Management. Dallas, TX, The Life Style Company, 2000.

28. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. Metab Syndr Relat Disord 2004;2(2):82-104.

29. Elobeid MA, Padilla MA, McVie T, Thomas O, Brock DW, Musser B, Lu K, Coffey CS, Desmond RA, St-Onge MP, Gadde KM, Heymsfield SB, Allison DB. Missing data in randomized clinical trials for weight loss: scope of the problem, state of the field, and performance of statistical methods. PLoS ONE 2009;4(8):e6624.

30. Rubin DB. Multiple Imputation for Nonresponse in Surveys. Wiley Series in Probability and Mathematical Statistics. New York, John Wiley & Sons, 1987.

31. Schafer JL. Analysis of Incomplete Multivariate Data. (Monographs on Statistics and Applied Probability 72) London, Chapman & Hall/CRC, 1997.

32. Laaksonen DE, Lindström J, Lakka TA, Eriksson JG, Niskanen L, Wikström K, Aunola S, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hämäläinen H, Rastas M, Salminen V, Cepaitis Z, Hakumäki M, Kaikkonen H, Härkönen P, Sundvall J, Tuomilehto J, Uusitupa M; Finnish Diabetes Prevention Study. Physical activity in the prevention of type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 2005;54(1):158-165.

33. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374(9702):1677-1686.

34. Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368(9548):1673–1679

35. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008;371(9626):1783–1789.
37. Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol 2007;18(3):263-270.

38. Reaven GM. Insulin resistance: the link between obesity and cardiovascular disease. Med Clin North Am 2011;95(5):875-892.

39. Wing R, Gillis B. The Diabetes Prevention Program’s Lifestyle Change Program. Pittsburgh, PA, University of Pittsburgh, 1996. Available from http://www.bsc.gwu.edu/dpp/lifestyle/DPP_duringcore.pdf. Accessed February 8, 2013.

40. Garvey WT, Najarian T, Peterson CA. Significant weight loss with controlled-release phentermine/topiramate (PHEN/TPM CR) is associated with significant reductions in use of concomitant medications for cardiometabolic diseases over 108 weeks. Obesity 2011;19:S176: 594-P.
Table 1. Baseline demographics and clinical characteristics of the cohort with Prediabetes and/or Metabolic Syndrome at baseline (intent to treat)*

| 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 body-mass index, kg/m² (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 (mm Hg)            |                  |                           |                          |
|                       |         |         |         |
|-----------------------|---------|---------|---------|
| 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 antidiabetic | 1 (0.6) | 1 (0.9) | 2 (1) |
| medication use, n (%)                      | group 1 | group 2 | group 3 |
|-------------------------------------------|---------|---------|---------|
| 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)   |

*Defined as subjects with Prediabetes, Metabolic Syndrome, or both at baseline.

†There were missing values for hs-CRP for 1 subject in the 15/92 group.

PHEN/TPM ER, phentermine and topiramate extended-release; SD, standard deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.
Figure Legends

Figure 1. Percent weight loss from baseline to week 108 in the cohort with Prediabetes and/or Metabolic Syndrome at baseline.

Least-squares mean percent weight loss in intent-to-treat population of subjects with Prediabetes and/or Metabolic Syndrome; $P < 0.0001$ vs placebo for all time points assessed. LS, least-squares; LOCF, last observation carried forward; MI, multiple imputation; PHEN/TPM ER, phentermine and topiramate extended-release.

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 Metabolic Syndrome cohort (ITT). B, Annualized incidence rates of type 2 diabetes at study end in the Prediabetes cohort and the Metabolic Syndrome cohort (ITT). C, Relationship between weight loss and type 2 diabetes incidence at study end in the Prediabetes and/or Metabolic Syndrome cohort (ITT-MI). Error bars represent 95% CI. Annualized incidence rate of type 2 diabetes was based on first occurrence of 2 consecutive FG $\geq 7.0$ mmol/L, 2 consecutive OGTT $\geq 11.1$ mmol/L, or taking antidiabetic 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.
ITT, intent to treat; CI, confidence interval; FG, fasting glucose; OGTT, oral glucose tolerance test; PHEN/TPM ER, phentermine and topiramate extended-release.

**Figure 3. Glycemic and lipid parameters at week 108 in the cohort with Prediabetes and/or Metabolic Syndrome at baseline (ITT-MI).**

A, Least-squares mean percent change from baseline in glucose in subjects in the Prediabetes and/or Metabolic Syndrome cohort. B, Least-squares mean percent change from baseline in insulin in the Prediabetes and/or Metabolic Syndrome cohort. C, Least-squares mean percent change from baseline in lipid parameters in the Prediabetes and/or Metabolic Syndrome 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.

ITT, intent to treat; MI, multiple imputation; CI, confidence interval; OGTT, oral glucose tolerance test; LS, least-squares; PHEN/TPM ER, phentermine and topiramate extended-release; HDL, high-density lipoprotein.
Figure 1. Percent weight loss from baseline to week 108 in the cohort with Prediabetes and/or Metabolic Syndrome at baseline. Least-squares mean percent weight loss in intent-to-treat population of subjects with Prediabetes and/or Metabolic Syndrome (combination group); $P < 0.0001$ vs placebo for all time points assessed. LS, least-squares; LOCF, last observation carried forward; MI, multiple imputation; PHEN/TPM ER, phentermine and topiramate extended-release.

172x121mm (300 x 300 DPI)
Figure 2. Incidence rates of type 2 diabetes from baseline to week 108 in SEQUEL study (ITT). 
A, Cumulative incidence rates of type 2 diabetes at study end (Kaplan-Meier) in the Prediabetes and/or 
Metabolic Syndrome cohort (ITT). B, Annualized incidence rates of type 2 diabetes at study end in the 
Prediabetes cohort. C, Annualized incidence rates of type 2 diabetes at study end in the 
Metabolic Syndrome cohort (ITT). DC, Relationship between weight loss and type 2 diabetes incidence at study end in the 
Prediabetes and/or Metabolic Syndrome cohort (ITT-MI). Error bars represent 95% CI. Annualized 
incidence rate of type 2 diabetes was based on first occurrence of 2 consecutive FG ≥7.0 mmol/L, 2 
consecutive OGTT ≥11.1 mmol/L, or taking antidiabetic 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. 
ITT, intent to treat; CI, confidence interval; FG, fasting glucose; OGTT, oral glucose tolerance test; 
PHEN/TPM ER, phentermine and topiramate extended-release.
Figure 3. Glycemic and lipid parameters at week 108 in the cohort with Prediabetes and/or Metabolic Syndrome at baseline (ITT-MI).

A, Least-squares mean percent change from baseline in glucose in subjects in the Prediabetes and/or Metabolic Syndrome cohort. B, Least-squares mean percent change from baseline in insulin in the Prediabetes and/or Metabolic Syndrome cohort. C, Least-squares mean percent change from baseline in lipid parameters in the Prediabetes and/or Metabolic Syndrome 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.

ITT, intent to treat; MI, multiple imputation; CI, confidence interval; OGTT, oral glucose tolerance test; LS, least-squares; PHEN/TPM ER, phentermine and topiramate extended-release; HDL, high-density lipoprotein.
Appendix Figure 1. Trial profile.

Standardized lifestyle intervention was used across all treatment groups.

*One subject in the 7.5/46 group enrolled in the study but discontinued before receiving the study drug. 7.5/46, phentermine 7.5 mg/topiramate extended-release 46 mg; 15/92, phentermine 15 mg/topiramate extended-release 92 mg;

MetS, Metabolic Syndrome
Appendix Table 1. Changes from baseline to week 108 in secondary end points in the cohort with Prediabetes and/or Metabolic Syndrome at baseline (ITT-MI)

|                          | Placebo (n = 159) | PHEN/TPM ER 7.5/46 (n = 115) | PHEN/TPM ER 15/92 (n = 201) |
|--------------------------|-------------------|------------------------------|-----------------------------|
| Mean waist circumference, cm (SE) | –4.6 (0.65)       | –11.3 (0.76)*                | –12.8 (0.58)*               |
| Mean HbA$_1$c, % (SE) [mmol/mol (SE)] | 0.07 (0.02) [0.8 (0.2)] | –0.03 (0.03) [–0.3 (0.3)]†  | –0.09 (0.02) [–1.0 (0.2)]*  |
| Mean systolic blood pressure, mm Hg (SE) | –3.9 (0.98)       | –5.0 (1.14)                  | –5.1 (0.91)                 |
| Mean diastolic blood pressure, mm Hg (SE) | –3.7 (0.73)       | –3.6 (0.82)                  | –3.8 (0.61)                 |
| Mean HOMA-IR (SE)             | –0.8 (0.21)       | –1.7 (0.25)†                 | –1.8 (0.21)§                |
| Mean WBISI (SE)              | 1.6 (0.36)        | 2.4 (0.47)                   | 3.4 (0.33)¶                 |

*P < 0.0001, †P = 0.0037, ‡P = 0.0047, §P = 0.0006, ¶P = 0.0003 vs placebo for all comparisons.

Data represent least-squares mean change in subjects with Prediabetes or Metabolic Syndrome at baseline, intent-to-treat with multiple imputation.

HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance; WBISI, Whole Body Insulin Sensitivity Index.
Appendix Table 2. Changes from baseline to week 108 in secondary end points in the cohort with Prediabetes and/or Metabolic Syndrome at baseline (ITT-LOCF)

|                                     | Placebo (n = 159) | PHEN/TPM ER 7.5/46 (n = 115) | PHEN/TPM ER 15/92 (n = 201) |
|-------------------------------------|------------------|-----------------------------|-----------------------------|
| Mean waist circumference, cm (SE)   | –4.4 (0.63)      | –11.4 (0.74)*               | –12.9 (0.56)*               |
| Mean fasting glucose, mmol/L (SE)  | 0.01 (0.05)      | –0.18 (0.06)†               | –0.32 (0.04)*               |
| Mean 2-hour OGTT glucose, mmol/L (SE) | –0.37 (0.14)    | –0.57 (0.16)                | –1.01 (0.12)‡               |
| Mean HbA1c, % (SE) [mmol/mol (SE)] | 0.08 (0.02) [0.9 (0.2)] | –0.03 (0.02) [-0.3 (0.2)]§ | –0.09 (0.02) [-1.0 (0.2)]* |
| Mean fasting insulin, pmol/L (SE)  | –18.4 (5.0)      | –39.2 (5.9)†                | –37.3 (4.5)"                |
| Mean 2-hour OGTT insulin, pmol/L (SE) | –157.2 (30.7)  | –264.0 (36.1)‖               | –327.0 (27.3)*              |
| Mean systolic blood pressure, mm Hg (SE) | –4.1 (0.92)     | –4.9 (1.08)                 | –5.2 (0.82)                  |
| Mean diastolic blood pressure, mm   | –3.7 (0.66)      | –3.2 (0.77)                 | –3.8 (0.58)                  |
|                  | Hg (SE)                  | Mean HOMA-IR (SE) | Mean WBISI (SE) | Mean non–HDL-C, % (SE) | Mean HDL-C, % (SE) | Mean triglycerides, % (SE) |
|-----------------|--------------------------|-------------------|-----------------|------------------------|-------------------|---------------------------|
| **P < 0.0001,** | †P = 0.011, ‡P = 0.005, | –0.8 (0.21)       | 1.5 (0.42)      | –9.1 (1.42)            | 6.6 (1.54)        | –1.1 (2.77)                |
| ††P = 0.0033,  | §§P = 0.0002            | –1.7 (0.25)**     | 2.8 (0.49)††     | –9.9 (1.67)            | 10.0 (1.81)       | –13.3 (3.26)†‖             |
| §§§P = 0.0002, | ¶¶P = 0.0047 vs placebo for all comparisons. | –1.7 (0.19)††     | 3.6 (0.37)§§     | –10.0 (1.26)          | 14.2 (1.37)§§       | –17.7 (2.46)*              |
|                 |                          |                   |                 |                        |                   |                           |

Data represent LS mean change in subjects with Prediabetes and/or Metabolic Syndrome at baseline, intent-to-treat with last observation carried forward.

ITT, intent to treat; LOCF, last observation carried forward; PHEN/TPM ER, phentermine and topiramate extended-release; SE, standard error; OGTT, oral glucose tolerance test; HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance; WBISI, Whole Body Insulin Sensitivity Index; HDL-C, high-density lipoprotein cholesterol.
Appendix Table 3. Most common treatment-emergent adverse events in the Prediabetes and/or Metabolic Syndrome group occurring in ≥5% of subjects in any group (and more frequently in PHEN/TPM ER than in placebo) over 108 weeks in the SEQUEL trial (ITT; Safety Set)

| Treatment-Emergent Adverse Events, n (%) | Placebo (n = 159) | PHEN/TPM ER 7.5/46 (n = 115) | PHEN/TPM ER 15/92 (n = 201) |
|-----------------------------------------|------------------|-------------------------------|-------------------------------|
| Paresthesia                             | 3 (1.9)          | 19 (16.5)                     | 56 (27.9)                     |
| Sinusitis                               | 19 (11.9)        | 21 (18.3)                     | 52 (25.9)                     |
| Dry mouth                               | 5 (3.1)          | 19 (16.5)                     | 47 (23.4)                     |
| Constipation                            | 17 (10.7)        | 24 (20.9)                     | 45 (22.4)                     |
| Headache                                | 18 (11.3)        | 9 (7.8)                       | 28 (13.9)                     |
| Dysgeusia                               | 4 (2.5)          | 14 (12.2)                     | 27 (13.4)                     |
| Insomnia                                | 16 (10.1)        | 16 (13.9)                     | 24 (11.9)                     |
| Influenza                               | 15 (9.4)         | 15 (13.0)                     | 23 (11.4)                     |
| Procedural pain                         | 9 (5.7)          | 10 (8.7)                      | 23 (11.4)                     |
| Diarrhea                                | 12 (7.5)         | 14 (12.2)                     | 21 (10.4)                     |
| Condition                        | Values         |
|---------------------------------|----------------|
| Cough                           | 6 (3.8)        |
|                                 | 9 (7.8)        |
|                                 | 21 (10.4)      |
| Fatigue                         | 8 (5.0)        |
|                                 | 7 (6.1)        |
|                                 | 18 (9.0)       |
| Bronchitis                      | 10 (6.3)       |
|                                 | 10 (8.7)       |
|                                 | 17 (8.5)       |
| Dizziness                       | 4 (2.5)        |
|                                 | 10 (8.7)       |
|                                 | 14 (7.0)       |
| Edema peripheral                | 8 (5.0)        |
|                                 | 3 (2.6)        |
|                                 | 14 (7.0)       |
| Pharyngolaryngeal pain          | 8 (5.0)        |
|                                 | 2 (1.7)        |
|                                 | 14 (7.0)       |
| Vision blurred                  | 6 (3.8)        |
|                                 | 5 (4.3)        |
|                                 | 12 (6.0)       |
| Hypokalemia                     | 1 (0.6)        |
|                                 | 4 (3.5)        |
|                                 | 12 (6.0)       |
| Nausea                          | 10 (6.3)       |
|                                 | 11 (9.6)       |
|                                 | 11 (5.5)       |
| Back injury                     | 8 (5.0)        |
|                                 | 6 (5.2)        |
|                                 | 11 (5.5)       |
| Anxiety                         | 2 (1.3)        |
|                                 | 6 (5.2)        |
|                                 | 11 (5.5)       |
| Rash                            | 5 (3.1)        |
|                                 | 6 (5.2)        |
|                                 | 9 (4.5)        |
| Musculoskeletal pain            | 7 (4.4)        |
|                                 | 9 (7.8)        |
|                                 | 10 (5.0)       |
| Osteoarthritis                  | 6 (3.8)        |
|                                 | 7 (6.1)        |
|                                 | 10 (5.0)       |
| Alopecia                        | 1 (0.6)        |
|                                 | 7 (6.1)        |
|                                 | 10 (5.0)       |
| Condition              | Group 1 | Group 2 | Group 3 |
|------------------------|---------|---------|---------|
| Myalgia                | 5 (3.1) | 5 (4.3) | 10 (5.0) |
| Sinus congestion       | 7 (4.4) | 10 (8.7) | 9 (4.5)  |
| Muscle strain          | 3 (1.9) | 6 (5.2) | 9 (4.5)  |
| Contusion              | 3 (1.9) | 6 (5.2) | 8 (4.0)  |
| Decreased appetite     | 3 (1.9) | 7 (6.1) | 7 (3.5)  |
| Joint sprain           | 6 (3.8) | 7 (6.1) | 6 (3.0)  |
| Neck pain              | 7 (4.4) | 7 (6.1) | 4 (2.0)  |
| Dyspepsia              | 7 (4.4) | 6 (5.2) | 4 (2.0)  |
| Vomiting               | 4 (2.5) | 6 (5.2) | 4 (2.0)  |

ITT, intent to treat; PHEN/TPM ER, phentermine and topiramate extended-release.
Appendix Table 4. Most common serious adverse events in the Prediabetes and/or Metabolic Syndrome group occurring in >0.5% of subjects in any group in the SEQUEL trial (ITT; Safety Set)

| Treatment-Emergent Adverse Events, n (%) | Placebo (n = 159) | PHEN/TPM ER 7.5/46 (n = 115) | PHEN/TPM ER 15/92 (n = 201) |
|-----------------------------------------|------------------|-----------------------------|-----------------------------|
| Appendicitis                            | 1 (0.6)          | 0                           | 2 (1.0)                     |
| Bursitis infection                      | 0                | 1 (0.9)                     | 0                           |
| Gastroenteritis                         | 1 (0.6)          | 0                           | 0                           |
| Pneumonia                               | 1 (0.6)          | 0                           | 0                           |
| Pyelonephritis                          | 0                | 1 (0.9)                     | 0                           |
| Intervertebral disc protrusion          | 1 (0.6)          | 0                           | 0                           |
| Myocardial infarction                   | 0                | 1 (0.9)                     | 1 (0.5)                     |
| Atrial fibrillation                     | 0                | 1 (0.9)                     | 0                           |
| Tachycardia                             | 0                | 1 (0.9)                     | 0                           |
| Intracranial hemorrhage                 | 1 (0.6)          | 0                           | 0                           |
| Transient ischemic attack               | 0                | 1 (0.9)                     | 0                           |
| Cholecystitis                           | 0                | 1 (0.9)                     | 1 (0.5)                     |
| Condition              | Count | S | 0   | 0   |
|------------------------|-------|---|-----|-----|
| Pelvic pain            | 1 (0.6) |   |     |     |
| Non-cardiac chest pain | 1 (0.6) |   |     |     |
| Serositis              | 1 (0.6) |   |     |     |
| Mesothelioma           | 1 (0.6) |   |     |     |
| Goiter                 | 0     |   | 1 (0.9) |     |
| Drug hypersensitivity  | 1 (0.6) |   |     |     |
| Depression             | 1 (0.6) |   |     |     |
| Hypotension            | 1 (0.6) |   |     |     |
Appendix Table 5. Baseline demographics of patients included vs those excluded from the analysis

| Parameter                                      | Prediabetes and/or Metabolic Syndrome Cohort (n = 475) | Excluded Cohort (n = 1973) | P Value |
|------------------------------------------------|--------------------------------------------------------|-----------------------------|---------|
| Age (years)                                    | 52.0 (10.4)                                             | 50.9 (10.4)                 | 0.0457  |
| Women, n (%)                                   | 308 (64.8)                                              | 1404 (71.2)                 | 0.0070  |
| HDL-C (mmol/mol)                               | 1.2 (0.3)                                               | 1.2 (0.4)                   | 0.0100  |
| Fasting glucose, mmol/L                        | 5.7 (0.7)                                               | 5.9 (1.3)                   | 0.0007  |
| HbA$_1c$ (%) [mmol/L (SD)]                     | 5.7 (0.5) [39 (4.9)]                                    | 5.9 (0.8) [41 (8.7)]       | <0.0001 |
| Subjects with antidiabetic medication use, n (%)| 4 (0.8)                                                 | 249 (12.6)                  | <0.0001 |
| Subjects with lipid-lowering medication use, n (%)| 194 (40.8)                                             | 700 (35.5)                  | 0.0293  |
Appendix Figure 1. Trial profile.

Standardized lifestyle intervention was used across all treatment groups.

*One subject in the 7.5/46 group enrolled in the study but discontinued before receiving the study drug. 7.5/46, phentermine 7.5 mg/topiramate extended-release 46 mg; 15/92, phentermine 15 mg/topiramate extended-release 92 mg; MetS, Metabolic Syndrome

172x169mm (300 x 300 DPI)