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

W. Timothy Garvey,[1,2] Donna H. Ryan,[3] Nancy J.V. Bohannon,[4] Robert F. Kushner,[5] Miriam Rueger,[6] Roman V. Dvorak,[7] and Barbara Troupin[7]

Diabetes Care 2014;37:3309–3316 | DOI: 10.2337/dc14-0930

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 HbA_{1c} 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 HbA_{1c} 8.7% [72 mmol/mol]) and 388 subjects with type 2 diabetes in the CONQUER Study (mean baseline HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} targets with reduced need for diabetic 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.

Management of type 2 diabetes has traditionally been centered on the control of glycemic levels through periodic blood glucose monitoring, lifestyle and nutritional modifications, and use of medications that augment insulin secretion or improve insulin sensitivity (1,2). Most patients with type 2 diabetes are overweight or obese, with accumulation of intra-abdominal fat, which is associated with exacerbation of insulin

[1]*Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL*
[2]*Birmingham VA Medical Center, Birmingham, AL*
[3]*Pennington Biomedical Research Center, Baton Rouge, LA*
[4]*Monteagle Medical Center, San Francisco, CA*
[5]*Northwestern University Feinberg School of Medicine, Chicago, IL*
[6]*University of Alabama at Birmingham, Birmingham, AL*
[7]*VIVUS, Inc., Mountain View, CA*

Corresponding author: W. Timothy Garvey, garveyt@uab.edu.

Received 14 April 2014 and accepted 21 August 2014.

Clinical trial reg. nos. NCT00600067 and NCT00553787, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0930/-/DC1.

resistance, dysregulated secretion of adipocytokines, 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 HbA_{1c} 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 Study 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/m^2, and HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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/m^2; 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),

or PHEN/TPM ER 15/92 (21). The full study design and the efforts made to lower HbA_{1c} level in a subset of patients with type 2 diabetes were previously published (21). This report addresses previously unpublished data from the predefined subset of CONQUER subjects with type 2 diabetes at entry. Subjects were excluded if their fasting glucose level was >13.32 mmol/L or if they were taking antidiabetic drugs other than metformin at baseline. Presented in this analysis are new data pertaining to the type 2 diabetes subset, including the percentage of subjects achieving HbA_{1c} levels of ≤7% and ≤6.5% (≤53 and ≤48 mmol/mol), changes in the concomitant use of antidiabetic medications, effects on BP and lipid parameters, and safety data such as TEAEs and hypoglycemic events.

Statistical Analysis for the OB-202/DM-230 Study and the CONQUER Substudy

In both studies, all efficacy analyses were conducted on the intent-to-treat (ITT) population, which includes all subjects who took one or more doses of the study drug or placebo and had undergone one or more post-treatment measurements. End points were analyzed at each assessment time through week 56, with the last observation carried forward (LOCF) to impute any missing values. Percentage of weight loss, HbA_{1c} level, and fasting glucose level were also assessed over time by an observed case analysis, including subjects receiving treatment who provided a measurement at each assessment time point (modified ITT [mITT]). The timing of visits and assessments was identical between studies.

ANCOVA was used to evaluate continuous efficacy variables using baseline values as a covariate and treatment as a fixed effect. Descriptive statistics as well as estimates of least squares (LS) mean, SE, and 95% CIs were computed for all continuous efficacy end points. Analyses of proportions of categorical end points were performed on the ITT population with LOCF by logistic regression. Changes in number and dosages of antidiabetic medications were evaluated using a net scoring system, and treatment group differences were analyzed by the χ^2 test. All statistical testing was two-sided and performed at the 0.05 significance level.

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. 1*A*). 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%) had received a diagnosis of type 2 diabetes ≥5 years previously at screening, 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 HbA_{1c} 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 7.5/46 group, and 164 to the PHEN/TPM ER 15/92 group); 74.5% of subjects completed all study visits (Supplementary Fig. 1*B*). 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 HbA_{1c} 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 percent weight loss of 9.6% vs. 2.6% with placebo by mITT analysis ($P < 0.0001$; Fig. 1*A*). An ITT-LOCF analysis also demonstrated significantly greater weight loss with PHEN/TPM ER therapy (Fig. 1*A*). 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 HbA_{1c} level 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. 1*B*). In addition, a significantly greater percentage of PHEN/TPM ER subjects achieved the HbA_{1c} goal of ≤7.0% (≤53 mmol/mol) compared with placebo subjects (53% vs. 40%), as well as the HbA_{1c} target of ≤6.5% (≤48 mmol/mol) compared with placebo (32% vs. 16%; ITT-LOCF; $P < 0.05$, all comparisons; Fig. 2*A*). 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. 2*A*). 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

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

	OB-202/DM-230		CONQUER type 2 diabetes population		
	Placebo (*n* = 55)	PHEN/TPM ER 15/92 (*n* = 75)	Placebo (*n* = 157)	PHEN/TPM ER 7.5/46 (*n* = 67)	PHEN/TPM ER 15/92 (*n* = 164)
Mean age, years (SD)	49.5 (8.6)	49.7 (7.5)	52.6 (9.8)	52.5 (9.3)	52.1 (10.1)
Female sex, *n* (%)	32 (58)	58 (77)	112 (71)	44 (66)	102 (62)
Race, *n* (%)					
Caucasian	46 (84)	66 (88)	133 (85)	63 (94)	136 (83)
African American	7 (13)	8 (11)	19 (12)	3 (5)	23 (14)
Asian	1 (2)	1 (1)	3 (2)	0	3 (2)
Other*	1 (2)	0	3 (2)	1 (2)	5 (3)
Ethnicity, *n* (%)					
Hispanic or Latino	30 (55)	47 (63)	46 (29)	21 (31)	50 (31)
Mean weight, kg (SD)	98.1 (17.0)	94.9 (17.9)	99.3 (18.6)	97.2 (16.1)	103.2 (20.1)
Mean BMI, kg/m^2 (SD)	35.2 (5.0)	35.5 (4.7)	36.2 (5.2)	35.3 (4.3)	37.1 (5.2)
Mean waist circumference, cm (SD)	111.0 (11.6)	109.0 (11.7)	112.7 (12.5)	111.4 (10.8)	114.1 (12.8)
HbA_{1c}, % (SD) [mmol/mol (SD)]	8.5 (1.3) [69 (14.2)]	8.8 (1.2) [73 (13.1)]	6.9 (1.3) [52 (14.2)]	6.8 (1.2) [51 (13.1)]	6.8 (1.1) [51 (12.0)]
Type 2 diabetes duration					
Mean years with diagnosis (SD)	8.0 (6.6)	9.0 (7.7)	5.0 (3.9)	5.1 (4.3)	4.6 (3.6)
≥5 years since diagnosis, *n* (%)	29 (53)	49 (65)	66 (42)	27 (40)	61 (37)
Antidiabetic medication use					
Mean number of medications per subject (SD)	1.6 (0.9)	1.6 (0.9)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
1 oral medication, *n* (%)	16 (29)	21 (28)	91 (58)	40 (60)	95 (58)
2 oral medications, *n* (%)	26 (47)	37 (49)	1 (1)	1 (1)	2 (1)
≥3 oral medications, *n* (%)	7 (13)	9 (12)	0 (0)	0 (0)	0 (0)
Diagnosed with dyslipidemia,† *n* (%)	30 (55)	39 (52)	50 (32)	27 (40)	52 (32)
Diagnosed with hypertension, *n* (%)	23 (42)	35 (47)	82 (52)	40 (60)	91 (55)
Number of metabolic risk factors,‡ *n* (%)					
≥3	52 (95)	69 (92)	143 (91)	60 (90)	144 (88)
≥4	39 (71)	55 (73)	105 (67)	53 (79)	120 (73)
5	22 (40)	34 (45)	63 (40)	32 (48)	74 (45)

*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).

in antidiabetic medications (21.3% vs. 29.1%, respectively; Fig. 2*C*).

CONQUER

PHEN/TPM ER–treated patients with type 2 diabetes exhibited greater reductions in both body weight and HbA_{1c} 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 HbA_{1c} targets than placebo subjects (Fig. 2*B*). 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. 2*D*).

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 Study (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 (treatment-related disturbance in attention and asthenia, which was considered moderate in severity and resolved without complication). A similar number of serious AEs (SAEs) were reported in the two study groups, none of which was classified as treatment related (Supplementary Table 3).

During the 56 weeks of treatment, 58 hypoglycemic events were reported in 17 OB-202/DM-230 subjects (5 treated with placebo; 12 treated with PHEN/TPM ER; safety population; Supplementary

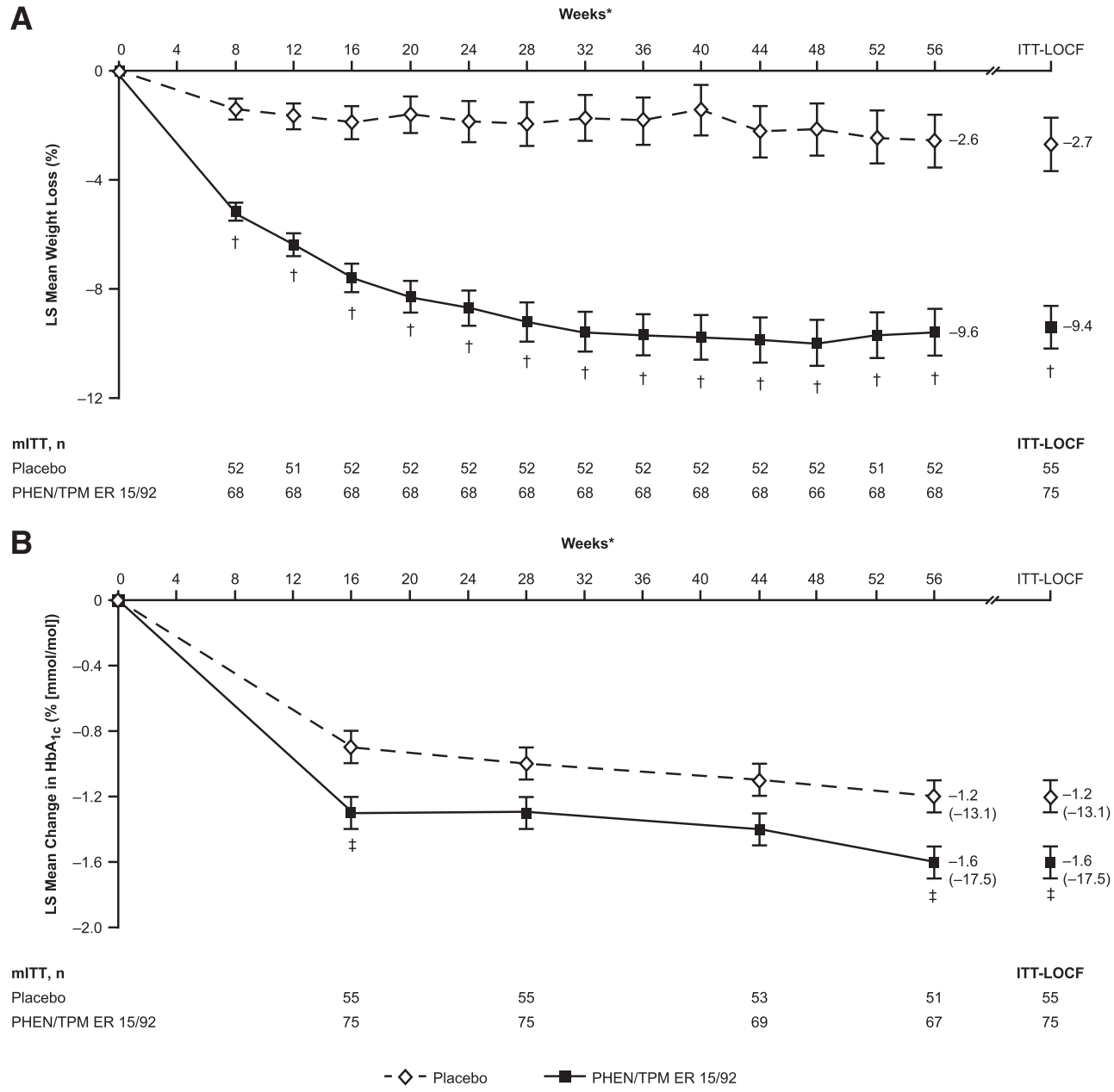

Figure 1—Weight loss and changes in HbA_{1c} from baseline to week 56 in the OB-202/DM-230 Study. Weight loss (*A*) and change in HbA_{1c} level (*B*). LS mean change (95% CI) plotted over time (mITT) and at week 56 (ITT-LOCF). *Week 28 marked the end of the OB-202 Study and the baseline for the DM-230 Study. †$P < 0.0001$ for PHEN/TPM ER groups vs. placebo at all time points except week 0. ‡$P < 0.05$ vs. placebo.

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

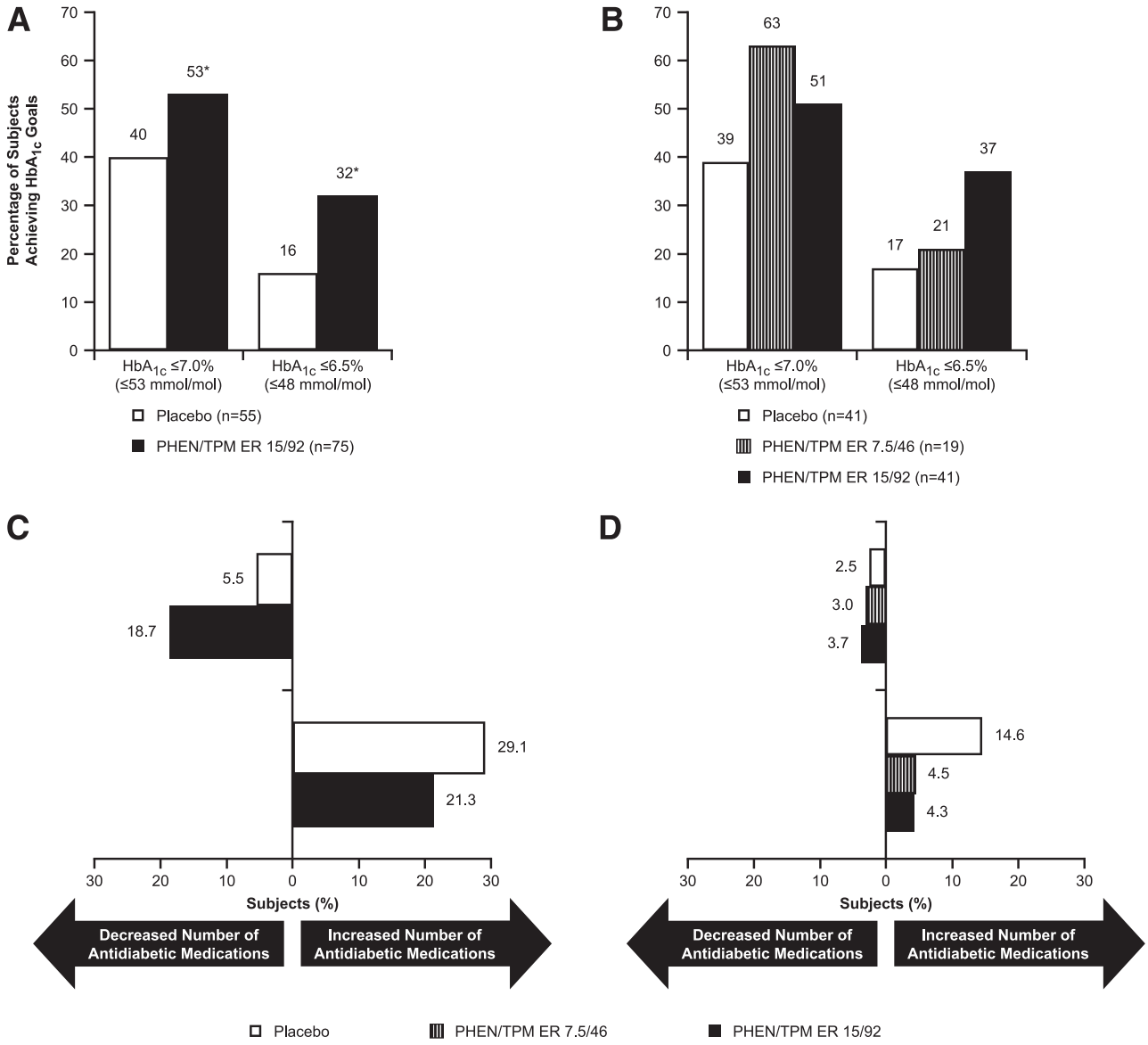

Figure 2—Achievement of HbA_{1c} goals and changes in antidiabetic medication use at week 56. Achievement of HbA_{1c} thresholds at week 56 (ITT-LOCF) in the OB-202/DM-230 Study (*A*) and the CONQUER Study (*B*) type 2 diabetes population. Percentage of subjects with changes in the number of antidiabetic medications in the OB-202/DM-230 (*C*) and CONQUER (*D*) type 2 diabetes populations. *$P < 0.05$ vs. placebo. Between-group differences in CONQUER (χ^2 test) were significant at $P = 0.0121$. *A*: OB-202/DM-230 subjects had a mean baseline HbA_{1c} level of 8.7% (72 mmol/mol). A significantly greater percentage of subjects treated with PHEN/TPM ER 15/92 achieved an HbA_{1c} of ≤7.0% (53 mmol/mol) and an HbA_{1c} of ≤6.5% (48 mmol/mol) at week 56 compared with placebo. Exact *P* values vs. placebo were $P = 0.0465$ for HbA_{1c} ≤7.0% (53 mmol/mol, ITT-LOCF) and $P = 0.0259$ for HbA_{1c} ≤6.5% (48 mmol/mol, ITT-LOCF). *B*: In CONQUER, differences in the achievement of HbA_{1c} targets at week 56 were not significant within a subgroup of subjects with type 2 diabetes and HbA_{1c} levels of >7.0% (53 mmol/mol) at baseline.

(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 HbA_{1c} 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 difficultly 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

plus lifestyle modification reduced HbA_{1c} levels by 1.6% (17.5 mmol/mol) from a baseline of 8.7% (72 mmol/mol), with 53% of patients achieving the HbA_{1c} goal of ≤7.0% (≤53 mmol/mol); in the CONQUER Study, PHEN/TPM ER lowered HbA_{1c} 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/m^2.

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 HbA_{1c}, fasting glucose, and other cardiometabolic parameters (6). Orlistat, a pancreatic lipase inhibitor approved for treatment of obesity, reduced HbA_{1c} 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 HbA_{1c} 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.

Acknowledgments. The authors thank the OB-202/DM-230 and CONQUER study subjects, investigators, and study coordinators; the Medpace team (study contract research organization); the University of Alabama at Birmingham Diabetes Research Center; The Lockwood Group (Andrea Burdett, MPH) and Sarah Odeh, BS, for editorial assistance; and VIVUS, Inc., internal contributors.

Funding. Funding for the study and for editorial assistance was provided by VIVUS, Inc.

Duality of Interest. W.T.G. has participated in clinical trials with Merck & Co., Inc., Weight Watchers, National Institutes of Health, the Veterans Administration, AstraZeneca Pharmaceuticals, VIVUS, Inc., Sanofi, and Eisai; has served as an advisor or consultant for Daiichi Sankyo Inc., LipoScience, VIVUS, Inc., Janssen Pharmaceuticals, Inc., Eisai, Novo Nordisk, Bristol-Myers Squibb/AstraZeneca, Takeda, and Boehringer Ingelheim; holds stock in Bristol-Myers Squibb, Novartis, Isis/Genzyme, Merck & Co., Inc., Pfizer Inc., and Eli Lily and Company; has received payment for lectures, including service on speakers' bureaus, from Merck & Co., Amylin Pharmaceuticals, VIVUS, Inc., and Eisai; and has received payment from VIVUS, Inc., for travel support to scientific meetings in order to present research data. D.H.R. has served as a paid consultant/advisor to VIVUS, Inc., Novo Nordisk, Eisai, Takeda, and Janssen Pharmaceuticals, Inc.; holds an equity position in Scientific Intake; and has received payment for lectures from VIVUS, Inc., and Eisai. N.J.V.B. has served as a speaker for Bristol-Myers Squibb/AstraZeneca, Amylin, Boehringer Ingelheim, Daiichi Sankyo Inc., Eli Lily and Company, Janssen Pharmaceuticals, Inc., Novo Nordisk, Santarus, Valeritas, and

VIVUS, Inc.; has participated in clinical trials for Cebix, Valeritas, and 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-Myers Squibb, Daiichi Sankyo, Inc., Eli Lilly and Company, Isis/Genzyme, Merck & Co., Roche Laboratories, and VIVUS, Inc. and has received travel support from VIVUS, Inc. R.V.D. and B.T. are employees of 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 current article was previously included in the article on the CONQUER Study by Gadde et al. (21). This included weight loss and change in HbA_{1c} 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, HbA_{1c} levels, and fasting glucose levels over time (modified intention-to-treat) as well as the percentage of patients achieving the HbA_{1c} targets of $\leq$6.5% and $\leq$7%, improvements in cardiometabolic parameters, and safety data for the type 2 diabetes population. The data for the OB-202/DM-230 Study have not been previously published.

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