Weight-Loss Therapy in Type 2 Diabetes: Effects of Phentermine and Topiramate Extended-Release

OBJECTIVE

Treatment algorithms for type 2 diabetes recommend weight loss for disease management. The safety and efficacy of treatment with phentermine (PHEN)/topiramate (TPM) extended-release (ER) plus lifestyle modification for weight loss and glycemic benefits were assessed in two randomized, double-blind, placebo-controlled 56-week studies of obese/overweight adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The OB-202/DM-230 Study was a 56-week phase 2 trial that randomized subjects to receive once-daily placebo or PHEN/TPM ER 15 mg/92 mg (15/92). The primary end point was change in HbA1c level. A post hoc analysis of a subpopulation with type 2 diabetes from a second study, CONQUER, is also presented. All subjects made lifestyle modifications, and comorbidities were managed to the standard of care.

RESULTS

The study groups comprised 130 subjects with type 2 diabetes enrolled in the OB-202/DM-230 study (mean baseline HbA1c 8.7% [72 mmol/mol]) and 388 subjects with type 2 diabetes in the CONQUER study (mean baseline HbA1c 6.8% [51 mmol/mol]). At week 56 in the OB-202/DM-230, change in weight (from intent-to-treat sample with last observation carried forward [ITT-LOCF]) was −2.7% for placebo and −9.4% for PHEN/TPM ER 15/92 (P < 0.0001 vs. placebo). Change in HbA1c level (from ITT-LOCF) was −1.2% (−13.1 mmol/mol) for placebo and −1.6% (−17.5 mmol/mol) for PHEN/TPM ER 15/92 (P = 0.0381). In both the OB-202/DM-230 and CONQUER, greater numbers of patients randomized to receive PHEN/TPM ER treatment achieved HbA1c targets with reduced need for diabetes medications when compared with the placebo group. Common adverse events included paraesthesia, constipation, and insomnia.

CONCLUSIONS

PHEN/TPM ER plus lifestyle modification can effectively promote weight loss and improve glycemic control as a treatment approach in obese/overweight patients with type 2 diabetes.
resistance, dysregulated secretion of adipokines, and systemic inflammation (2,3). Additionally, weight loss has long been known to enhance insulin sensitivity and improve glycemia in type 2 diabetes patients (4,5). This has been underscored more recently by the Look AHEAD Study, which demonstrated that structured lifestyle modifications led to progressive decrements in HbA1c level as a function of the amount of weight loss achieved over the range of 5% to ∼15%, together with improvements in dyslipidemia and blood pressure (6,7). Despite these results, treatment algorithms for type 2 diabetes, while advocating changes in diet and physical activity, have not until recently emphasized the treatment of obesity as a primary strategy for the management of type 2 diabetes (1,8–12). The underemphasis on weight-loss therapy may relate to difficulties in maintaining clinically meaningful reductions in body weight through diet and lifestyle changes alone (4,9,13), and to the paucity of effective and safe obesity medications (14). Indeed, approved pharmacologic weight-loss agents have historically demonstrated only modest efficacy (13,15,16), emphasizing the clear need for therapeutic options that produce more robust and sustained weight loss in patients with type 2 diabetes.

The recent approval of new medications with an indication for long-term weight management, together with lifestyle modification, have enabled the development of more effective strategies and medical models for the treatment of obesity as a disease (17). For example, the complications-centric approach of the American Association of Clinical Endocrinologists (AACE) emphasizes that the presence and severity of complications—rather than BMI—should be the primary factors used in clinical decision making regarding weight-loss treatment modality and intensity (2). In this context, given that type 2 diabetes is a major complication of obesity, it is imperative that the new, enhanced treatment options for obesity be examined as a primary therapeutic modality (18).

The combination of phentermine (PHEN)/topiramate (TPM) extended-release (ER) is a weight-loss medication approved by the U.S. Food and Drug Administration in 2012 as an adjunct to lifestyle modification for long-term treatment of obesity and overweight (19). PHEN/TPM ER has been shown to improve cardiometabolic parameters (20,21) and prevent progression to type 2 diabetes in patients with prediabetes and/or metabolic syndrome (22). This article presents two randomized, placebo-controlled clinical studies (the OB-202/DM-230 Study and a post hoc analysis of the CONQUER Study, a 56-week phase 3 trial in obese adults with obesity-related comorbid conditions) in patients with a type 2 diabetes over a broad range of severity, treated with lifestyle modification and PHEN/TPM ER. The subset of patients with type 2 diabetes in the CONQUER were treated with metformin or diet alone at study entry (21), while patients in the OB-202/DM-230 had more longstanding diabetes that required more intensive therapy.

**RESEARCH DESIGN AND METHODS**

**OB-202/DM-230 Study**

**Study Design**

The DM-230 Study was a 28-week, double-blind continuation of a 28-week, phase 2, randomized, double-blind, placebo-controlled study (OB-202) assessing the efficacy and safety of PHEN and TPM in the glycemic management of obese subjects with type 2 diabetes. Subjects were actively managed to standard of care for their comorbidities including the options to add, discontinue, or adjust the dose of medications for type 2 diabetes, hypertension, and/or dyslipidemia. All subjects received lifestyle counseling at randomization in the OB-202 Study and again at their first DM-230 Study visit, including recommendations for caloric reduction (by 500 kcal/day), daily exercise as tolerated, and increased water intake. This study was conducted between 12 June 2007 and 17 October 2008, and was approved by institutional review boards at each site. All subjects provided written informed consent.

**Randomization and Masking**

In the OB-202 Study, subjects were randomized 1:1 to receive placebo or active treatment, consisting of once-daily PHEN 15 mg, taken in the morning, and once-daily TPM 100 mg, taken in the afternoon. There was a 4-week titration to the randomized dose, followed by an additional 24 weeks of treatment. All subjects who completed the OB-202 Study receiving treatment and continued to meet participation requirements were eligible to continue for an additional 28 weeks in the DM-230 Study, for a total treatment period of 56 weeks. Subjects continued in their original randomized, blinded treatment group assignment for the OB-202 Study. Active treatment in the DM-230 Study was a fixed-dose, once-daily capsule containing a combination of PHEN/TPM ER 15 mg/92 mg (15/92) taken in the morning.

**Study Subjects**

To be eligible for the OB-202 Study, subjects were required to be 18 to 70 years old with type 2 diabetes controlled by diet or oral antidiabetic medications, BMI of 27–45 kg/m², and HbA1c of 7.0–12.0% (53–108 mmol/mol). To continue into the DM-230 Study, subjects had to have completed both the entire 28-week treatment period in the OB-202 Study and dosing on blinded study medication. Exclusion criteria prohibited subjects with systolic blood pressure (SBP) >150 mm Hg or diastolic blood pressure (DBP) >95 mm Hg, a history of glaucoma, or participation in a formal weight-loss program within the previous 3 months. All subjects provided written informed consent. Full exclusion criteria are listed in Supplementary Table 1.

**Study Outcomes**

The primary end point was the change in HbA1c levels between entry into the OB-202 Study and the end of treatment (week 56) in the DM-230 Study. Additional efficacy end points included percentage of weight loss; percentage of subjects achieving HbA1c levels of ≤7% and ≤6.5% (=53 and ≤48 mmol/mol); changes in concomitant use of antidiabetic medications; and changes in fasting glucose and fasting insulin levels, insulin sensitivity (by HOMA of insulin resistance and whole-body insulin sensitivity index), blood pressure, and lipid parameters. Safety end points included treatment-emergent adverse events (TEAEs) and hypoglycemic events.

**CONQUER**

The CONQUER Study was a 56-week, double-blind, placebo-controlled study in which obese and overweight adults (BMI 27–45 kg/m²; no lower limit for subjects with type 2 diabetes) with two or more weight-related comorbidities were randomized to receive placebo, PHEN/TPM ER 7.5 mg/46 mg (7.5/46),
RESULTS

Subject Disposition and Baseline Clinical Characteristics

**OB-202/DM-230**

Of the 210 subjects enrolled in the OB-202 Study, 165 (79%) completed the study. The most common reason for discontinuation from the OB-202 was lack of compliance (12%). Of those who completed the OB-202, 130 enrolled in the DM-230 Study (55 in the placebo group; 75 in the PHEN/TPM ER 15/92 group); with 92.3% completing the study (Supplementary Fig. 1A). The most common reason for withdrawal from the DM-230 was loss to follow-up (3.8%). At baseline (OB-202 week 0), clinical characteristics of the placebo and PHEN/TPM ER treatment arms were comparable (Table 1), with the exception of a higher percentage of females in the PHEN/TPM ER group. The majority of subjects (60.0%) received a diagnosis of type 2 diabetes ≤5 years previously and the mean disease duration was 9 years, with only two placebo subjects (4%) and five PHEN/TPM ER subjects (7%) having received a diagnosis of type 2 diabetes <1 year previously. Eighty-nine percent of subjects were taking one or more oral antidiabetic medications, and 60% were taking two or more medications. In total, 60.8% of subjects were taking metformin, 32.3% were taking sulfonylureas (SFUs), 3.1% were taking thiazolidinediones, and 3.1% were taking dipeptidyl peptidase-4 inhibitors; 33.8% were taking another class of medication, including SFUs but excluding insulin. The study excluded subjects receiving injectable antidiabetic medications, including insulin and GLP-1 receptor agonists. The baseline HbA1c level was 8.7% (72 mmol/mol).

**CONQUER**

Of the 2,487 subjects randomized in the CONQUER Study, 388 (15.6%) had type 2 diabetes at baseline and thus were eligible to be included in this analysis (157 of whom were randomized to receive placebo, 67 to the PHEN/TPM ER 7.5/15 group, and 164 to the PHEN/TPM ER 15/92 group); 74.5% of subjects completed all study visits (Supplementary Fig. 1B). Baseline demographic and clinical characteristics of the subjects with type 2 diabetes were similar across treatment groups (Table 1). The patients in CONQUER had shorter duration and less severe diabetes compared with those in the OB-202/DM-230. At baseline, the mean number of medications per subject was 0.6 (58.0% were taking metformin; <1% were taking an SFU, a thiazolidinedione, or a dipeptidyl peptidase-4). The majority of subjects (60.3%) had received a diagnosis of type 2 diabetes within ≤5 years. The baseline HbA1c level was 6.8% (51 mmol/mol).

Weight Loss and Glycemic Control at Week 56

**OB-202/DM-230**

Subjects randomized to receive PHEN/TPM ER had LS mean percentage of weight loss of 9.6% vs. 2.6% with placebo by mITT analysis (P < 0.0001; Fig. 1A). An ITT-LOCF analysis also demonstrated significantly greater weight loss with PHEN/TPM ER therapy (Fig. 1A). At week 56, 65% of PHEN/TPM ER subjects had achieved ≥5% weight loss vs. 24% of the placebo group (ITT-LOCF; P < 0.0001), and 37% of PHEN/TPM ER subjects had ≥10% weight loss vs. 9% of placebo subjects (ITT-LOCF; P = 0.0004).

Regarding the effects on glycemic control in the OB-202/DM-230, subjects assigned to receive PHEN/TPM ER had a greater LS mean decrease in HbA1c of −1.6% (−17.5 mmol/mol) vs. −1.2% (−13.1 mmol/mol) in the placebo group (mITT and ITT-LOCF; P < 0.05; Fig. 1B). In addition, a significantly greater percentage of PHEN/TPM ER subjects achieved the HbA1c goal of ≤7.0% (≤53 mmol/mol) compared with placebo subjects (53% vs. 40%), as well as the HbA1c target of ≤6.5% (≤48 mmol/mol) compared with placebo (32% vs. 16%; ITT-LOCF; P < 0.05, all comparisons; Fig. 2A). Significantly greater improvements in fasting glucose levels were also observed in the PHEN/TPM ER group versus the placebo group (−2.3 and −1.5 mmol/L, respectively, from baseline levels of 9.8 and 9.5 mmol/L; P < 0.05; Supplementary Fig. 2A). Other glycemic parameters are presented in Supplementary Table 2.

In these actively managed subjects, a greater percentage of PHEN/TPM ER–treated subjects decreased the number of antidiabetic medications taken during the study period compared with the placebo group (18.7% vs. 5.5%, respectively); conversely, fewer PHEN/TPM ER–treated subjects required an increase...
in antidiabetic medications (21.3% vs. 29.1%, respectively; Fig. 2C).

**CONQUER**

PHEN/TPM ER–treated patients with type 2 diabetes exhibited greater reductions in both body weight and HbA1c values than observed in the placebo group, as previously reported (21). We now report that a greater number of PHEN/TPM ER–treated subjects achieved HbA1c targets than placebo subjects (Fig. 2B). These improvements in glycemia were achieved despite greater reductions in antidiabetic medications, as well as less need to augment diabetes therapy, in the PHEN/TPM ER groups compared with the placebo group (Fig. 2D).

**Effects on Cardiometabolic Parameters**

Treatment with PHEN/TPM ER and lifestyle modifications led to reductions in SBP, DBP, and triglyceride levels, and increments in HDL cholesterol, as shown in Supplementary Table 2. In particular, in the OB-202/DM-230 Study, treatment with PHEN/TPM ER resulted in a −7.2 mm Hg LS mean reduction in SBP at week 56, which was significantly greater than the −2.4 mm Hg decrease observed after treatment with placebo (P < 0.05; ITT-LOCF; Supplementary Table 2). DBP was decreased in both treatment groups (−2.6 vs. −1.7 mm Hg), although the difference was not significant.

**Safety**

**OB-202/DM-230**

The most commonly reported TEAEs in the PHEN/TPM ER group that occurred more often than in the placebo group over 56 weeks were paraesthesia, constipation, and nausea (Supplementary Table 3). The majority of adverse events (AEs) were mild (placebo group 69.1%, PHEN/TPM ER group 60.0%). There were markedly fewer TEAEs reported during the DM-230 extension (weeks 28 through 56) than during the OB-202 (weeks 0–28), particularly in the PHEN/TPM ER group. Discontinuation of study drug due to AEs was rare and occurred only in one subject from the PHEN/TPM ER group. None of which was considered serious.

### Table 1—OB-202/DM-230 and CONQUER baseline demographics and clinical characteristics (randomized type 2 diabetes population)

<table>
<thead>
<tr>
<th></th>
<th>OB-202/DM-230</th>
<th>CONQUER type 2 diabetes population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 55)</td>
<td>PHEN/TPM ER 15/92 (n = 75)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>49.5 (8.6)</td>
<td>49.7 (7.5)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>32 (58)</td>
<td>58 (77)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>46 (84)</td>
<td>66 (88)</td>
</tr>
<tr>
<td>African American</td>
<td>7 (13)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other*</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>30 (55)</td>
<td>47 (63)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>98.1 (17.0)</td>
<td>94.9 (17.9)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>35.2 (5.0)</td>
<td>35.5 (4.7)</td>
</tr>
<tr>
<td>Mean waist circumference, cm (SD)</td>
<td>111.0 (11.6)</td>
<td>109.0 (11.7)</td>
</tr>
<tr>
<td>HbA1c, % (SD) [mmol/mol (SD)]</td>
<td>8.5 (1.3)</td>
<td>[69 (14.2)]</td>
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<td></td>
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<tr>
<td>Type 2 diabetes duration</td>
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<tr>
<td>Mean years with diagnosis (SD)</td>
<td>8.0 (6.6)</td>
<td>9.0 (7.7)</td>
</tr>
<tr>
<td>≥5 years since diagnosis, n (%)</td>
<td>29 (53)</td>
<td>49 (65)</td>
</tr>
<tr>
<td>Antidiabetic medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of medications per subject (SD)</td>
<td>1.6 (0.9)</td>
<td>1.6 (0.9)</td>
</tr>
<tr>
<td>1 oral medication, n (%)</td>
<td>16 (29)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>2 oral medications, n (%)</td>
<td>26 (47)</td>
<td>37 (49)</td>
</tr>
<tr>
<td>≥3 oral medications, n (%)</td>
<td>7 (13)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Diagnosed with dyslipidemia, n (%)</td>
<td>30 (55)</td>
<td>39 (52)</td>
</tr>
<tr>
<td>Diagnosed with hypertension, n (%)</td>
<td>23 (42)</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Number of metabolic risk factors, n (%)</td>
<td>≥3</td>
<td>52 (95)</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>39 (71)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>22 (40)</td>
</tr>
</tbody>
</table>

*Other includes American Indian, Alaskan native, native Hawaiian, or other Pacific Islander. †Dyslipidemia was defined as triglycerides ≥200 and ≤400 mg/dL or requirement for two or more medications to achieve control, defined as <200 mg/dL. ‡Metabolic risk factors included elevated fasting glucose levels, elevated waist circumference, elevated triglyceride levels, reduced HDL cholesterol level, and elevated blood pressure, per the criteria for metabolic syndrome outlined by Alberti et al. (28).
Table 3). These events appeared to be related to concomitant antidiabetic medication use; in 90% of events ($n=52$), subjects were also being treated with an SFU. All events were mild to moderate in severity; none was considered severe. Ten hypoglycemic events (15.6%) in three study subjects (one in the placebo group; two in the PHEN/TPM ER group) were deemed treatment related.

CONQUER
In assessing safety in the subset of CONQUER patients with type 2 diabetes, the majority of AEs were mild to moderate in severity and were similar to the overall safety set population (Supplementary Table 3) (21). Fewer than half of the TEAEs were classified as treatment related. Discontinuation rates due to TEAEs were 5.7%, 3.0%, and 12.8% for the placebo, PHEN/TPM ER 7.5/46, and PHEN/TPM ER 15/92 groups, respectively (Supplementary Table 3). Fifteen subjects (5 receiving placebo, 4 receiving PHEN/TPM ER 7.5/46, 6 receiving PHEN/TPM ER 15/92) reported 24 SAEs through 56 weeks. Two SAEs (chest pain and nephrolithiasis) (PHEN/TPM ER 15/92 group) were classified as treatment related. Study drug was withdrawn, and both events resolved. No single type of SAE was reported in more than one PHEN/TPM ER–treated subject or in more than two subjects overall (21).

During 56 weeks of treatment, there were six reports of hypoglycemia in five subjects, as follows: four events in the placebo group (three mild, one severe), one in the PHEN/TPM ER 7.5/46 group
(mild), and one in the PHEN/TPM ER 15/92 group (mild). None was classified as treatment related or led to study drug discontinuation; all events resolved.

CONCLUSIONS

The analysis of two clinical trials, OB-202/DM-230 and CONQUER, allowed for the assessment of efficacy and safety of PHEN/TPM ER treatment in patients with type 2 diabetes over a wide range of disease severity and chronicity. The OB-202/DM-230 Study enrolled patients with chronic, moderate-to-severe type 2 diabetes, with the majority of patients taking multiple glucose-lowering medications, while CONQUER patients had shorter-term type 2 diabetes with a lower baseline mean HbA1c level treated with diet and/or metformin. In both studies, treatment with lifestyle modification plus PHEN/TPM ER resulted in weight loss (on average 7–10%), which was sustained for 1 year. While individuals with type 2 diabetes tend to have more difficulty achieving and maintaining weight loss than those without type 2 diabetes (23,24), these data indicate that weight-loss treatment with PHEN/TPM ER plus lifestyle modification can be highly effective. Importantly, PHEN/TPM ER–assisted weight loss was accompanied by improvements in glycemic control, together with less need for conventional glucose-lowering medications. In the OB-202/DM-230 Study, treatment with PHEN/TPM ER

Figure 2—Achievement of HbA1c goals and changes in antidiabetic medication use at week 56. Achievement of HbA1c thresholds at week 56 (ITT-LOCF) in the OB-202/DM-230 Study (A) and the CONQUER Study (B) type 2 diabetes population. Percentage of subjects with changes in the number of antidiabetic medications in the OB-202/DM-230 (C) and CONQUER (D) type 2 diabetes populations. *P < 0.05 vs. placebo; †P = 0.0121 for between-group differences in CONQUER, χ² test. A: OB-202/DM-230 subjects had a mean baseline HbA1c level of 8.7% (72 mmol/mol). A significantly greater percentage of subjects treated with PHEN/TPM ER 15/92 achieved an HbA1c of \( \leq 7.0\% \) (53 mmol/mol) and an HbA1c of \( \leq 6.5\% \) (48 mmol/mol) at week 56 compared with placebo. Exact P values vs. placebo were \( P = 0.0465 \) for HbA1c \( \leq 7.0\% \) (53 mmol/mol, ITT-LOCF) and \( P = 0.0259 \) for HbA1c \( \leq 6.5\% \) (48 mmol/mol, ITT-LOCF). B: In CONQUER, differences in the achievement of HbA1c targets at week 56 were not significant within a subgroup of subjects with type 2 diabetes and HbA1c levels of \( > 7.0\% \) (53 mmol/mol) at baseline.
plus lifestyle modification reduced HbA1c levels by 1.6% (17.5 mmol/mol) from a baseline of 8.7% (72 mmol/mol), with 53% of patients achieving the HbA1c goal of ≤7.0% (≤53 mmol/mol); in the CONQUER Study, PHEN/TPM ER lowered HbA1c by 0.4% (4.4 mmol/mol) from a baseline of 6.8% (51 mmol/mol). The data indicate that PHEN/TPM ER and lifestyle modifications can be used to effectively improve glycemic control in overweight/obese patients with type 2 diabetes.

The degree of weight loss in the PHEN/TPM ER–treated groups, sustained over 1 year, met or exceeded the 5–7% weight-loss goal recommended by the American Diabetes Association for patients with type 2 diabetes (1). Approximately 60% of all PHEN/TPM ER–treated patients with type 2 diabetes in OB-202/DM-230 and CONQUER achieved ≥5% weight loss. These results align with AACE 2013 algorithms advocating weight loss, including medication-assisted weight loss, as a primary treatment approach in type 2 diabetes (2). These algorithms emphasize the utility of using lifestyle modification with or without the addition of weight-loss medications for the treatment of obesity-related complications, including type 2 diabetes, in patients with a BMI ≥27 kg/m².

Our results are compatible with those of previous studies demonstrating the beneficial effects of weight loss in patients with type 2 diabetes, whether achieved by lifestyle modification alone (4–7) or assisted by weight-loss medications (25,26). From the Look AHEAD Trial, it is clear that weight loss achieved by lifestyle modification is associated with improvements in HbA1c, fasting glucose, and other cardiometabolic parameters (6). Orlistat, a pancreatic lipase inhibitor approved for treatment of obesity, reduced HbA1c by 0.75% (8.2 mmol/mol) after 1 year of therapy (baseline 8.9% [73 mmol/mol]) in obese and overweight patients with type 2 diabetes taking metformin (P = 0.0001 vs. baseline) (25).

More recently, in the 52-week BLOOM-DM Trial, treatment with lorcaserin 10 mg twice daily plus lifestyle modification in obese/overweight patients with type 2 diabetes treated with metformin and/or an SFU reported a mean 0.9% (9.8 mmol/mol) reduction in HbA1c level (baseline 8.1% [65 mmol/mol]; P < 0.001 vs. placebo) together with 4.5% weight loss (26). The BLOOM-DM Trial also demonstrated that lorcaserin treatment reduced the need for antidiabetic medications (26).

In general, PHEN/TPM ER was well tolerated, with similar safety observed between patients with type 2 diabetes and those without type 2 diabetes in the overall CONQUER Study population (21). Hypoglycemic events were relatively uncommon, and were observed in both studies in the placebo- and drug-treated groups. The most significant finding was the higher prevalence of hypoglycemia in the OB-202/DM-230 Study, which was often associated with the use of insulin secretagogues without dose adjustments despite improvements in glycemic parameters as patients lost weight. Although almost all hypoglycemic events were mild to moderate in severity, it is important to emphasize that weight loss increases the risk of hypoglycemia in patients with type 2 diabetes, and efforts should be undertaken to minimize these risks (2).

Accordingly, blood glucose levels should be measured prior to and during treatment with PHEN/TPM ER in patients with type 2 diabetes, and reductions in doses of non–glucose-dependent antidiabetic medications should be considered at the start of negative energy balance in order to reduce the risk of hypoglycemia (19,27).

The current studies have certain limitations. The DM-230 Study was an extension of the OB-202 Study; although all patients who completed the OB-202 were eligible to enroll in the DM-230, more placebo patients (n = 21) elected not to enroll compared with the PHEN/TPM ER–treated patients (n = 14), and thus the original 1:1 randomization ratio was not maintained in the DM-230. In both the DM-230 and CONQUER, all patients received lifestyle modification treatment, and thus the benefits presented here reflect a combination of PHEN/TPM ER plus lifestyle modification (21). Also, since both studies involved active management to standards of care, changes in the use of concomitant medications for the treatment of hypertension, dyslipidemia, and hyperglycemia are likely to have affected related study variables, often masking the true clinical difference between patients randomized to receive PHEN/TPM ER versus placebo. However, active management was applied consistently by treatment-blinded clinicians across placebo and PHEN/TPM ER treatment groups in an effort to approximate real-world clinical practice. Even so, additional longer-term data will add to the understanding of the benefits and risks of prolonged PHEN/TPM ER use in patients with type 2 diabetes.

In conclusion, treatment with PHEN/TPM ER plus lifestyle modification produced significant weight loss and improvements in glycemic control, together with reductions in blood pressure and triglyceride levels, over 56 weeks in obese/overweight patients with type 2 diabetes. The medication was generally well tolerated. These data indicate that medication-assisted weight loss, using PHEN/TPM ER, may constitute a new and effective approach for treating obese and overweight patients with type 2 diabetes. Indeed, consistent with the AACE algorithm (2), weight-loss therapy can be considered integral to the treatment of type 2 diabetes together with conventional glucose-lowering medications, and, in fact, can be used as a primary therapeutic modality to improve glycemic control in type 2 diabetes.

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VIVUS, Inc.; has participated in clinical trials for or sponsored by VIVUS, Inc.; and is a consultant for Valeritas and VIVUS, Inc. R.F.K. has served as a paid consultant/advisor to VIVUS, Inc., Novo Nordisk, Takeda, Retrofit, and Zafgen; and has participated in clinical trials with Weight Watchers, Novo Nordisk, and Aspire Bariatrics. M.R. has participated in clinical trials with Abbott Laboratories, Amylin Pharmaceuticals, Bristol-Meyers Squibb, Daiichi-Sankyo, Inc., Eli Lilly and Company, Isis/Genzyme, Merck and Co., Roche Laboratories, and VIVUS, Inc.; and R.V.D. has received travel support from VIVUS, Inc. R.V.D. and B.T. are employees of VIVUS, Inc. Funding for the study and for editorial assistance was provided by VIVUS, Inc.

The sponsor of the study collaborated with the investigators in protocol design, data analyses, interpretation, and preparation of the report. The authors had full freedom to express their views.

**Author Contributions.** W.T.G. and D.H.R. were involved in the study design; the collection, analysis, and interpretation of the data; and the writing and approval of the manuscript. N.J.V.B. was involved in the collection, analysis, and interpretation of the data; and the writing and approval of the manuscript. R.F.K., M.R., and R.V.D. were involved in the data interpretation, and the writing and approval of the manuscript. B.T. was involved in the study design, the data interpretation, and the writing and approval of the manuscript. W.T.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** A portion of the data in the present article was previously included in the article on the CONQUER Study by Gadde et al. (21). This included weight loss and change in HbA1c levels among subjects with type 2 diabetes at week 56 (intention-to-treat last observation carried forward only), and change in antidiabetic medications. The current article expands on these data and includes weight loss, HbA1c levels, and fasting glucose levels over time (modified intention-to-treat as well as the percentage of patients achieving the HbA1c targets of ≤6.5% and ≤7.0%, improvements in cardiometabolic parameters, and safety data for the type 2 diabetes population. The data for the OB202/DM-230 Study has not been previously published.

**References**