SUPPLEMENTARY DATA

Supplementary 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_{1c}, % (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.

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SUPPLEMENTARY DATA

Supplementary 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 HbA_{1c}, % (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 Hg (SE)	–3.7 (0.66)	–3.2 (0.77)	–3.8 (0.58)
Mean HOMA-IR (SE)	–0.8 (0.21)	–1.7 (0.25)**	–1.7 (0.19)††
Mean WBISI (SE)	1.5 (0.42)	2.8 (0.49)‡‡	3.6 (0.37)§§
Mean non–HDL-C, % (SE)	–9.1 (1.42)	–9.9 (1.67)	–10.0 (1.26)
Mean HDL-C, % (SE)	6.6 (1.54)	10.0 (1.81)	14.2 (1.37)§§
Mean triglycerides, % (SE)	–1.1 (2.77)	–13.3 (3.26)¶¶	–17.7 (2.46)*

*$P < 0.0001$, †$P = 0.011$, ‡ $P = 0.005$, §$P = 0.0015$, ¶$P = 0.0075$, #$P = 0.0052$, ‖$P = 0.025$, **$P = 0.0087$, ††$P = 0.0033$, ‡‡$P = 0.0441$, §§$P = 0.0002$, ¶¶$P = 0.0047$ vs placebo for all comparisons.

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.

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Supplementary 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)
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)
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.

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Supplementary 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)
Pelvic pain	1 (0.6)	0	0
Non-cardiac chest pain	1 (0.6)	0	0
Serositis	1 (0.6)	0	0
Mesothelioma	1 (0.6)	0	0
Goiter	0	1 (0.9)	0
Drug hypersensitivity	1 (0.6)	0	0
Depression	1 (0.6)	0	0
Hypotension	1 (0.6)	0	0

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Supplementary Table 5. Baseline demographics of patients included vs those excluded from the analysis.

Parameter	Prediabetes and/or Metabolic Syndrome Cohort (n = 475) Mean (SD)	Excluded Cohort (n = 1973) Mean (SD)	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

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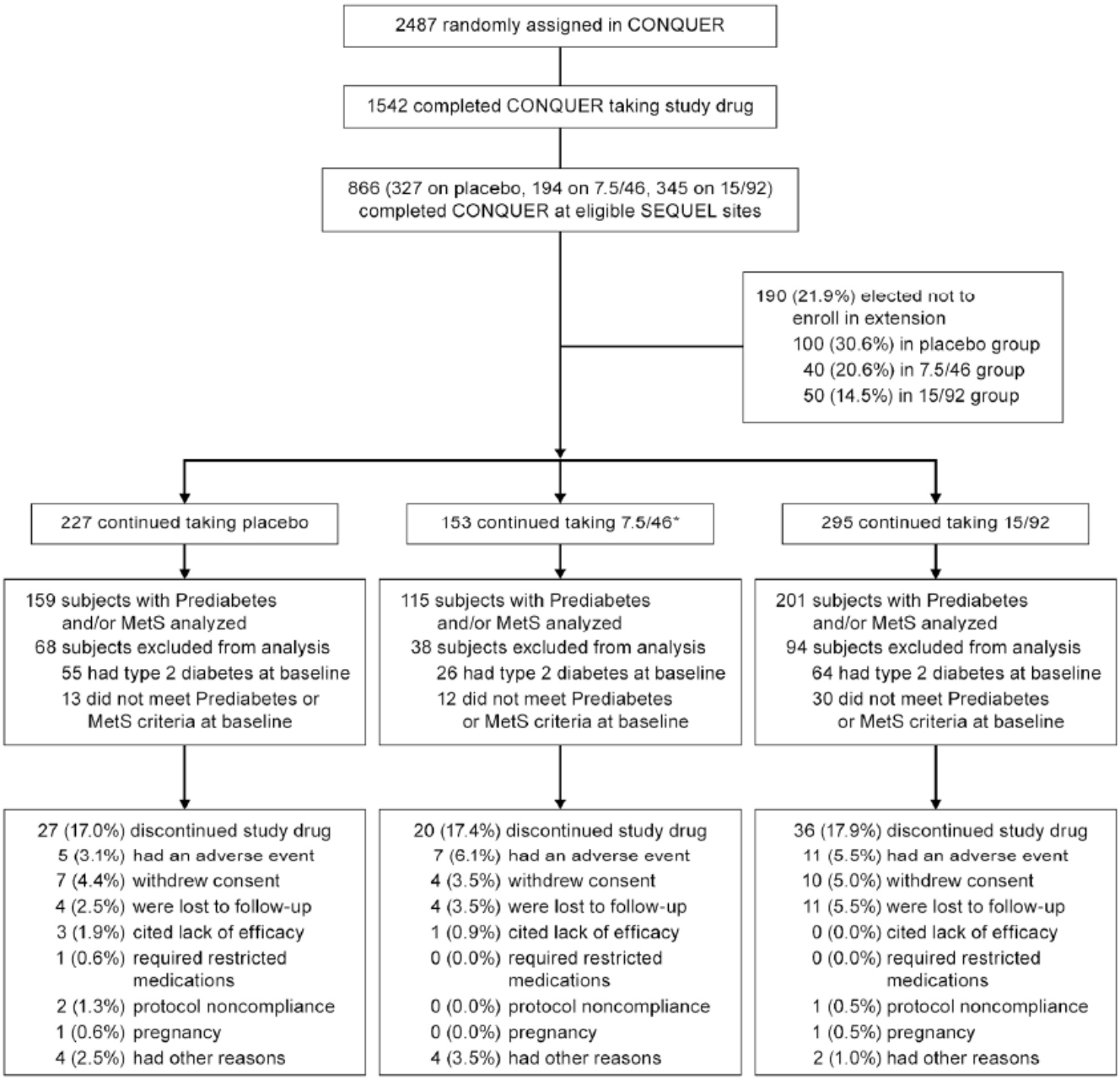
Supplementary Figure 1. Trial profile. Standardized lifestyle intervention was used across all treatment groups.



*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.

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