SUPPLEMENTARY DATA

Methods. OB-202/DM-230

Continuous efficacy variables included HbA_{1c}, percent weight loss, and changes in fasting glucose, fasting insulin, measures of insulin sensitivity, and various cardiometabolic parameters.

All subjects who received at least one dose of study drug or placebo and had any safety data were included in the safety analyses and were summarized using descriptive statistics.

Effects on cardiometabolic parameters

OB-202/DM-230. At week 56, treatment with phentermine and topiramate extended-release (PHEN/TPM ER) resulted in least-squares (LS) mean decrements in systolic blood pressure (SBP) of −7.2 mm Hg versus −2.4 mm Hg with placebo (ITT-LOCF; *P*=0.0391; supplemental Table 2). Diastolic blood pressure (DBP) was decreased in both treatment groups (−2.6 vs −1.7 mm Hg; *P* is not significant). Mean changes in lipid parameters were not significantly different between treatment groups (supplemental Table 2).

CONQUER. Both SBP and DBP were decreased across all treatment groups at week 56 without any significant differences among treatment arms. Both PHEN/TPM ER treatment groups saw increases in high-density lipoprotein cholesterol (HDL-C), and decreases in low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides; however, these changes were comparable among treatment groups (supplemental Table 2).

SUPPLEMENTARY DATA

Supplementary Table 1. OB-202/DM-230 exclusion criteria

Exclusion Criteria
Subjects presenting with any of the following at OB-202 screening were not included in the study: • Known allergy or hypersensitivity to PHEN or TPM or the use of PHEN or TPM for any indication within the past 3 months • Current use of insulin or incretin therapy • Current use of anticonvulsant medications for any indication • SBP >150 mm Hg or DBP >95 mm Hg • Stroke, MI, life-threatening arrhythmia, or coronary revascularization within the past 6 months • Unstable angina, NYHA-defined class II-IV congestive heart failure, or known clinically significant cardiac valvulopathy • Evidence of any clinically significant renal, hepatic, psychiatric, or other condition that, in the opinion of the investigator, would contraindicate the administration of study medication, interfere with study evaluations, or confound the interpretation of study results • Clinically significant thyroid dysfunction, or use of any thyroid treatment that has not been stable for at least 3 months • Any history of bipolar disorder or psychosis, history of psychiatric hospitalization, greater than one lifetime episode of major depression, current depression of moderate or greater severity (PHQ-9 score >9), or any signs or history of suicidal ideation • Current use of any antidepressant medication that has not been stable for at least 3 months • Current use of CNS or psychiatric medications, other than SSRIs, SNRIs, Wellbutrin (bupropion), or non-benzodiazepine sleep medications (Sonata, Ambien, Lunesta) • Cholelithiasis (in the absence of treatment by cholecystectomy) within the past 6 months • Any history of nephrolithiasis • Obesity that is of a known genetic or endocrine origin • Participation in a formal weight-loss program, investigational or otherwise, within the past 3 months (includes Weight Watchers and related dietary/lifestyle intervention programs, prepared food programs, prescribed or over-the-counter weight-loss medications, dietary supplement or herbal preparations, teas, tinctures intended for weight loss; or any sort of supervised fast or very low-calorie diet) • Any past or present use of medications to treat increased intraocular pressure • Smoking cessation within the previous 3 months or plans to quit smoking during study participation • Pregnancy, breastfeeding, or plans for pregnancy during the study period • Use of any investigational medication or device for any indication within the last month • History of eating disorders (eg, bulimia, binge-eating disorder) within the

past 6 months • History of alcohol abuse (>14 drinks per week) • Previous bariatric surgery • Abnormalities in baseline physical examination, ECG, or laboratory findings considered clinically significant by the investigator • Laboratory values OUTSIDE OF the following ranges: o HbA_{1c} 7%-10% (53–108 mmol/mol), inclusive o Bicarbonate within normal limits o AST, ALT, and GGT <3× upper limit of normal o CrCl ≥60 mL/mm o Triglycerides ≤4.52 mmol/L o TSH <1.5× upper limit of normal o Negative for HIV, hepatitis B surface antigen, and hepatitis C virus o Negative pregnancy test (females of childbearing potential only) o Negative urine drug screen Subjects with either of the following were not allowed to continue into DM-230: • Subjects who developed ≥1 morbidities during OB-202 that would pose a safety concern to their continuation on blinded treatment in DM-230 • Subjects requiring treatment with excluded medications

ALT=alanine transaminase. AST=aspartate aminotransferase. BMI=body-mass index. CNS=central nervous system. CrCl=creatinine clearance. DBP=diastolic blood pressure. ECG=electrocardiogram. GGT=gamma-glutamyl transpeptidase. HIV=human immunodeficiency virus. MI=myocardial infarction. NYHA=New York Heart Association. PHEN=phentermine. SBP=systolic blood pressure. SNRI=selective norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor. TPM=topiramate. TSH=thyroid-stimulating hormone.

SUPPLEMENTARY DATA

Supplementary Table 2. OB-202/DM-230 and CONQUER changes in cardiometabolic parameters from baseline to week 56 (ITT-LOCF)

	OB-202/DM-230		CONQUER type 2 diabetes population*		
Variable	**Placebo**	**PHEN/TPMER 15/92**	**Placebo**	**PHEN/TPMER 7.5/46**	**PHEN/TPMER 15/92**
Fasting insulin, n	55	75	149	63	152
Baseline mean, pmol/L (SD)	92.0 (66.3)	73.8 (43.5)	148.3 (123.4)	119.8 (78.2)	167.4 (160.0)
LS mean change, pmol/L (SE)	40.8 (9.0)	14.5 (7.8)†	−33.7 (6.6)	−33.1 (10.2)	−37.7 (6.5)
HOMA-IR, n‡	51	65	149	63	152
Baseline mean (SD)	5.3 (3.6)	4.3 (2.4)	8.1 (10.8)	5.8 (3.8)	8.4 (8.8)
LS mean change (SE)	1.6 (0.5)	−0.4 (0.5)§	−2.3 (0.5)	−2.6 (0.7)	−2.3 (0.5)
WBISI, n‡	51	65	148	63	148
Baseline mean (SD)	3.4 (2.7)	3.3 (2.0)	2.4 (2.2)	2.6 (2.0)	2.3 (2.4)
LS mean change (SE)	−0.8 (0.2)	−0.1 (0.2)□	0.5 (0.4)	2.0 (0.6)¶	1.4 (0.4)
SBP, n	55	75	157	67	163
Baseline mean, mm Hg (SD)	124·4 (11·5)	122.3 (13.0)	125.7 (13.9)	127.0 (12.1)	126.0 (14.0)
LS mean change, mm Hg (SE)	−2·4 (1·7)	−7.2 (1.5)#	−2.1 (1.1)	−2.9 (1.6)	−4.2 (1.0)
DBP, n	55	75	157	67	163
Baseline mean, mm Hg (SD)	76.4 (7.9)	74.8 (7.8)	78.3 (9.5)	78.4 (8.6)	78.0 (9.1)
LS mean change, mm Hg (SE)	−1.7 (1.1)	−2.6 (1.0)	−1·8 (0.6)	−2.3 (1.0)	−2.4 (0.6)
LDL-C, n	55	75	152	65	158
Baseline mean, mmol/L (SD)	2.8 (0.7)	2.8 (0.8)	3.0 (0.9)	2.8 (0.9)	3.0 (1.0)
LS mean change, % (SE)	2.2 (3.7)	5.6 (3.1)	−2·3 (2·1)	−3.6 (3.2)	−2.8 (2.0)
HDL-C, n	55	75	153	65	160
Baseline mean, mmol/L (SD)	1.2 (0.4)	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)	1.2 (0.3)
LS mean change, % (SE)	−0.5 (1.9)	4.2 (1.6)	4.9 (1.4)	8.1 (2.1)	6.2 (1.4)
Total cholesterol, n	55	75	153	65	160
Baseline mean, mmol/L (SD)	4.9 (0.9)	4.9 (0.9)	5.1 (1.1)	4.9 (0.9)	5.0 (1.0)
LS mean change, % (SE)	−0.5 (2.4)	2.0 (2.1)	−0.6 (1.4)	−3.8 (2.1)	−3.8 (1.4)
Triglycerides, n	55	75	153	65	160

SUPPLEMENTARY DATA

Baseline mean, mmol/L (SD)	1.9 (0.9)	1.9 (0.9)	1.8 (0.9)	1.9 (0.8)	1.8 (0.8)
LS mean change, % (SE)	0.7 (6.5)	−2.7 (5.6)	11.0 (5.7)	−8.0 (8.8)	−10.6 (5.6)**

*For CONQUER, n values differ between variables because not all subjects had both a baseline and post-baseline measure. †*P*<0.0296 vs placebo. ‡The HOMA-IR and WBISI analyses for DM-230 include only subjects with baseline and end point measurements. §*P*=0.0051 vs placebo. ‖*P*=0.0254 vs placebo. ¶*P*=0.0420 vs placebo. #*P*=0.0391 vs placebo. **P*=0.0069 vs placebo. DBP=diastolic blood pressure. HDL-C=high-density lipoprotein cholesterol. HOMA-IR=Homeostatic Model Assessment-Insulin Resistance. LDL-C= low-density lipoprotein cholesterol. LS= least-squares. SBP=systolic blood pressure. SD=standard deviation. SE=standard error. WBISI=whole-body insulin sensitivity index.

SUPPLEMENTARY DATA

Supplementary Table 3. OB-202/DM-230 and CONQUER adverse event overview from week 0 to 56 (safety set)

	OB-202/DM-230		CONQUER type 2 diabetes population		
Preferred Term, n (%)	**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)**
Subjects reporting at least 1 AE	51 (92.7)	71 (94.7)	125 (79.6)	54 (80.6)	141 (86.0)
Summary of TEAEs ≥5% of subjects in any treatment group and greater than placebo					
Paraesthesia	0	15 (20.0)	6 (3.8)	5 (7.5)	29 (17.7)
Constipation	2 (3.6)	10 (13.3)	10 (6.4)	10 (14.9)	29 (17.7)
Insomnia	2 (3.6)	7 (9.3)	8 (5.1)	5 (7.5)	23 (14.0)
Dry mouth	0	7 (9.3)	6 (3.8)	5 (7.5)	22 (13.4)
Upper respiratory tract infection	–	–	17 (10.8)	8 (11.9)	21 (12.8)
Nausea	3 (5.5)	9 (12.0)	8 (5.1)	1 (1.5)	13 (7.9)
Urinary tract infection	1 (1.8)	4 (5.3)	8 (5.1)	8 (11.9)	9 (5.5)
Dizziness	1 (1.8)	8 (10.7)	7 (4.5)	2 (3.0)	18 (11.0)
Headache	3 (5.5)	5 (6.7)	9 (5.7)	3 (4.5)	18 (11.0)
Influenza	2 (3.6)	8 (10.7)	–	–	–
Sinusitis	–	–	8 (5.1)	7 (10.4)	9 (5.5)
Diarrhoea	5 (9.1)	7 (9.3)	7 (4.5)	2 (3.0)	10 (6.1)
Dysgeusia	–	–	0	4 (6.0)	14 (8.5)
Hypokalemia	1 (1.8)	6 (8.0)	–	–	–
Back pain	–	–	6 (3.8)	5 (7.5)	13 (7.9)
Vision blurred	–	–	4 (2.5)	3 (4.5)	13 (7.9)
Nasopharyngitis	2 (3.6)	5 (6.7)	10 (6.4)	3 (4.5)	12 (7.3)
Anxiety	2 (3.6)	5 (6.7)	–	–	–
Bronchitis	1 (1.8)	5 (6.7)	–	–	–
Depression	0	5 (6.7)	5 (3.2)	2 (3.0)	10 (6.1)
Gastroesophageal reflux disease	0	5 (6.7)	–	–	–

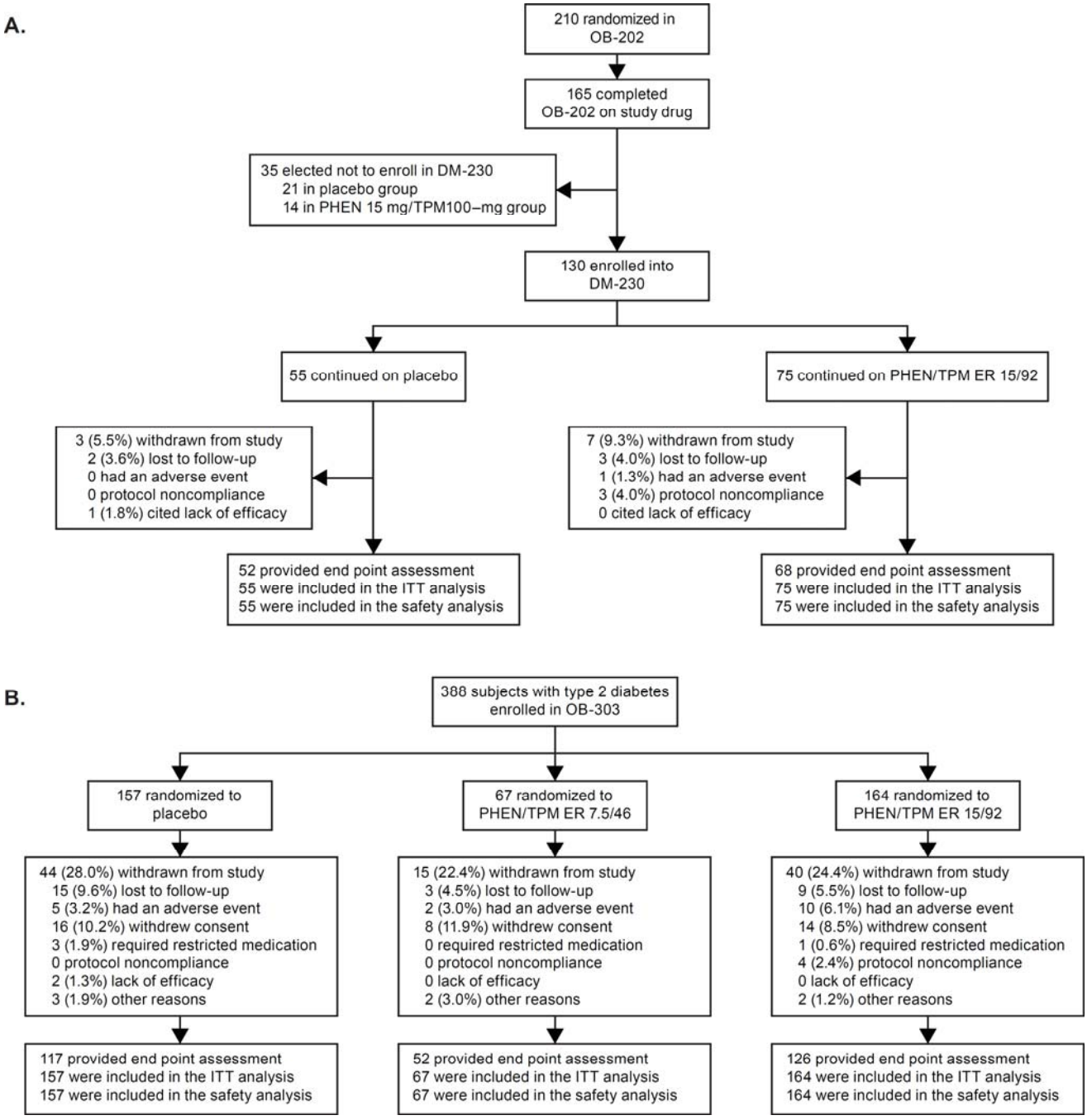
SUPPLEMENTARY DATA

Muscle spasms	–	–	6 (3.8)	4 (6.0)	8 (4.9)
Cough	–	–	2 (1.3)	1 (1.5)	9 (5.5)
Arthralgia	2 (3.6)	4 (5.3)	–	–	–
Pain in extremity	2 (3.6)	4 (5.3)	–	–	–
Incidence of SAEs	2 (3.6)	4 (5.3)	5 (3.2)	4 (6.0)	6 (3.7)
Number of events classified as treatment-related*	0	0	0	0	2 (1.2)
Discontinuation due to AEs	0	1 (1.3)	13 (8.3)	6 (9.0)	31 (18.9)
Number of events classified as treatment-related†	0	1 (1.3)	9 (5.7)	2 (3.0)	21 (12.8)
Number of hypoglycemic events	17	41	4	1	1
Number of events classified as treatment-related	4	6	0	0	0
Number of events classified as‡:					
Mild	15	33	3	1	1
Moderate	2	8	0	0	0
Severe	0	0	1	0	0

*The 2 treatment-related SAEs reported in the CONQUER 15/92 group were chest pain and nephrolithiasis. †Treatment-related AEs in OB-202/DM-230 resulting in discontinuation of one subject were described as disturbance in attention and asthenia; the events were moderate in severity and resolved without sequelae. Among CONQUER type 2 diabetes subjects, there were 39 treatment-related AEs resulting in discontinuation of 32 subjects; in the placebo group: 2 cases of palpitations, and 1 case each of alopecia, cold sweat, confusional state, dizziness, increased hepatic enzyme, insomnia, nausea, nephrolithiasis, ocular hypertension, and vision blurred; in the 7.5/46 group: 2 cases of depression; in the 15/92 group: 4 cases of depression, 3 cases of insomnia, 2 cases of nephrolithiasis, and 1 case each of agitation, amnesia, anxiety, chest pain, constipation, disturbance in attention, dysgeusia, excessive skin, feeling jittery, headache, hypertension, irritability, lung neoplasm, pain in extremity, sinus congestion, and tension headache. ‡Hypoglycemic events were defined as mild: glucose 3–4 mmol/L with subject not requiring assistance to get carbohydrates; moderate: glucose 2–3 mmol/L with subject not requiring assistance; or severe: glucose 2–3 mmol/L with subject requiring assistance or glucose <2 mmol/L with or without assistance. AE=adverse event. SAE=serious adverse event. TEAE=treatment-emergent adverse event.

SUPPLEMENTARY DATA

Supplementary Figure 1. OB-202/DM-230 and CONQUER trial profiles
(A) In DM-230, subjects who completed the 28-week OB-202 study on study drug were eligible to enrol into DM-230, where they remained on their original blinded, randomised treatment for another 28 weeks: placebo (n=55) or PHEN/TPM ER 15/92 (n=75; converted from phentermine 15 mg and topiramate 100 mg in OB-202). (B) In CONQUER, of the 15.6% (n=388) of subjects with type 2 diabetes at baseline, n=157 were randomised to placebo, n=67 to PHEN/TPM ER 7.5/46, and n=164 to PHEN/TPM ER 15/92. ITT=intention-to-treat.



SUPPLEMENTARY DATA

Supplementary Figure 2. Changes in fasting glucose from baseline to week 56
OB-202/DM-230. Least-squares mean change (95% CI) plotted over time (mITT) and at week 56 (ITT-LOCF).
†*P*<0.05 vs placebo
Mean baseline fasting glucose values (±SD): placebo, 9.5 ± 2.8 mmol/L; 15/92, 9.8 ± 3.0 mmol/L. Exact *P* values vs placebo in OB-202/DM-230: *P*=0.0104 at week 16 (mITT), *P*=0.0117 at week 28 (mITT), *P*=0.0090 at week 44 (mITT), *P*=0.0057 at week 56 (mITT) and *P*=0.0205 at week 56 (ITT-LOCF)