UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of
The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported)
May 25, 2011

VIVUS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-33389**	**94-3136179**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

1172 CASTRO STREET
MOUNTAIN VIEW, CA 94040
(Address of principal executive offices, including zip code)

(650) 934-5200
(Registrant's telephone number, including area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 7.01. Regulation FD Disclosure

On May 25, 2011, VIVUS, Inc. presented three poster presentations at the 2011 European Congress on Obesity (ECO) meeting being held May 25 to May 28, 2011, at the ICEC Lütfi Kirdar Convention & Exhibition Center in Istanbul, Turkey. The posters are entitled as follows:

· Efficacy and Tolerability of Topiramate Alone and in Combination with Phentermine;

· Weight Loss With Low-Dose, Controlled-Release Phentermine/Topiramate Therapy Improves Glycaemic Status and Prevents Progression to Type 2 Diabetes Mellitus; and

· Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks.

A graphical representation of each poster (including the reproduction of its contents) presented by the Company are attached hereto as Exhibits 99.1, 99.2 and 99.3, respectively.

The information in this Form 8-K and the exhibits attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or incorporated by reference into any of the Registrant's filings under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in any such filing.

Item 9.01. Financial Statements and Exhibits

(d) Exhibits.

Exhibit No.	Description
99.1	Poster entitled, "Efficacy and Tolerability of Topiramate Alone and in Combination with Phentermine" and a reproduction of the contents thereof.
99.2	Poster entitled, "Weight Loss With Low-Dose, Controlled-Release Phentermine/Topiramate Therapy Improves Glycaemic Status and Prevents Progression to Type 2 Diabetes Mellitus" and a reproduction of the contents thereof.
99.3	Poster entitled, "Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks" and a reproduction of the contents thereof.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

VIVUS, INC.

By: /s/ Lee B. Perry
Lee B. Perry
Vice President and Chief Accounting Officer

Date: **May 25, 2011**

EXHIBIT INDEX

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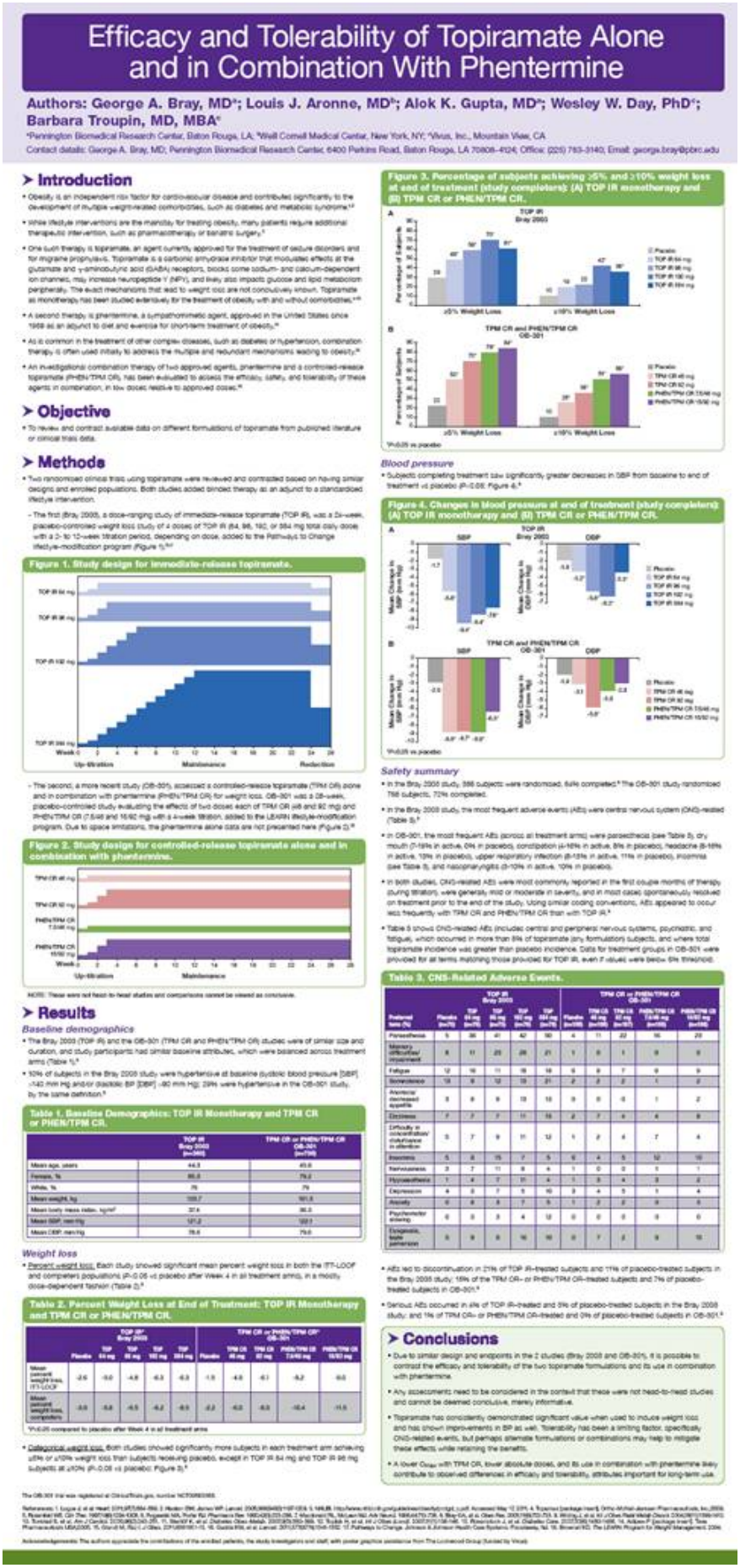
99.3	Poster entitled, "Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks" and a reproduction of the contents thereof.

Below is a graphical representation of the poster entitled "Efficacy and Tolerability of Topiramate Alone and in Combination with Phentermine":



Efficacy and Tolerability of Topiramate Alone and in Combination With Phentermine

Authors: George A. Bray, MD[a]; Louis J. Aronne, MD[b]; Alok K. Gupta, MD[a]; Wesley W. Day, PhD[c]; Barbara Troupin, MD, MBA[c]

[a]Pennington Biomedical Research Center, Baton Rouge, LA; [b]Weill Cornell Medical Center, New York, NY; [c]Vivus, Inc., Mountain View, CA

Contact details: George A. Bray, MD; Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808–4124; Office: (225) 763-3140; Email: george.bray@pbrc.edu

➤ Introduction

- Obesity is an independent risk factor for cardiovascular disease and contributes significantly to the development of multiple weight-related comorbidities, such as diabetes and metabolic syndrome.[1,2]
- While lifestyle interventions are the mainstay for treating obesity, many patients require additional therapeutic intervention, such as pharmacotherapy or bariatric surgery.[3]
- One such therapy is topiramate, an agent currently approved for the treatment of seizure disorders and for migraine prophylaxis. Topiramate is a carbonic anhydrase inhibitor that modulates effects at the glutamate and γ-aminobutyric acid (GABA) receptors, blocks some sodium- and calcium-dependent ion channels, may increase neuropeptide Y (NPY), and likely also impacts glucose and lipid metabolism peripherally. The exact mechanisms that lead to weight loss are not conclusively known. Topiramate as monotherapy has been studied extensively for the treatment of obesity with and without comorbidities.[4–6]
- A second therapy is phentermine, a sympathomimetic agent, approved in the United States since 1959 as an adjunct to diet and exercise for short-term treatment of obesity.[4]
- As is common in the treatment of other complex diseases, such as diabetes or hypertension, combination therapy is often used initially to address the multiple and redundant mechanisms leading to obesity.[4]
- An investigational combination therapy of two approved agents, phentermine and a controlled-release topiramate (PHEN/TPM CR), has been evaluated to assess the efficacy, safety, and tolerability of these agents in combination, in low doses relative to approved doses.[4]

➤ Objective

- To review and contrast available data on different formulations of topiramate from published literature or clinical trials data.

➤ Methods

- Two randomized clinical trials using topiramate were reviewed and contrasted based on having similar designs and enrolled populations. Both studies added blinded therapy as an adjunct to a standardized lifestyle intervention.
  - The first (Bray 2000), a dose-ranging study of immediate-release topiramate (TOP IR), was a 24-week, placebo-controlled weight loss study of 4 doses of TOP IR (64, 96, 192, or 384 mg total daily dose) with a 2- to 12-week titration period, depending on dose, added to the Pathways to Change lifestyle-modification program (Figure 1).[5,6]

Figure 1. Study design for immediate-release topiramate.

  - The second, a more recent study (OB-301), assessed a controlled-release topiramate (TPM CR) alone and in combination with phentermine (PHEN/TPM CR) for weight loss. OB-301 was a 28-week, placebo-controlled study evaluating the effects of two doses each of TPM CR (46 and 92 mg) and PHEN/TPM CR (7.5/46 and 15/92 mg) with a 4-week titration, added to the LEARN lifestyle-modification program. Due to space limitations, the phentermine alone data are not presented here (Figure 2).[4]

Figure 2. Study design for controlled-release topiramate alone and in combination with phentermine.

NOTE: These were not head-to-head studies and comparisons cannot be viewed as conclusive.

➤ Results

Baseline demographics

- The Bray 2000 (TOP-IR) and the OB-301 (TPM CR and PHEN/TPM CR) studies were of similar size and duration, and study participants had similar baseline attributes, which were balanced across treatment arms (Table 1).[4]
- 50% of subjects in the Bray 2000 study were hypertensive at baseline (systolic blood pressure [SBP] ≥140 mm Hg and/or diastolic BP [DBP] ≥90 mm Hg); 29% were hypertensive in the OB-301 study by the same definition.[5]

Table 1. Baseline Demographics: TOP IR Monotherapy and TPM CR or PHEN/TPM CR.

	TOP IR Bray 2000 [n=385]	TPM CR or PHEN/TPM CR OB-301 [n=756]
Mean age, years	44.8	45.6
Female, %	86.8	79.2
White, %	79	79
Mean weight, kg	109.7	101.8
Mean body mass index, kg/m²	37.6	36.0
Mean SBP, mm Hg	121.2	122.1
Mean DBP, mm Hg	78.6	79.0

Weight loss

- Percent weight loss: Each study showed significant mean percent weight loss in both the ITT-LOCF and completers populations (P<0.05 vs placebo after Week 4 in all treatment arms), in a mostly dose-dependent fashion (Table 2).[4]

Table 2. Percent Weight Loss at End of Treatment: TOP IR Monotherapy and TPM CR or PHEN/TPM CR.

	TOP IR* Bray 2000					TPM CR or PHEN/TPM CR* OB-301				
	Placebo	TOP 64 mg	TOP 96 mg	TOP 192 mg	TOP 384 mg	Placebo	TPM CR 46 mg	TPM CR 92 mg	PHEN/TPM CR 7.5/46 mg	PHEN/TPM CR 15/92 mg
Mean percent weight loss, ITT-LOCF	-2.6	-5.0	-4.8	-6.3	-6.3	-1.9	-4.8	-6.1	-8.2	-9.0
Mean percent weight loss, completers	-3.0	-5.8	-5.5	-6.2	-6.5	-2.2	-5.0	-6.5	-10.4	-11.5

*P<0.05 compared to placebo after Week 4 in all treatment arms

- Categorical weight loss: Both studies showed significantly more subjects in each treatment arm achieving ≥5% or ≥10% weight loss than subjects receiving placebo, except in TOP IR 64 mg and TOP IR 96 mg subjects at ≥10% (P<0.05 vs placebo; Figure 3).[4]

Figure 3. Percentage of subjects achieving ≥5% and ≥10% weight loss at end of treatment (study completers): (A) TOP IR monotherapy and (B) TPM CR or PHEN/TPM CR.

*P<0.05 vs placebo

Blood pressure

- Subjects completing treatment saw significant greater decreases in SBP from baseline to end of treatment vs placebo (P<0.05; Figure 4).[4]

Figure 4. Changes in blood pressure at end of treatment (study completers): (A) TOP IR monotherapy and (B) TPM CR or PHEN/TPM CR.

*P<0.05 vs placebo

Safety summary

- In the Bray 2000 study, 386 subjects were randomized, 64% completed.[5] The OB-301 study randomized 756 subjects, 72% completed.
- In the Bray 2000 study, the most frequent adverse events (AEs) were central nervous system (CNS)-related (Table 3).[5]
- In OB-301, the most frequent AEs (across all treatment arms) were paresthesia (see Table 3), dry mouth (7–19% in active, 0% in placebo), constipation (4–10% in active, 0% in placebo), headache (8–18% in active, 10% in placebo), upper respiratory infection (8–13% in active, 11% in placebo), insomnia (see Table 3), and nasopharyngitis (3–10% in active, 10% in placebo).
- In both studies, CNS-related AEs were most commonly reported in the first couple months of therapy (during titration), were generally mild or moderate in severity, and in most cases spontaneously resolved on treatment prior to the end of the study. Using similar coding conventions, AEs appeared to occur less frequently with TPM CR and PHEN/TPM CR than with TOP IR.[4]
- Table 3 shows CNS-related AEs (includes central and peripheral nervous systems, psychiatric, and fatigue), which occurred in more than 5% of topiramate (any formulation) subjects, and where total topiramate incidence was greater than placebo incidence. Data for treatment groups in OB-301 were provided for all terms matching those provided for TOP IR, even if values were below 5% threshold.

Table 3. CNS-Related Adverse Events.

Preferred term (%)	Placebo (n=75)	TOP 64 mg (n=75)	TOP 96 mg (n=75)	TOP 192 mg (n=75)	TOP 384 mg (n=75)	Placebo (n=756)	TPM CR 46 mg (n=156)	TPM CR 92 mg (n=157)	PHEN/TPM CR 7.5/46 mg (n=155)	PHEN/TPM CR 15/92 mg (n=156)
Paresthesia	5	36	41	42	60	4	11	22	16	29
Memory difficulties/ impairment	8	11	23	28	21	1	0	1	0	0
Fatigue	12	16	11	16	16	6	8	7	8	9
Somnolence	13	9	12	13	21	2	2	2	1	2
Anorexia/ decreased appetite	5	8	8	13	13	0	0	0	1	2
Dizziness	7	7	7	11	16	2	7	4	4	8
Difficulty in concentration/ distraction in attention	5	7	9	11	12	1	2	4	7	4
Insomnia	5	8	15	7	5	6	4	5	12	10
Nervousness	3	7	11	8	4	1	0	0	1	1
Hypoesthesia	1	4	7	11	4	1	3	4	3	2
Depression	4	3	7	5	10	3	4	5	1	4
Anxiety	6	4	8	7	5	1	2	2	3	3
Psychomotor slowing	0	3	3	4	12	0	0	0	0	0
Dysgeusia, taste perversion	5	9	8	16	10	0	7	2	8	10

- AEs led to discontinuation in 21% of TOP IR–treated subjects and 11% of placebo-treated subjects in the Bray 2000 study; 18% of the TPM CR– or PHEN/TPM CR–treated subjects and 7% of placebo-treated subjects in OB-301.[4]
- Serious AEs occurred in 4% of TOP IR–treated and 3% of placebo-treated subjects in the Bray 2000 study; and 1% of TPM CR– or PHEN/TPM CR–treated and 0% of placebo-treated subjects in OB-301.[4]

➤ Conclusions

- Due to similar design and endpoints in the 2 studies (Bray 2000 and OB-301), it is possible to contrast the efficacy and tolerability of the two topiramate formulations and its use in combination with phentermine.
- Any assessments need to be considered in the context that these were not head-to-head studies and cannot be deemed conclusive, merely informative.
- Topiramate has consistently demonstrated significant value when used to induce weight loss and has shown improvements in BP as well. Tolerability has been a limiting factor, specifically CNS-related events, but perhaps alternate formulations or combinations may help to mitigate these effects while retaining the benefits.
- A lower C_{max} with TPM CR, lower absolute doses, and its use in combination with phentermine likely contribute to observed differences in efficacy and tolerability, attributes important for long-term use.

The OB-301 trial was registered at ClinicalTrials.gov, number NCT00553085.

References: 1. Logue J, et al. Heart. 2011;97(7):564–568. 2. Haslam DW, James WP. Lancet. 2005;366(9492):1197–1209. 3. NHLBI. http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf. Accessed May 12 2011. 4. Topamax [package insert]. Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2009. 5. Rosenstock MB, Clin Ther. 1997;19(6):1278–1288. 6. Rupprecht MA, Porter RJ. Pharmacol Ther. 1995;65(2):253–286. 7. MacKenzie TA, McCann RM. Ann Neurol. 1994;44(5):733–738. 8. Bray GA, et al. Obes Res. 2003;11(6):722–733. 9. Whitney J, et al. Int J Obes Relat Metab Disord. 2003;27(12):1559–1572. 10. Tonstad S, et al. Am J Cardiol. 2012;109(2):245–251. 11. Wenthold K, et al. Diabetes Obes Metab. 2003;5(5):360–368. 12. Toubro H, et al. Int J Obes (Lond). 2007;31(11):1696–1705. 13. Rosenstock J, et al. Diabetes Care. 2007;30(6):1480–1486. 14. Adipex-P [package insert]. Teva Pharmaceuticals USA;2005. 15. Gadde KM, Raj U. J Obes. 2011;2011:651–715. 16. Gadde KM, et al. Lancet. 2011;377(9776):1341–1352. 17. Pathways to Change. Johnson & Johnson Health Care Systems Incorporated; 2004.

Acknowledgements: The authors appreciate the contributions of the enrolled patients, the study investigators and staff, with poster graphics assistance from The Lockwood Group (funded by Vivus).

Below is a reproduction of the contents of the poster entitled "Efficacy and Tolerability of Topiramate Alone and in Combination with Phentermine":

Authors: George A. Bray, MD(a); Louis J. Aronne, MD(b); Alok K. Gupta, MD(a); Wesley W. Day, PhD(c); Barbara Troupin, MD, MBA(c)

(a)Pennington Biomedical Research Center, Baton Rouge, LA; (b)Weill Cornell Medical Center, New York, NY; (c)Vivus, Inc., Mountain View, CA

Contact details: George A. Bray, MD; Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808-4124; Office: (225) 763-3140; Email: george.bray@pbrc.edu

· Introduction

· Obesity is an independent risk factor for cardiovascular disease and contributes significantly to the development of multiple weight-related comorbidities, such as diabetes and metabolic syndrome.(1),(2)

· While lifestyle interventions are the mainstay for treating obesity, many patients require additional therapeutic intervention, such as pharmacotherapy or bariatric surgery.(3)

· One such therapy is topiramate, an agent currently approved for the treatment of seizure disorders and for migraine prophylaxis. Topiramate is a carbonic anhydrase inhibitor that modulates effects at the glutamate and γ-aminobutyric acid (GABA) receptors, blocks some sodium- and calcium-dependent ion channels, may increase neuropeptide Y (NPY), and likely also impacts glucose and lipid metabolism peripherally. The exact mechanisms that lead to weight loss are not conclusively known. Topiramate as monotherapy has been studied extensively for the treatment of obesity with and without comorbidities.(4)-(13)

· A second therapy is phentermine, a sympathomimetic agent, approved in the United States since 1959 as an adjunct to diet and exercise for short-term treatment of obesity.(14)

· As is common in the treatment of other complex diseases, such as diabetes or hypertension, combination therapy is often used initially to address the multiple and redundant mechanisms leading to obesity.(15)

· An investigational combination therapy of two approved agents, phentermine and a controlled-release topiramate (PHEN/TPM CR), has been evaluated to assess the efficacy, safety, and tolerability of these agents in combination, in low doses relative to approved doses.(16)

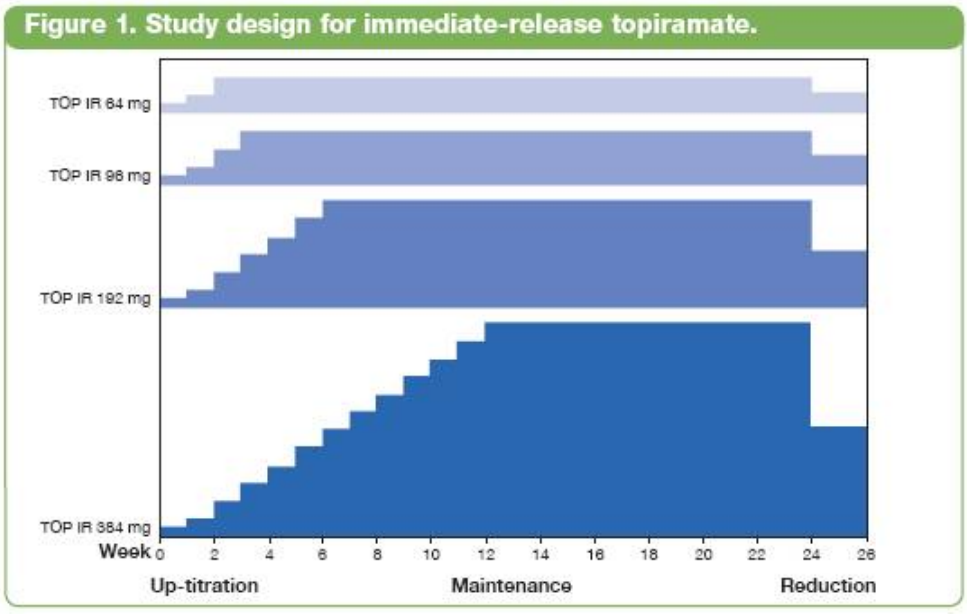
· Objective

· To review and contrast available data on different formulations of topiramate from published literature or clinical trials data.

· Methods

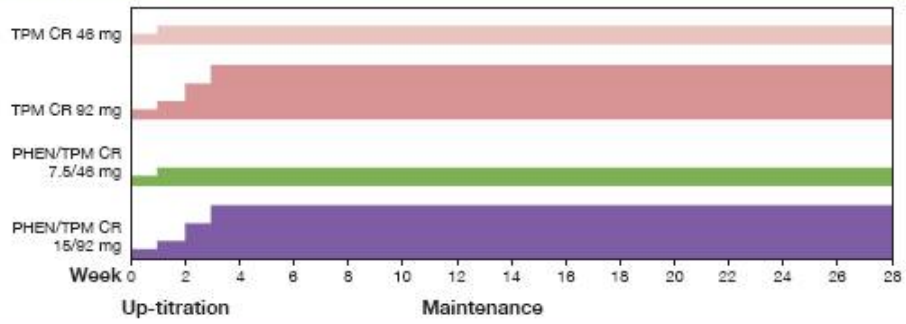
· Two randomised clinical trials using topiramate were reviewed and contrasted based on having similar designs and enrolled populations. Both studies added blinded therapy as an adjunct to a standardised lifestyle intervention.

  · The first (Bray 2003), a dose-ranging study of immediate-release topiramate (TOP IR), was a 24-week, placebo-controlled weight loss study of 4 doses of TOP IR (64, 96, 192, or 384 mg total daily dose) with a 2- to 12-week titration period, depending on dose, added to the Pathways to Change lifestyle-modification program (Figure 1).(8),(17)



  · The second, a more recent study (OB-301), assessed a controlled-release topiramate (TPM CR) alone and in combination with phentermine (PHEN/TPM CR) for weight loss. OB-301 was a 28-week, placebo-controlled study evaluating the effects of two doses each of TPM CR (46 and 92 mg) and PHEN/TPM CR (7.5/46 and 15/92 mg) with a 4-week titration, added to the LEARN lifestyle-modification program. Due to space limitations, the phentermine alone data are not presented here (Figure 2).(18)

Figure 2. Study design for controlled-release topiramate alone and in combination with phentermine.



NOTE: These were not head-to-head studies and comparisons cannot be viewed as conclusive.

· Results

Baseline demographics

· The Bray 2003 (TOP IR) and the OB-301 (TPM CR and PHEN/TPM CR) studies were of similar size and duration, and study participants had similar baseline attributes, which were balanced across treatment arms (Table 1).(8)

· 10% of subjects in the Bray 2003 study were hypertensive at baseline (systolic blood pressure [SBP] >140 mm Hg and/or diastolic BP [DBP] >90 mm Hg); 29% were hypertensive in the OB-301 study, by the same definition.(8)

Table 1. Baseline Demographics: TOP IR Monotherapy and TPM CR or PHEN/TPM CR.

	TOP IR Bray 2003 (n=380)	TPM CR or PHEN/TPM CR OB-301 (n=756)
Mean age, years	44.3	45.6
Female, %	85.3	79.2
White, %	76	79
Mean weight, kg	103.7	101.3
Mean body mass index, kg/m^2	37.4	36.3
Mean SBP, mm Hg	121.2	122.1
Mean DBP, mm Hg	78.6	79.0

Weight loss

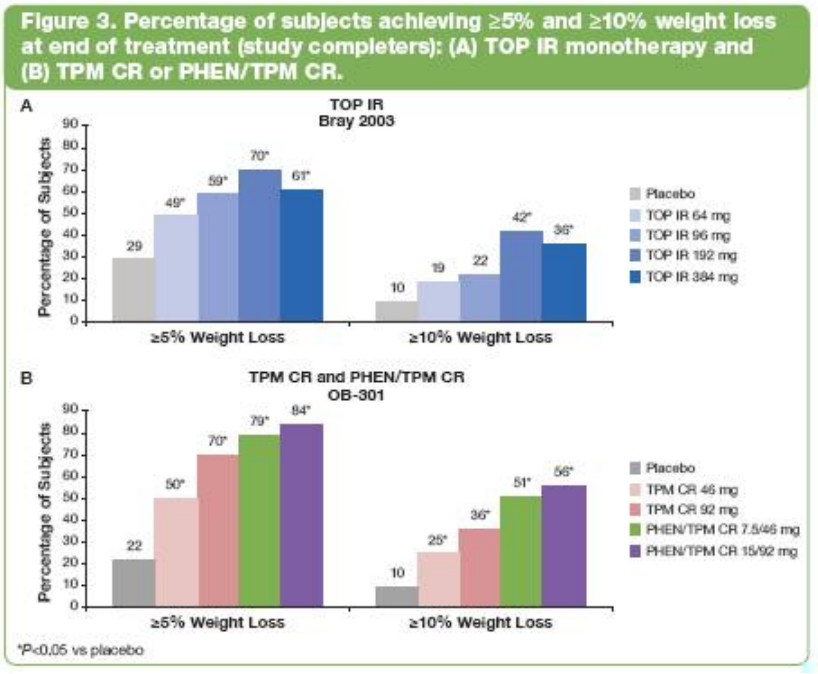
· Percent weight loss: Each study showed significant mean percent weight loss in both the ITT-LOCF and completers populations (P<0.05 vs placebo after Week 4 in all treatment arms), in a mostly dose-dependent fashion (Table 2).(8)

Table 2. Percent Weight Loss at End of Treatment: TOP IR Monotherapy and TPM CR or PHEN/TPM CR.

	TOP IR* Bray 2003					TPM CR or PHEN/TPM CR* OB-301				
	Placebo	TOP 64 mg	TOP 96 mg	TOP 192 mg	TOP 384 mg	Placebo	TPM CR 46 mg	TPM CR 92 mg	PHEN/TPM CR 7.5/46 mg	PHEN/TPM CR 15/92 mg
Mean percent weight loss, ITT-LOCF	-2.6	-5.0	-4.8	-6.3	-6.3	-1.5	-4.9	-6.1	-8.2	-9.0
Mean percent weight loss, completers	-3.6	-5.8	-6.5	-8.2	-8.5	-2.2	-6.0	-8.5	-10.4	-11.5

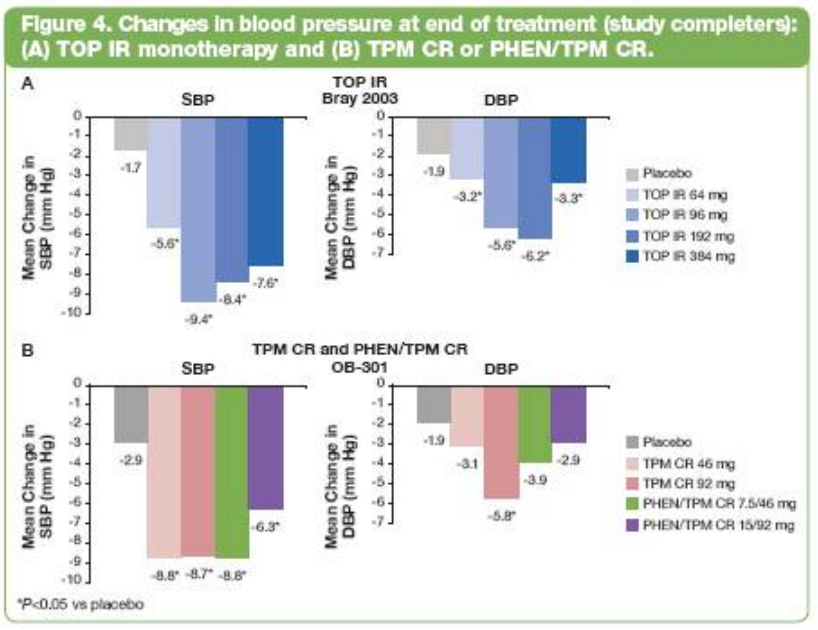
*P<0.05 compared to placebo after Week 4 in all treatment arms

· Categorical weight loss: Both studies showed significantly more subjects in each treatment arm achieving ≥5% or ≥10% weight loss than subjects receiving placebo, except in TOP IR 64 mg and TOP IR 96 mg subjects at ≥10% (P<0.05 vs placebo; Figure 3).(8)



Blood pressure

· Subjects completing treatment saw significantly greater decreases in SBP from baseline to end of treatment vs placebo (P<0.05; Figure 4).(8)



Safety summary

· In the Bray 2003 study, 385 subjects were randomised, 64% completed.(8) The OB-301 study randomised 756 subjects, 72% completed.

· In the Bray 2003 study, the most frequent adverse events (AEs) were central nervous system (CNS)-related (Table 3).(8)

· In OB-301, the most frequent AEs (across all treatment arms) were paraesthesia (see Table 3), dry mouth (7-19% in active, 0% in placebo), constipation (4-16% in active, 8% in placebo), headache (8-16% in active, 13% in placebo), upper respiratory infection (8-13% in active, 11% in placebo), insomnia (see Table 3), and nasopharyngitis (3-10% in active, 10% in placebo).

· In both studies, CNS-related AEs were most commonly reported in the first couple months of therapy (during titration), were generally mild or moderate in severity, and in most cases spontaneously resolved on treatment prior to the end of the study. Using similar coding conventions, AEs appeared to occur less frequently with TPM CR and PHEN/TPM CR than with TOP IR.(8)

· Table 3 shows CNS-related AEs (includes central and peripheral nervous systems, psychiatric, and fatigue), which occurred in more than 5% of topiramate (any formulation) subjects, and where total topiramate incidence was greater than placebo incidence. Data for treatment groups in OB-301 were provided for all terms matching those provided for TOP IR, even if values were below 5% threshold.

Table 3. CNS-Related Adverse Events.

	TOP IR Bray 2003					TPM CR or PHEN/TPM CR OB-301				
Preferred term (%)	**Placebo (n=75)**	**TOP 64 mg (n=76)**	**TOP 96 mg (n=75)**	**TOP 192 mg (n=76)**	**TOP 384 mg (n=78)**	**Placebo (n=109)**	**TPM CR 46 mg (n=106)**	**TPM CR 92 mg (n=107)**	**PHEN/TPM CR 7.5/46 mg (n=106)**	**PHEN/TPM CR 15/92 mg (n=108)**
Paraesthesia	5	36	41	42	50	4	11	22	16	23
Memory difficulties/	8	11	23	28	21	1	0	1	0	0

impairment										
Fatigue	12	16	11	18	18	6	8	7	6	9
Somnolence	13	9	12	13	21	2	2	2	1	2
Anorexia/decreased appetite	3	8	9	13	13	0	0	0	1	2
Dizziness	7	7	7	11	15	2	7	4	4	8
Difficulty in concentration/ disturbance in attention	5	7	9	11	12	1	2	4	7	4
Insomnia	5	8	15	7	5	6	4	5	12	10
Nervousness	3	7	11	8	4	1	0	0	1	1
Hypoaesthesia	1	4	7	11	4	1	3	4	3	2
Depression	4	3	7	5	10	3	4	5	1	4
Anxiety	0	8	3	7	5	1	2	2	0	3
Psychomotor slowing	0	3	3	4	12	0	0	0	0	0
Dysgeusia, taste perversion	0	9	9	16	10	0	7	2	9	15

- AEs led to discontinuation in 21% of TOP IR—treated subjects and 11% of placebo-treated subjects in the Bray 2003 study; 15% of the TPM CR— or PHEN/TPM CR—treated subjects and 7% of placebo-treated subjects in OB-301.(8)

- Serious AEs occurred in 4% of TOP IR—treated and 3% of placebo-treated subjects in the Bray 2003 study; and 1% of TPM CR— or PHEN/TPM CR—treated and 0% of placebo-treated subjects in OB-301.(8)

· Conclusions

- Due to similar design and endpoints in the 2 studies (Bray 2003 and OB-301), it is possible to contrast the efficacy and tolerability of the two topiramate formulations and its use in combination with phentermine.

- Any assessments need to be considered in the context that these were not head-to-head studies and cannot be deemed conclusive, merely informative.

- Topiramate has consistently demonstrated significant value when used to induce weight loss and has shown improvements in BP as well. Tolerability has been a limiting factor, specifically CNS-related events, but perhaps alternate formulations or combinations may help to mitigate these effects while retaining the benefits.

- A lower C_{max} with TPM CR, lower absolute doses, and its use in combination with phentermine likely contribute to observed differences in efficacy and tolerability, attributes important for long-term use.

The OB-301 trial was registered at ClinicalTrials.gov, number NCT00563368.

References: (1) Logue J, et al. *Heart*. 2011;97(7):564-568. (2) Haslam DW, James WP. *Lancet*. 2005;366(9492):1197-1209. (3) NHLBI. http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf. Accessed May 17, 2011. (4) Topamax [package insert]. Ortho-McNeil-Janssen Pharmaceuticals, Inc.;2009. (5) Rosenfeld WE. *Clin Ther*. 1997;19(6):1294-1308. (6) Rogawski MA, Porter RJ. *Pharmacol Rev*. 1990;42(3):223-286. (7) Macdonald RL, McLean MJ. *Adv Neurol*. 1986;44:713-736. (8) Bray GA, et al. *Obes Res*. 2003;11(6):722-733. (9) Wilding J, et al. *Int J Obes Relat Metab Disord*. 2004;28(11):1399-1410. (10) Tonstad S, et al. *Am J Cardiol*. 2005;96(2):243-251. (11) Stenlöf K, et al. *Diabetes Obes Metab*. 2007;9(3):360-368. (12) Toplak H, et al. *Int J Obes (Lond)*. 2007;31(1):138-146. (13) Rosenstock J, et al. *Diabetes Care*. 2007;30(6):1480-1486. (14) Adipex-P [package insert]. Teva Pharmaceuticals USA;2005. (15) Glandt M, Raz I. *J Obes*. 2011;636181:1-13. (16) Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352. (17) Pathways to Change. Johnson & Johnson Health Care Systems: Piscataway, NJ. (18) Brownell KD. *The LEARN Program for Weight Management*. 2004.

Acknowledgements: The authors appreciate the contributions of the enrolled patients, the study investigators and staff, with poster graphics assistance from The Lockwood Group (funded by Vivus).

Below is a graphical representation of the poster entitled "Weight Loss With Low-Dose, Controlled-Release Phentermine/Topiramate Therapy Improves Glycaemic Status and Prevents Progression to Type 2 Diabetes Mellitus":

Weight Loss With Low-Dose, Controlled-Release Phentermine/Topiramate Therapy Improves Glycaemic Status and Prevents Progression to Type 2 Diabetes Mellitus

Authors: W. Timothy Garvey, MD[a]; Craig A. Peterson, MS[b]; Barbara Troupin, MD[b]

[a]University of Alabama at Birmingham, Birmingham, Alabama, USA; [b]Vivus, Inc., Mountain View, California, USA

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➤ Abstract

Introduction

Obesity is associated with increased mortality due to comorbidities, such as type 2 diabetes mellitus (T2DM). Once-daily, controlled-release phentermine/topiramate (PHEN/TPM CR) previously demonstrated significant and well-tolerated weight loss, which may mitigate the risk of the growing T2DM epidemic in obese patients.

Methods

To evaluate the effects of PHEN/TPM CR on glycaemic parameters and rates of progression to T2DM, we conducted prespecified analyses of data from the CONQUER study, a double-blind, Phase 3 trial, which randomised 2487 overweight/obese adults with ≥2 weight-related comorbidities to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks. Glycaemic parameters were evaluated at baseline and at Week 56.

Results

Glycated haemoglobin, fasting glucose, and fasting insulin were significantly improved at Week 56 (ITT-LOCF; $P<0.005$ vs placebo). Among subjects with ADA-defined Prediabetes at baseline (n=1119), normoglycaemia was achieved in 39.1% and 45.2% of subjects in the 7.5/46 and 15/92 arms, respectively. In this same sample, progression to T2DM was reported in 9.0% of subjects on placebo, 6.7% on 7.5/46, and 4.4% on 15/92 ($P<0.05$ vs placebo). Treatment with PHEN/TPM CR was generally well tolerated.

Conclusion

In obese patients with metabolic comorbidities, treatment with PHEN/TPM CR over 56 weeks improved glycaemic parameters. In subjects with Prediabetes at baseline, PHEN/TPM CR therapy normalized glycaemic parameters in >39% of subjects and led to significant reductions in the progression to T2DM.

Note that in the original abstract submission, the WHO criteria for Prediabetes were used to define the Prediabetes sample. In the presented abstract and poster, the current ADA definition of Prediabetes was utilized.

➤ Introduction

- Obesity is an independent risk factor for cardiovascular disease and also contributes to the development of weight-related comorbidities, such as type 2 diabetes mellitus (T2DM).[1-3]
- The presence of Prediabetes, defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), increases the risk of developing T2DM.[4]
- Even modest weight loss in patients with Prediabetes has been shown to delay progression to T2DM and lead to improvements in glycaemic parameters.[4,7]
- Controlled-release phentermine/topiramate (PHEN/TPM CR) is an investigational combination therapy that was developed to maximize weight loss and improve weight-related comorbidities.
- The CONQUER study was a double-blind, Phase 3 trial that randomised 2487 overweight/obese adults with ≥2 weight-related comorbidities to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks.[4]

➤ Objectives

- To assess the effects of PHEN/TPM CR on weight loss and glycaemic parameters over a 56-week period in the overall CONQUER sample.
- To evaluate changes in glycaemic parameters and rates of progression to T2DM over a 56-week period in a prespecified subset of patients in CONQUER with Prediabetes.

➤ Methods

- This 56-week, double-blind, parallel-group Phase 3 trial (CONQUER) randomised 2487 overweight/obese adult subjects with ≥2 weight-related comorbidities to placebo (n=994), 7.5/46 (n=498), or 15/92 (n=995).
- All subjects were managed to standard of care for their respective comorbidities, including the option to add or modify medications, and received lifestyle modification, including nutrition guidance and increased physical activity, based on the LEARN program.[8]

➤ Assessments

- The primary efficacy endpoint in this trial was percent weight loss at Week 56 in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
- Other endpoints included change in HbA1c, fasting glucose, and fasting insulin at Week 56.
- A subanalysis assessed changes at Week 56 in glycaemic parameters and the change in diabetic status among subjects with Prediabetes (defined as IFG [5.6 to 6.9 mmol/L] or IGT [7.8 to 11.0 mmol/L as measured by oral glucose tolerance test (OGTT)] at baseline.
- Analysis of covariance (ANCOVA) was used to evaluate changes in weight loss and other outcomes. The ANCOVA model used factors of treatment, gender, and diabetic status as fixed effects, with baseline weight as a covariate.

➤ Results

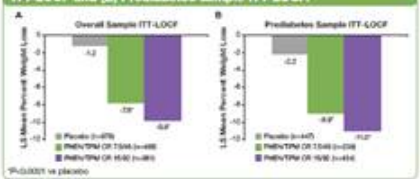
Baseline Characteristics

- Subjects randomised in CONQUER were mostly female (70%) and Caucasian (86%) with a mean age of 51 years, mean weight of 103.1 kg, and mean body mass index of 36.6 kg/m². Mean baseline HbA1c was 5.9%, fasting glucose was 5.9 mmol/L, and fasting insulin was 125.7 µmol/L.

Weight Loss

- In the overall ITT-LOCF sample, least-squares (LS) mean percent weight loss was significantly greater at 56 weeks for both PHEN/TPM CR groups vs placebo ($P<0.0001$; Figure 1A). LS mean percent weight loss was also significant among subjects with Prediabetes at baseline (n=1119) vs placebo ($P<0.0001$; Figure 1B).

Figure 1. Percent weight loss at 56 Weeks: (A) overall sample ITT-LOCF and (B) Prediabetes sample ITT-LOCF.



$^{a}P<0.0001$ vs placebo

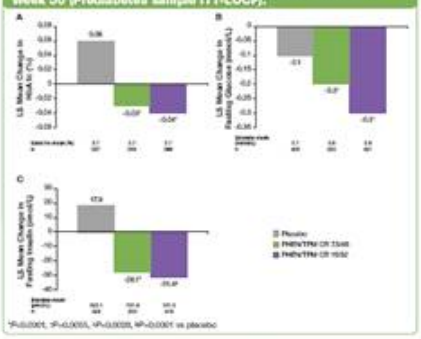
Glycaemic Parameters: Overall Study Sample

- LS mean change in HbA1c, fasting glucose, and fasting insulin at Week 56 were significantly greater with PHEN/TPM CR treatment compared with placebo.
  - HbA1c (%): 0.1, 0.0, and -0.1 for placebo, 7.5/46, and 15/92, respectively ($P<0.0001$ vs placebo)
  - Fasting glucose (mmol/L): 0.13, -0.01, and -0.07 for placebo, 7.5/46, and 15/92, respectively ($P<0.005$ vs placebo)
  - Fasting insulin (µmol/L): 5.1, -24.0, and -27.6 for placebo, 7.5/46, and 15/92, respectively ($P<0.0005$ vs placebo)

Glycaemic Parameters and Insulin Sensitivity: Prediabetes Sample

- In subjects with Prediabetes at baseline, glycaemic parameters (Figure 2) and insulin sensitivity were also improved.
  - LS mean change in homeostasis model assessment–insulin resistance was significant vs placebo at Week 56 ($P<0.005$): 0.8, -1.3, and -1.5 for placebo, 7.5/46, and 15/95, respectively.

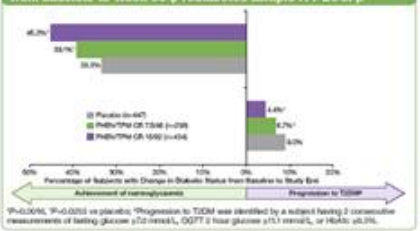
Figure 2. Change in glycaemic parameters from baseline to Week 56 (Prediabetes sample ITT-LOCF).



$^{a}P<0.0001$, $^{b}P<0.0005$, $^{c}P<0.0035$, $^{d}P<0.0001$ vs placebo

- Normoglycaemia in subjects with Prediabetes (defined as IFG <5.6 mmol/L or IGT <7.8 mmol/L as measured by OGTT) occurred more frequently in PHEN/TPM CR–treated subjects than in placebo-treated subjects ($P=0.0016$).
- Progression to T2DM was more common in placebo-treated subjects than PHEN/TPM CR–treated subjects ($P=0.0053$; Figure 3).

Figure 3. Percentage of subjects with a change in diabetic status from baseline to Week 56 (Prediabetes sample ITT-LOCF).



$^{a}P<0.0016$, $^{b}P<0.0053$ vs placebo; ^{c}Progression to T2DM was identified by a subject having 2 consecutive measurements of fasting glucose ≥7.0 mmol/L, OGTT 2 hour glucose ≥11.1 mmol/L, or HbA1c ≥6.5%.

Safety Summary

- The most common treatment-emergent adverse events (TEAEs) are presented in Table 1. Among PHEN/TPM CR subjects, the incidence of serious AEs was comparable to placebo: 4%, 3%, and 5% for placebo, 7.5/46, and 15/92, respectively.

Table 1. Most Common TEAEs (Safety Sample)

TEAE (%)	Placebo (n=993)	PHEN/TPM CR 7.5/46 (n=498)	PHEN/TPM CR 15/92 (n=994)
Dry mouth	2	13	21
Paraesthesia	2	14	21
Constipation	6	15	17
Upper respiratory tract infection	13	12	13
Nasopharyngitis	9	11	10
Dysgeusia	1	7	10
Insomnia	5	6	10
Headache	9	7	10

- Completion rates on therapy were higher in the PHEN/TPM CR groups: 57%, 69%, and 64% for placebo, 7.5/46, and 15/92, respectively.
  - Discontinuation rates due to TEAEs were dose-related at 9%, 12%, and 19% for placebo, 7.5/46, and 15/92, respectively.
  - There was 1 death in the placebo group.

➤ Conclusions

- Treatment with PHEN/TPM CR led to significant weight loss vs placebo.
- In addition to weight loss, subjects treated with PHEN/TPM CR achieved significant improvements in glycaemic parameters vs placebo in both the overall and Prediabetes groups, indicative of an improvement in insulin sensitivity.
- Furthermore, in subjects with Prediabetes at baseline, PHEN/TPM CR therapy normalized glycaemic parameters in almost 40% of subjects.
- PHEN/TPM CR led to significant reductions in the proportion of subjects progressing to T2DM.
- PHEN/TPM CR was generally well tolerated based on rates of study completion, discontinuation rates, and overall adverse events.
- Therapies that can address glycaemic parameters, ameliorate insulin resistance, and potentially impact the epidemic rates of progression to diabetes would have significant clinical benefit to overweight and obese patients with Prediabetes.

This trial is registered at ClinicalTrials.gov, number NCT00553767.

References: 1. Reaven GM. *Ann Intern Med* 2003;138:420–423. 2. Flegal KM, et al. *JAMA* 2002;288:1723–1727. 3. Haslam DW, et al. *Lancet* 2005;366:1197–1209. 4. Adams KF, et al. *N Engl J Med* 2006;355:763–778. 5. Logue J, et al. *Heart* 2011;97:634–640. 6. American Diabetes Association. *Diabetes Care* 2010;33(suppl 1):S11–S61. 7. UKPDS Group. *Metabolism* 1990;39:905–912. 8. Gaddis KM, et al. *Lancet* 2011;377:1345–1352. 9. Brownell KD. *The LEARN Program for Weight Management* 2004.

Acknowledgements: We would like to acknowledge and thank the CONQUER investigators and study coordinators, the Medpace team (study CRO), The Lockwood Group (for poster development assistance), and VIVUS internal contributors.

Below is a reproduction of the contents of the poster entitled "Weight Loss With Low-Dose, Controlled-Release Phentermine/Topiramate Therapy Improves Glycaemic Status and Prevents Progression to Type 2 Diabetes Mellitus":

Authors: W. Timothy Garvey, MD(a); Craig A. Peterson, MS(b); Barbara Troupin, MD(b)

(a)University of Alabama at Birmingham, Birmingham, Alabama, USA; (b)Vivus, Inc., Mountain View, California, USA

Contact details: Dr. W. T. Garvey, MD; University of Alabama at Birmingham, 1675 University Blvd, Birmingham, AL 35294-3360; Office: (205) 996-7433; Email: garveyt@uab.edu

· Abstract

Introduction

Obesity is associated with increased mortality due to comorbidities, such as type 2 diabetes mellitus (T2DM). Once-daily, controlled-release phentermine/topiramate (PHEN/TPM CR) previously demonstrated significant and well-tolerated weight loss, which may mitigate the risk of the growing T2DM epidemic in obese patients.

Methods

To evaluate the effects of PHEN/TPM CR on glycaemic parameters and rates of progression to T2DM, we conducted prespecified analyses of data from the CONQUER study, a double-blind, Phase 3 trial, which randomised 2487 overweight/obese adults with ≥2 weight-related comorbidities to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks. Glycaemic parameters were evaluated at baseline and at Week 56.

Results

Glycated haemoglobin, fasting glucose, and fasting insulin were significantly improved at Week 56 (ITT-LOCF; $P<0.005$ vs placebo). Among subjects with ADA-defined Prediabetes at baseline (n=1119), normoglycaemia was achieved in 39.1% and 45.2% of subjects in the 7.5/46 and 15/92 arms, respectively. In this same sample, progression to T2DM was reported in 9.0% of subjects on placebo, 6.7% on 7.5/46, and 4.4% on 15/92 ($P<0.05$ vs placebo). Treatment with PHEN/TPM CR was generally well tolerated.

Conclusion

In obese patients with metabolic comorbidities, treatment with PHEN/TPM CR over 56 weeks improved glycaemic parameters. In subjects with Prediabetes at baseline, PHEN/TPM CR therapy normalized glycaemic parameters in >39% of subjects and led to significant reductions in the progression to T2DM.

Note that in the original abstract submission, the WHO criteria for Prediabetes were used to define the Prediabetes sample. In the presented abstract and poster, the current ADA definition of Prediabetes was utilized.

· Introduction

- Obesity is an independent risk factor for cardiovascular disease and also contributes to the development of weight-related comorbidities, such as type 2 diabetes mellitus (T2DM).(1)-(5)
- The presence of Prediabetes, defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), increases the risk of developing T2DM.(6)
- Even modest weight loss in patients with Prediabetes has been shown to delay progression to T2DM and lead to improvements in glycaemic parameters.(6),(7)
- Controlled-release phentermine/topiramate (PHEN/TPM CR) is an investigational combination therapy that was developed to maximize weight loss and improve weight-related comorbidities.
- The CONQUER study was a double-blind, Phase 3 trial that randomised 2487 overweight/obese adults with ≥2 weight-related comorbidities to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92) for 56 weeks.(8)

· Objectives

- To assess the effects of PHEN/TPM CR on weight loss and glycaemic parameters over a 56-week period in the overall CONQUER sample.
- To evaluate changes in glycaemic parameters and rates of progression to T2DM over a 56-week period in a prespecified subset of patients in CONQUER with Prediabetes.

· Methods

- This 56-week, double-blind, parallel-group Phase 3 trial (CONQUER) randomised 2487 overweight/obese adult subjects with ≥2 weight-related comorbidities to placebo (n=994), 7.5/46 (n=498), or 15/92 (n=995).
- All subjects were managed to standard of care for their respective comorbidities, including the option to add or modify medications, and received lifestyle modification, including nutrition guidance and increased physical activity, based on the LEARN program.(9)

· Assessments

- The primary efficacy endpoint in this trial was percent weight loss at Week 56 in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
- Other endpoints included change in HbA1c, fasting glucose, and fasting insulin at Week 56.

- A subanalysis assessed changes at Week 56 in glycaemic parameters and the change in diabetic status among subjects with Prediabetes (defined as IFG [5.6 to 6.9 mmol/L] or IGT [7.8 to 11.0 mmol/L as measured by oral glucose tolerance test (OGTT)]) at baseline.

- Analysis of covariance (ANCOVA) was used to evaluate changes in weight loss and other outcomes. The ANCOVA model used factors of treatment, gender, and diabetic status as fixed effects, with baseline weight as a covariate.

· Results

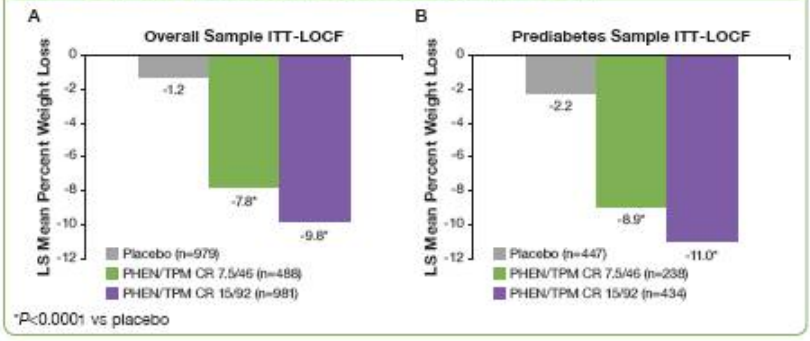
Baseline Characteristics

- Subjects randomised in CONQUER were mostly female (70%) and Caucasian (86%) with a mean age of 51 years, mean weight of 103.1 kg, and mean body mass index of 36.6 kg/m^2. Mean baseline HbA1c was 5.9%, fasting glucose was 5.9 mmol/L, and fasting insulin was 125.7 ρmol/L.

Weight Loss

- In the overall ITT-LOCF sample, least-squares (LS) mean percent weight loss was significantly greater at 56 weeks for both PHEN/TPM CR groups vs placebo (*P*<0.0001; Figure 1A). LS mean percent weight loss was also significant among subjects with Prediabetes at baseline (n=1119) vs placebo (*P*<0.0001; Figure 1B).

Figure 1. Percent weight loss at 56 Weeks: (A) overall sample ITT-LOCF and (B) Prediabetes sample ITT-LOCF.

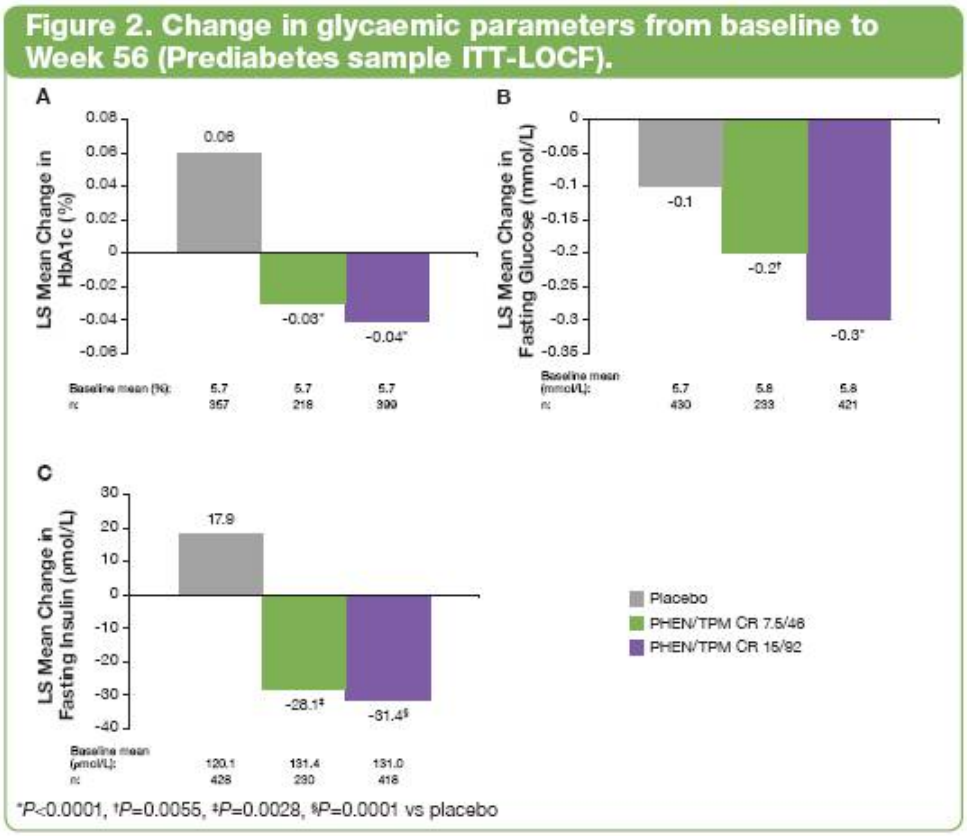


Glycaemic Parameters: Overall Study Sample

- LS mean change in HbA1c, fasting glucose, and fasting insulin at Week 56 were significantly greater with PHEN/TPM CR treatment compared with placebo.
  - HbA1c (%): 0.1, 0.0, and -0.1 for placebo, 7.5/46, and 15/92, respectively (*P*<0.0001 vs placebo)
  - Fasting glucose (mmol/L): 0.13, -0.01, and -0.07 for placebo, 7.5/46, and 15/92, respectively (*P*<0.005 vs placebo)
  - Fasting insulin (ρmol/L): 5.1, -24.0, and -27.6 for placebo, 7.5/46, and 15/92, respectively (*P*<0.0005 vs placebo)

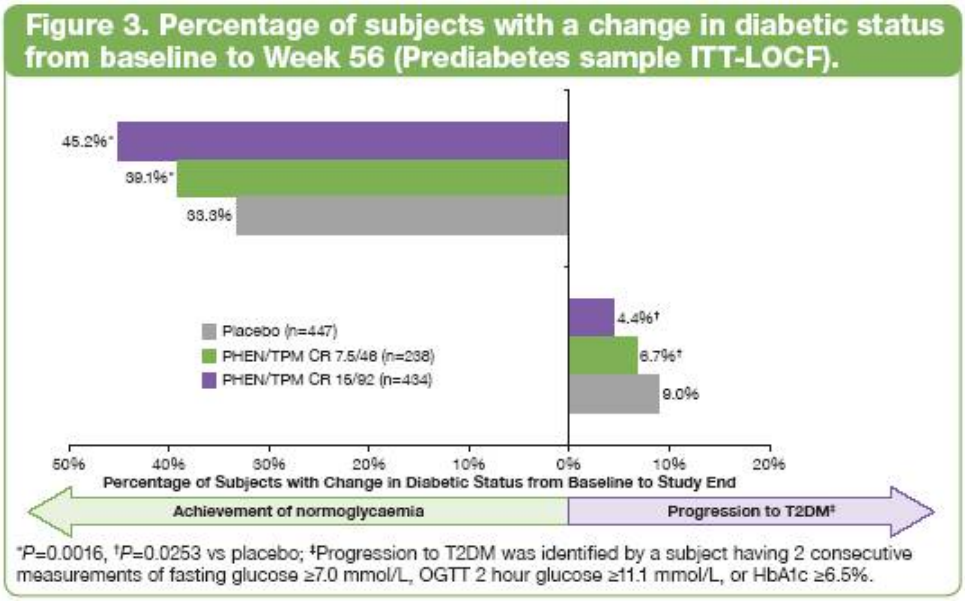
Glycaemic Parameters and Insulin Sensitivity: Prediabetes Sample

- In subjects with Prediabetes at baseline, glycaemic parameters (Figure 2) and insulin sensitivity were also improved.
  - LS mean change in homeostasis model assessment—insulin resistance was significant vs placebo at Week 56 (*P*<0.005): 0.8, -1.3, and -1.5 for placebo, 7.5/46, and 15/95, respectively.



· Normoglycaemia in subjects with Prediabetes (defined as IFG <5.6 mmol/L or IGT <7.8 mmol/L as measured by OGTT) occurred more frequently in PHEN/TPM CR—treated subjects than in placebo-treated subjects (*P*=0.0016).

· Progression to T2DM was more common in placebo-treated subjects than PHEN/TPM CR—treated subjects (*P*=0.0253; Figure 3).



Safety Summary

· The most common treatment-emergent adverse events (TEAEs) are presented in Table 1. Among PHEN/TPM CR subjects, the incidence of serious AEs was comparable to placebo: 4%, 3%, and 5% for placebo, 7.5/46, and 15/92, respectively.

Table 1. Most Common TEAEs (Safety Sample)

TEAE (%)	Placebo (n=993)	PHEN/TPM CR 7.5/46 (n=498)	PHEN/TPM CR 15/92 (n=994)
Dry mouth	2	13	21
Paraesthesia	2	14	21
Constipation	6	15	17
Upper respiratory tract infection	13	12	13
Nasopharyngitis	9	11	10
Dysgeusia	1	7	10
Insomnia	5	6	10
Headache	9	7	10

· Completion rates on therapy were higher in the PHEN/TPM CR groups: 57%, 69%, and 64% for placebo, 7.5/46, and 15/92, respectively.

- Discontinuation rates due to TEAEs were dose-related at 9%, 12%, and 19% for placebo, 7.5/46, and 15/92, respectively.
- There was 1 death in the placebo group.

· Conclusions

- Treatment with PHEN/TPM CR led to significant weight loss vs placebo.
- In addition to weight loss, subjects treated with PHEN/TPM CR achieved significant improvements in glycaemic parameters vs placebo in both the overall and Prediabetes groups, indicative of an improvement in insulin sensitivity.
- Furthermore, in subjects with Prediabetes at baseline, PHEN/TPM CR therapy normalized glycaemic parameters in almost 40% of subjects.
- PHEN/TPM CR led to significant reductions in the proportion of subjects progressing to T2DM.
- PHEN/TPM CR was generally well tolerated based on rates of study completion, discontinuation rates, and overall adverse events.
- Therapies that can address glycaemic parameters, ameliorate insulin resistance, and potentially impact the epidemic rates of progression to diabetes would have significant clinical benefit to overweight and obese patients with Prediabetes.

This trial is registered at ClinicalTrials.gov, number NCT00553787.

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Acknowledgements: We would like to acknowledge and thank the CONQUER investigators and study coordinators, the Medpace team (study CRO), The Lockwood Group (for poster development assistance), and VIVUS internal contributors.

Exhibit 99.3

Below is a graphical representation of the poster entitled “Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks”:

Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks

Authors: W. Timothy Garvey, MD[a]; Wesley W. Day, PhD[b]; Charles H. Bowden, MD[b]

[a]University of Alabama at Birmingham, Birmingham, Alabama, USA; [b]Vivus, Inc., Mountain View, California, USA

Contact details: Dr. W. T. Garvey, MD; University of Alabama at Birmingham, 1675 University Blvd, Birmingham, AL 35294-3360; Office: (205) 996-7433; Email: garveyt@uab.edu

➤ Introduction

- Obesity is a chronic disease that is associated with and contributes to poor outcomes with various comorbid conditions, including diabetes, cardiovascular disease, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis.[1-4]
- As a result, excess body weight has been shown to reduce life expectancy and is the sixth most important cause of disease burden globally.[5]
- Weight loss of >5% significantly reduces the health risks associated with obesity, and greater weight loss is associated with increasing benefit on weight-related comorbidities.[6-8]
- Lifestyle interventions alone are not always sufficient to induce and maintain significant weight loss; therefore, an effective and well-tolerated medical therapy may be needed for the effective treatment of obesity in the longer term.[9]
- An investigational low-dose, controlled-release combination of phentermine and topiramate (PHEN/TPM CR) previously demonstrated significant weight loss compared with placebo in overweight and obese subjects through 56 weeks in the CONQUER study.[10]

➤ Objective

- To determine the long-term weight-loss benefits resulting from 108 weeks of treatment with PHEN/TPM CR in overweight/obese subjects with weight-related comorbidities.

➤ Methods

- PHEN/TPM CR was evaluated over 108 weeks in 2 consecutive clinical studies:
  - CONQUER was a 56-week, double-blind, placebo-controlled, Phase 3 trial of 2487 overweight/obese adult subjects with ≥2 weight-related comorbidities who were randomized to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92).[10]
  - Subjects from selected sites who completed CONQUER on treatment were eligible to enter SEQUEL, a double-blind, placebo-controlled extension of the CONQUER study consisting of a further 52-week treatment period in which subjects continued on their original double-blind treatment.
- All subjects were managed to standard of care for their respective comorbidities, including medication management as needed, and received lifestyle modification counseling, including guidance on nutrition and increased physical activity, based on the LEARN program.[11]

➤ Assessments

- Primary efficacy endpoints for the SEQUEL trial were percent weight loss and the percentage of subjects achieving ≥5% weight loss from baseline (CONQUER Week 0) to Week 108 in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
- Secondary endpoints included percentage of subjects achieving ≥10%, ≥15%, or ≥20% weight loss and change in waist circumference from baseline (CONQUER Week 0) to Week 108.
- Analysis of covariance (ANCOVA) was used to evaluate changes in weight loss and other outcomes. The ANCOVA model used factors of treatment, gender, and diabetic status as fixed effects, with baseline weight as a covariate.

➤ Results

Baseline demographics

- In total, 866 subjects were eligible to participate in SEQUEL; 676 subjects (78%) were enrolled in the study, and the remainder (190 subjects) elected not to continue.
  - A higher percentage of eligible CONQUER subjects on 15/92 (86%) chose to enrol in the extension study than in either the 7.5/46 (79%) or placebo (69%) group.
- Of the 676 enrolled subjects, 574 (84.9%) subjects completed all study visits.
  - The percentages of subjects completing the study were similar between treatment groups (placebo, 86.8%; 7.5/46, 83.8%; and 15/92, 84.1%).
- One subject in the 7.5/46 group enrolled but discontinued from the study prior to receiving study drug (ITT; N=675).
- Baseline demographics were similar in each treatment group (Table 1).

Table 1. Baseline Demographics (Safety Sample).

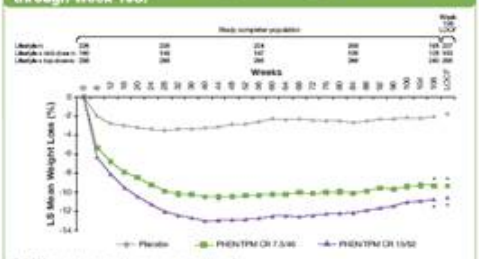
	Placebo (n=227)	PHEN/TPM CR 7.5/46 (n=153)	PHEN/TPM CR 15/92 (n=295)
Mean age, years	52.7	52.2	51.2
Gender, female, %	64.8	69.3	66.1
Race, Caucasian, %	87.2	87.6	82.7
Mean weight, kg	101.1	102.2	101.9
Mean body mass index, kg/m^2	36.0	36.1	36.2
Mean waist circumference, cm	113.0	112.9	112.2

Baseline was defined as the last measurement on or before the first dose of double-blind study drug in the CONQUER study (Week 0).

Overall weight loss

- Following a total of 108 weeks of treatment, significantly greater least-squares (LS) mean percent weight loss was achieved with both doses of PHEN/TPM CR compared with placebo (P<0.0001): 1.8%, 9.3%, and 10.5% (ITT-LOCF) for placebo, 7.5/46, and 15/92, respectively (Figure 1).
  - The differences between both treatment groups and placebo were significant from Week 8 through Week 108 (P<0.0001 vs placebo).

Figure 1. Least-squares mean percent weight loss from baseline through Week 108.

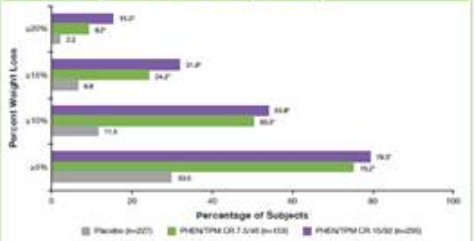


*P<0.0001 vs placebo at all time points except Week 0

Categorical weight loss

- Significantly more patients treated with PHEN/TPM CR achieved ≥5%, ≥10%, ≥15%, or ≥20% weight loss after 108 weeks in a dose-related fashion than with placebo (Ps≤0.0072 for all comparisons; Figure 2).

Figure 2. Percentage of subjects achieving ≥5%, ≥10%, ≥15%, or ≥20% weight loss at Week 108 (ITT-LOCF).



*P<0.0001 vs placebo; †P≤0.0072 vs placebo

Waist circumference

- At Week 108, treatment with PHEN/TPM CR resulted in a significantly greater LS mean reduction in waist circumference than placebo (P<0.0001 vs placebo; ITT-LOCF): -3.6 cm, -9.8 cm, and -10.6 cm for placebo, 7.5/46, and 15/92, respectively.
  - The differences between both treatment groups vs placebo were again significant from Week 8 through Week 108 (P<0.0005 vs placebo).

Safety summary

- Treatment with PHEN/TPM CR was generally well tolerated, with no new safety signals seen between 56 and 108 weeks. The most common treatment-emergent adverse events (TEAEs) are shown in Table 2.
  - The percentage of subjects who discontinued study drug due to AEs was 3.1% in the placebo group, 4.6% in the 7.5/46 group, and 4.4% in the 15/92 group.

Table 2. Most Common Treatment-Emergent AEs Between Baseline and Week 108.

TEAE (%)	Placebo (n=227)	PHEN/TPM CR 7.5/46 (n=153)	PHEN/TPM CR 15/92 (n=295)
Upper respiratory tract infection	32.6	27.5	28.5
Constipation	9.7	22.2	22.7
Paraesthesia	2.6	14.4	22.4
Sinusitis	13.7	15.7	21.0
Dry mouth	2.6	14.4	20.7
Nasopharyngitis	22.0	19.0	17.3
Dysgeusia	1.8	11.8	13.6
Headache	11.5	7.2	12.9
Insomnia	9.7	12.4	11.5
Back pain	11.5	11.1	11.6

- In total, 47 subjects had a serious AE (SAE) between baseline and Week 108: 14 (6.2%) subjects in the placebo group, 9 (5.9%) in the 7.5/46 group, and 24 (8.1%) in the 15/92 group.
  - There were no treatment-related SAEs.

➤ Conclusions

- Therapies that can provide sustained weight loss are needed to address the current and future effects of the obesity epidemic.
- PHEN/TPM CR produced significant rapid, initial weight loss and reductions in waist circumference that were observed from Week 8 and sustained throughout the 2-year treatment period.
  - Further, significantly more subjects in both PHEN/TPM CR treatment groups achieved ≥5%, ≥10%, ≥15%, or ≥20% weight loss in a dose-related fashion at Week 108 compared with placebo.
- PHEN/TPM CR was generally well tolerated based on percentages of subjects choosing to join the extension study, 2-year study completion and discontinuation rates, and the overall incidence of AEs.
- These findings from the SEQUEL study demonstrate the sustained effectiveness and consistent safety and tolerability profile of PHEN/TPM CR in the long-term treatment of obesity, suggesting the potential of PHEN/TPM CR to reduce the health risks associated with this serious disease.

This trial is registered at ClinicalTrials.gov, number NCT00796367.

References: 1. Wree A, et al. *Digestion* 2011;83:12a-133. 2. NHLBI. http://www.nhlbi.nih.gov/guidelines/obesity/prctgs_c.pdf. Accessed April 3, 2011. 3. Fiegal KM, et al. *JAMA* 2007;298:2028-2037. 4. Tobcass T, et al. *Obes Rev* 2010 Nov 3. doi: 10.1111/j.1467-789X.2010.00807.x. [Epub ahead of print]. 5. Haslam DW, et al. *Lancet* 2006;366:1197-1209. 6. Hainer V, et al. *Diabetes Care* 2008;31(suppl 2):S269-S277. 7. Horton ES. *Obesity* 2009;17(suppl 3):S43-S48. 8. Pi-Sunyer X. *Postgrad Med* 2009;121:21-33. 9. Klein S. *Obes Rev* 2004;12 Suppl:635-1685. 10. Gadde KM, et al. *Lancet* 2011;377:1341-1352. 11. Brownell KD. *The LEARN Program for Weight Management* 2004.

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Below is a reproduction of the contents of the poster entitled “Long-term Treatment With Controlled-Release Phentermine/Topiramate Demonstrates Sustained Weight Loss Over 108 Weeks”:

Authors: W. Timothy Garvey, MD(a); Wesley W. Day, PhD(b); Charles H. Bowden, MD(b)

(a)University of Alabama at Birmingham, Birmingham, Alabama, USA; (b)Vivus, Inc., Mountain View, California, USA

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· Introduction

- Obesity is a chronic disease that is associated with and contributes to poor outcomes with various comorbid conditions, including diabetes, cardiovascular disease, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis.(1)-(4)
- As a result, excess body weight has been shown to reduce life expectancy and is the sixth most important cause of disease burden globally.(5)
- Weight loss of >5% significantly reduces the health risks associated with obesity, and greater weight loss is associated with increasing benefit on weight-related comorbidities.(6)-(8)
- Lifestyle interventions alone are not always sufficient to induce and maintain significant weight loss; therefore, an effective and well-tolerated medical therapy may be needed for the effective treatment of obesity in the longer term.(9)
- An investigational low-dose, controlled-release combination of phentermine and topiramate (PHEN/TPM CR) previously demonstrated significant weight loss compared with placebo in overweight and obese subjects through 56 weeks in the CONQUER study.(10)

· Objective

- To determine the long-term weight-loss benefits resulting from 108 weeks of treatment with PHEN/TPM CR in overweight/obese subjects with weight-related comorbidities.

· Methods

- PHEN/TPM CR was evaluated over 108 weeks in 2 consecutive clinical studies:
  - CONQUER was a 56-week, double-blind, placebo-controlled, Phase 3 trial of 2487 overweight/obese adult subjects with ≥2 weight-related comorbidities who were randomized to placebo, PHEN 7.5 mg/TPM CR 46 mg (7.5/46), or PHEN 15 mg/TPM CR 92 mg (15/92).(10)
  - Subjects from selected sites who completed CONQUER on treatment were eligible to enter SEQUEL, a double-blind, placebo-controlled extension of the CONQUER study consisting of a further 52-week treatment period in which subjects continued on their original double-blind treatment.
- All subjects were managed to standard of care for their respective comorbidities, including medication management as needed, and received lifestyle modification counseling, including guidance on nutrition and increased physical activity, based on the LEARN program.(11)

· Assessments

- Primary efficacy endpoints for the SEQUEL trial were percent weight loss and the percentage of subjects achieving ≥5% weight loss from baseline (CONQUER Week 0) to Week 108 in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
- Secondary endpoints included percentage of subjects achieving ≥10%, ≥15%, or ≥20% weight loss and change in waist circumference from baseline (CONQUER Week 0) to Week 108.
- Analysis of covariance (ANCOVA) was used to evaluate changes in weight loss and other outcomes. The ANCOVA model used factors of treatment, gender, and diabetic status as fixed effects, with baseline weight as a covariate.

· Results

Baseline demographics

- In total, 866 subjects were eligible to participate in SEQUEL; 676 subjects (78%) were enrolled in the study, and the remainder (190 subjects) elected not to continue.
  - A higher percentage of eligible CONQUER subjects on 15/92 (86%) chose to enrol in the extension study than in either the 7.5/46 (79%) or placebo (69%) group.
- Of the 676 enrolled subjects, 574 (84.9%) subjects completed all study visits.
  - The percentages of subjects completing the study were similar between treatment groups (placebo, 86.8%; 7.5/46, 83.8%; and 15/92, 84.1%).
- One subject in the 7.5/46 group enrolled but discontinued from the study prior to receiving study drug (ITT; N=675).
- Baseline demographics were similar in each treatment group (Table 1).

Table 1. Baseline Demographics (Safety Sample).

	Placebo (n=227)	PHEN/TPM CR 7.5/46 (n=153)	PHEN/TPM CR 15/92 (n=295)
Mean age, years	52.7	52.2	51.2
Gender, female, %	64.8	69.3	66.1
Race, Caucasian, %	87.2	87.6	82.7
Mean weight, kg	101.1	102.2	101.9
Mean body mass index, kg/m^2	36.0	36.1	36.2
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Baseline was defined as the last measurement on or before the first dose of double-blind study drug in the CONQUER study (Week 0).

Overall weight loss

- Following a total of 108 weeks of treatment, significantly greater least-squares (LS) mean percent weight loss was achieved with both doses of PHEN/TPM CR compared with placebo (*P*<0.0001): 1.8%, 9.3%, and 10.5% (ITT-LOCF) for placebo, 7.5/46, and 15/92, respectively (Figure 1).
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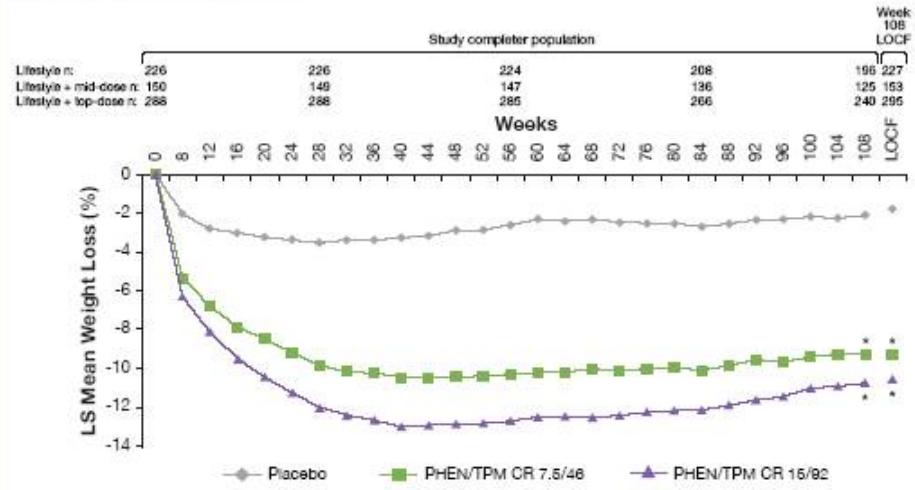

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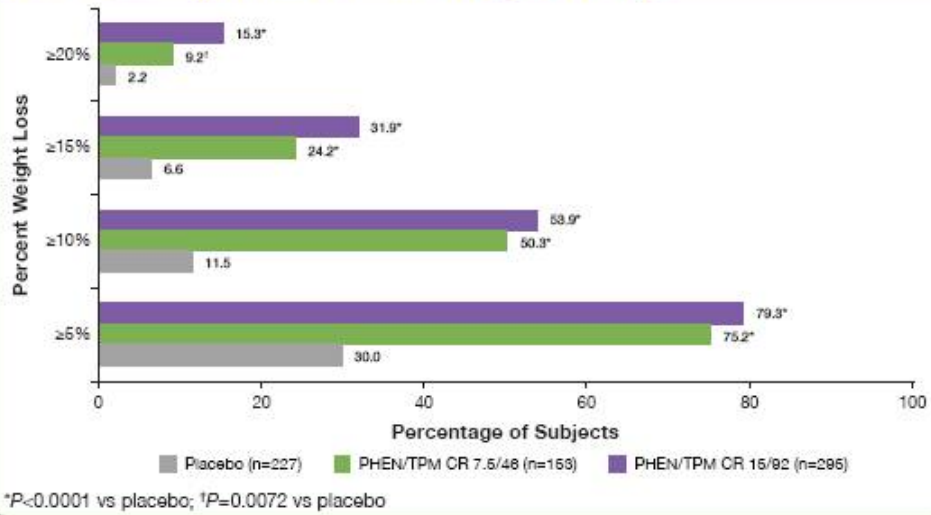

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