Farmaci anti-obesità: essere o non essere?

Anti-obesity drugs: to be or not to be?

Dvorak RV, Sharma AM, Astrup A.

Dopo questo articolo vi è stato un ampio dibattito negli Usa sull’uso dei farmaci antiobesità
**Fentermina + Topiramato**
(\textit{Qnexa}) >>> (\textit{Qysmia})

**Fentermina**
- Farmaco noradrenergico
- In commercio dagli anni '50
- E' tuttora il farmaco anti-obesità più usato
- Non ha azione sul sistema serotoninergico
- Dose massima giornaliera 30 mg

**Topiramato**
- Farmaco GABAergico
- In commercio dal 1996
- AIC: anti epilettico/profilassi emicrania
- Dose massima giornaliera 400 mg

Mono-somministrazione orale a rilascio prolungato di fentermina e topiramato

- **Topiramato**
  - Dose max approvata: 400 mg

- **Phentermine**
  - Dose: 37.5 mg

Low \quad Mid \quad Full
In commercio negli USA: approvate 4 formulazioni

FENTERMINA – TOPIRAMATO: 3,75/23 -----7,5/46------11,25/69----15/92
ADIPLEX-P®
(Phentermine Hydrochloride USP, 37.5 mg)

DESCRIPTION

Phentermine hydrochloride USP has the chemical name of α,α-Dimethylphenethylamine hydrochloride. The structural formula is as follows:

\[
\text{C}_{10}\text{H}_{15}\text{N} \cdot \text{HCl} \quad \text{M.W.} \quad 185.7
\]
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Suprenza safely and effectively. See full prescribing information for Suprenza.

Suprenza™ (phentermine hydrochloride) orally disintegrating tablet

C IV

[Initial U.S. Approval: 1959]

INDICATIONS AND USAGE

Suprenza is a sympathomimetic amine anorectic indicated as a short-term adjunct (a few weeks) in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥30 kg/m², or ≥27 kg/m² in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia) (1).

The limited usefulness of agents of this class, including Suprenza, should be measured against possible risk factors inherent in their use (1).

DOSEAGE AND ADMINISTRATION

Dosage should be individualized to obtain an adequate response with the lowest effective dose (2).

Late evening administration should be avoided (risk of insomnia) (2).

Suprenza can be taken with or without food (12).

DOSEAGE FORMS AND STRENGTHS

Orally disintegrating tablets containing 15 mg or 30 mg phentermine hydrochloride (3).

CONTRAINICATIONS

- History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension) (4)
- During or within 14 days following the administration of monoamine oxidase inhibitors (4)
- Hyperthyroidism (4)
- Glaucoma (4)
- Agitated states (4)
- History of drug abuse (4)
- Pregnancy (4, 8.1)
- Nursing (4, 8.3)
- Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines (4).

DRUG INTERACTIONS

- Monoamine oxidase inhibitors: Risk of hypertensive crisis (4, 7.1)
- Alcohol: Consider potential interaction (7.2)
- Insulin and oral hypoglycemics: Requirements may be altered (7.3)
- Adrenergic neuron blocking drugs: Hypotensive effect may be decreased by Suprenza (7.4)

FENTERMINA negli USA in commercio dal 1959

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Phentermine is a Schedule IV controlled substance.

Controindicazioni

History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension)
During or within 14 days following the administration of monoamine oxidase inhibitors
Hyperthyroidism
Glaucoma
Agitated states
History of drug abuse
Pregnancy [see Use in Specific Populations (8.1)]
Nursing [see Use in Specific Populations (8.3)]
Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines
Calo ponderale con terapia intermittente.
TOPAMAX® (topiramate) TABLETS for oral use
TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES for oral use
Initial U.S. Approval – 1996

RECENT MAJOR CHANGES

- Indications and Usage (1 1) 07/2011
- Dosage and Administration (2 1) 07/2011
- Metabolic Acidosis (5 3) 07/2011
- Hypothermia with Concomitant Valproic Acid (VPA) Use (5 11) 07/2011

INDICATIONS AND USAGE

TOPAMAX® is an antiepileptic (AED) agent indicated for:

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures (1 1)
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS) (1 2)
- Migraine: Treatment for adults for prophylaxis of migraine headache (1 3)
### DOSAGE AND ADMINISTRATION

See DOSAGE AND ADMINISTRATION, Epilepsy: Monotherapy and Adjunctive Therapy Use for additional details (2.1)

<table>
<thead>
<tr>
<th></th>
<th><strong>Initial Dose</strong></th>
<th><strong>Titration</strong></th>
<th><strong>Recommended Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy monotherapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>children 2 to &lt;10 years</td>
<td>25 mg/day</td>
<td>The dosage should be titrated over 5-7 weeks</td>
<td>Daily doses in two</td>
</tr>
<tr>
<td></td>
<td>administered</td>
<td></td>
<td>divided doses based</td>
</tr>
<tr>
<td></td>
<td>nightly for the</td>
<td></td>
<td>on weight (Table 2)</td>
</tr>
<tr>
<td></td>
<td>first week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy monotherapy:</td>
<td>50 mg/day in two</td>
<td>The dosage should be increased weekly by increments of 50 mg for the first</td>
<td>400 mg/day in two</td>
</tr>
<tr>
<td>adults and pediatric</td>
<td>divided doses</td>
<td>4 weeks then 100 mg for weeks 5 to 6</td>
<td>divided doses</td>
</tr>
<tr>
<td>patients ≥10 years (2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy adjunctive</td>
<td>25 to 50 mg/day</td>
<td>The dosage should be increased weekly to an effective dose by increments of</td>
<td>200-400 mg/day in two</td>
</tr>
<tr>
<td>therapy: adults with</td>
<td></td>
<td>25 to 50 mg</td>
<td>divided doses</td>
</tr>
<tr>
<td>partial onset seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or LGS (2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy adjunctive</td>
<td>25 to 50 mg/day</td>
<td>The dosage should be increased weekly to an effective dose by increments of</td>
<td>400 mg/day in two</td>
</tr>
<tr>
<td>therapy: adults with</td>
<td></td>
<td>25 to 50 mg</td>
<td>divided doses</td>
</tr>
<tr>
<td>primary generalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tonic-clonic seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WARNINGS AND PRECAUTIONS

Acute myopia and secondary angle closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible (5.1).

Oligohidrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients (5.2).

Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX® if clinically appropriate (5.3).

Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation (5.4).

Cognitive/neuropsychiatric: TOPAMAX® may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations (5.5).

Fetal Toxicity: TOPAMAX® use during pregnancy can cause cleft lip and/or palate (5.6).

Withdrawal of AEDs: Withdrawal of TOPAMAX® should be done gradually (5.7).

Hyperammonemia and encephalopathy associated with or without concomitant valproic acid use: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur (5.9).

Kidney stones: Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided (5.10).

Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.11).

ADVERSE REACTIONS
Weight Loss with Topiramate

Bray et al Obes Res 2003 in press
### Table 3: Meta-analysis of adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of reports describing the event</th>
<th>No. of participants reporting the event/total no. of participants</th>
<th>Pooled OR</th>
<th>95% CI</th>
<th>I²</th>
<th>P value (heterogeneity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>intervention group</td>
<td>control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event leading to topiramate withdrawal</td>
<td>12/2628</td>
<td>245/2525</td>
<td>1.94</td>
<td>1.64-2.29</td>
<td>0</td>
<td>0.87</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>17/3035</td>
<td>289/3027</td>
<td>8.70</td>
<td>6.90-11.0</td>
<td>58.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>16/2981</td>
<td>30/2970</td>
<td>8.61</td>
<td>5.35-13.87</td>
<td>25.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Psychomotor impairment</td>
<td>7/1264</td>
<td>6/1266</td>
<td>7.82</td>
<td>3.71-16.46</td>
<td>0</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>9/1146</td>
<td>20/1133</td>
<td>4.51</td>
<td>2.76-7.40</td>
<td>0</td>
<td>0.52</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11/2056</td>
<td>69/2034</td>
<td>3.33</td>
<td>2.51-4.41</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Concentration difficulty</td>
<td>16/2981</td>
<td>91/2970</td>
<td>3.30</td>
<td>2.55-4.27</td>
<td>4.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Nervousness</td>
<td>7/1265</td>
<td>26/1266</td>
<td>2.93</td>
<td>1.89-4.63</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>Visual disturb</td>
<td>5/1315</td>
<td>37/1326</td>
<td>2.48</td>
<td>1.66-3.70</td>
<td>0</td>
<td>0.69</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12/2676</td>
<td>88/2670</td>
<td>2.21</td>
<td>1.62-3.02</td>
<td>20.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>15/2603</td>
<td>142/2611</td>
<td>2.05</td>
<td>1.63-2.58</td>
<td>8.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Mood problems</td>
<td>11/1942</td>
<td>59/1992</td>
<td>2.00</td>
<td>1.44-2.77</td>
<td>0</td>
<td>0.82</td>
</tr>
<tr>
<td>Cough</td>
<td>9/1697</td>
<td>86/1682</td>
<td>1.58</td>
<td>1.20-2.11</td>
<td>0</td>
<td>0.47</td>
</tr>
<tr>
<td>Depression</td>
<td>15/2778</td>
<td>141/2770</td>
<td>1.55</td>
<td>1.24-1.94</td>
<td>0</td>
<td>0.83</td>
</tr>
<tr>
<td>Nausea</td>
<td>9/1716</td>
<td>109/1704</td>
<td>1.52</td>
<td>1.17-1.96</td>
<td>0</td>
<td>0.90</td>
</tr>
<tr>
<td>Constipation</td>
<td>12/2099</td>
<td>92/2099</td>
<td>1.71</td>
<td>1.31-2.25</td>
<td>0</td>
<td>0.60</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7/773</td>
<td>29/773</td>
<td>1.71</td>
<td>1.06-2.76</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9/1618</td>
<td>92/1618</td>
<td>1.37</td>
<td>0.98-1.92</td>
<td>14.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14/2477</td>
<td>221/2465</td>
<td>1.35</td>
<td>1.11-1.63</td>
<td>2.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16/2843</td>
<td>413/2825</td>
<td>1.34</td>
<td>1.16-1.55</td>
<td>0.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Back pain</td>
<td>6/737</td>
<td>58/716</td>
<td>1.32</td>
<td>0.92-1.90</td>
<td>0</td>
<td>0.84</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12/2091</td>
<td>90/2091</td>
<td>1.31</td>
<td>0.98-1.74</td>
<td>0</td>
<td>0.63</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11/1877</td>
<td>107/1877</td>
<td>1.27</td>
<td>0.98-1.67</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11/2375</td>
<td>609/2367</td>
<td>1.26</td>
<td>1.10-1.43</td>
<td>0</td>
<td>0.66</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11/2071</td>
<td>171/2056</td>
<td>1.26</td>
<td>1.02-1.56</td>
<td>0</td>
<td>0.70</td>
</tr>
<tr>
<td>Migraine</td>
<td>7/1342</td>
<td>113/1330</td>
<td>1.11</td>
<td>0.84-1.47</td>
<td>0</td>
<td>0.52</td>
</tr>
</tbody>
</table>

CI, confidence interval; No., number; OR, odds ratio.
Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Kishore M Gadde, MD, David B Allison, PhD, Donna H Ryan, MD, Craig A Peterson, MS, Barbara Troupin, MD, Michael L Schwiers, MS and Wesley W Day, PhD

The Lancet
DOI: 10.1016/S0140-6736(11)60205-5

Published Online April 11, 2011

Studio OB 303 : 56 settimane, 27-45-BMI con 2 o più comorbilità
Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Kishore M Gadde, David R Allison, Donna H Ryan, Craig A Peterson, Barbara Troupin, Michael L Schwiers, Winsley W Day

www.thelancet.com Published online April 11, 2011 DOI:10.1016/S0140-6736(11)60205-5
### Table S3: Progression to type 2 diabetes* among patients without type 2 diabetes at baseline

<table>
<thead>
<tr>
<th></th>
<th>PHEN/TPM-CR</th>
<th>PHEN/TPM-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=430)</td>
<td>(n=828)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7·5/46</td>
<td>15/92</td>
</tr>
<tr>
<td>(n=834)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of diabetes, no. (%)</td>
<td>12 (2·8)</td>
<td>14 (1·7)</td>
</tr>
<tr>
<td>Subject years of treatment follow-up</td>
<td>388</td>
<td>747</td>
</tr>
<tr>
<td>Annualized incidence rate</td>
<td>3·1</td>
<td>1·9</td>
</tr>
<tr>
<td>Relative risk vs placebo (95% CI)</td>
<td>0·78 (0·40, 1·50)</td>
<td>0·47 (0·25, 0·88)</td>
</tr>
</tbody>
</table>

### Table S4: Changes from baseline in concomitant antidiabetic medications

<table>
<thead>
<tr>
<th></th>
<th>PHEN/TPM-CR</th>
<th>PHEN/TPM-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=67)</td>
<td>(n=164)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7·5/46</td>
<td>15/92</td>
</tr>
<tr>
<td>(n=157)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>4 (2·5%)</td>
<td>2 (3·0%)</td>
</tr>
<tr>
<td>No change</td>
<td>130 (82·8%)</td>
<td>62 (92·5%)</td>
</tr>
<tr>
<td>Increase</td>
<td>23 (14·6%)</td>
<td>3 (4·5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

The Lancet April 2011
Variazioni della Frequenza Cardiaca con fentermina più topiramato

Negli studi di fase 3 non vi sono state variazioni significative della frequenza cardiaca tra il gruppo trattato con dose raccomandata e il gruppo placebo. Il gruppo trattato con la dose piena, invece, ha avuto un lieve aumento della FC rispetto al placebo (tratto e adattato da Gadde KM, Allison DB, Ryan DH et al. Lancet. 2011 Apr 16;377:1341-52. Supplementary Webappendix)
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo (n=993)</th>
<th>Phentermine 7.5 mg plus topiramate 46-0 mg (n=898)</th>
<th>p value</th>
<th>Phentermine 15.0 mg plus topiramate 92-0 mg (n=994)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>24 (2%)</td>
<td>67 (13%)</td>
<td>&lt;0.0001</td>
<td>107 (21%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>20 (2%)</td>
<td>68 (14%)</td>
<td>&lt;0.0001</td>
<td>154 (21%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Constipation</td>
<td>59 (6%)</td>
<td>75 (15%)</td>
<td>&lt;0.0001</td>
<td>140 (28%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>128 (13%)</td>
<td>64 (12%)</td>
<td>0.7422</td>
<td>113 (13%)</td>
<td>0.7906</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>86 (9%)</td>
<td>53 (11%)</td>
<td>0.2204</td>
<td>86 (10%)</td>
<td>0.3947</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11 (1%)</td>
<td>37 (7%)</td>
<td>&lt;0.0001</td>
<td>105 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>47 (5%)</td>
<td>29 (6%)</td>
<td>0.3892</td>
<td>103 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>90 (9%)</td>
<td>35 (7%)</td>
<td>0.1983</td>
<td>101 (10%)</td>
<td>0.4467</td>
</tr>
<tr>
<td>Dizziness</td>
<td>31 (3%)</td>
<td>36 (7%)</td>
<td>0.0005</td>
<td>99 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>67 (7%)</td>
<td>34 (7%)</td>
<td>1.0000</td>
<td>85 (9%)</td>
<td>0.1511</td>
</tr>
<tr>
<td>Back pain</td>
<td>49 (5%)</td>
<td>28 (6%)</td>
<td>0.6199</td>
<td>72 (7%)</td>
<td>0.0386</td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (4%)</td>
<td>18 (4%)</td>
<td>0.6254</td>
<td>68 (7%)</td>
<td>0.0139</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50 (5%)</td>
<td>22 (4%)</td>
<td>0.7010</td>
<td>67 (7%)</td>
<td>0.1270</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>48 (5%)</td>
<td>32 (6%)</td>
<td>0.2229</td>
<td>58 (6%)</td>
<td>0.3690</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>36 (4%)</td>
<td>20 (4%)</td>
<td>0.7129</td>
<td>60 (6%)</td>
<td>0.0157</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>37 (4%)</td>
<td>26 (5%)</td>
<td>0.1753</td>
<td>54 (5%)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>54 (5%)</td>
<td>23 (5%)</td>
<td>0.5373</td>
<td>44 (4%)</td>
<td>0.3025</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>43 (4%)</td>
<td>22 (4%)</td>
<td>1.0000</td>
<td>52 (5%)</td>
<td>0.4924</td>
</tr>
</tbody>
</table>

**Psychiatric adverse events**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo (n=993)</th>
<th>Phentermine 7.5 mg plus topiramate 46-0 mg (n=898)</th>
<th>p value</th>
<th>Phentermine 15.0 mg plus topiramate 92-0 mg (n=994)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>29 (3%)</td>
<td>14 (3%)</td>
<td>0.9054</td>
<td>39 (4%)</td>
<td>0.2188</td>
</tr>
<tr>
<td>Anxiety</td>
<td>21 (2%)</td>
<td>9 (2%)</td>
<td>0.6899</td>
<td>41 (4%)</td>
<td>0.0100</td>
</tr>
<tr>
<td>Irritability</td>
<td>8 (&lt;1%)</td>
<td>13 (2%)</td>
<td>0.0053</td>
<td>34 (3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to onset (days, median, IQR)</td>
<td>92 (26-164)</td>
<td>36 (8-138)</td>
<td>0.0568</td>
<td>29 (12-118)</td>
<td>0.0049</td>
</tr>
<tr>
<td>Duration (days, median, IQR)</td>
<td>44 (17-123)</td>
<td>35 (11-81)</td>
<td>0.2989</td>
<td>29 (12-61)</td>
<td>0.0252</td>
</tr>
<tr>
<td>Resolution among patients discontinuing drug</td>
<td>4/5 (80%)</td>
<td>10/10 (100%)</td>
<td>0.3333</td>
<td>33/37 (89%)</td>
<td>0.3783</td>
</tr>
</tbody>
</table>

**Cognitive adverse events**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo (n=993)</th>
<th>Phentermine 7.5 mg plus topiramate 46-0 mg (n=898)</th>
<th>p value</th>
<th>Phentermine 15.0 mg plus topiramate 92-0 mg (n=994)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbance in attention</td>
<td>7 (&lt;1%)</td>
<td>10 (2%)</td>
<td>0.0362</td>
<td>35 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to onset (days, median, IQR)</td>
<td>22 (8-119)</td>
<td>23 (10-100)</td>
<td>0.8958</td>
<td>25 (11-51)</td>
<td>0.8223</td>
</tr>
<tr>
<td>Duration (days, median, IQR)</td>
<td>39 (13-76)</td>
<td>51 (8-149)</td>
<td>0.4452</td>
<td>36 (18-81)</td>
<td>0.7535</td>
</tr>
<tr>
<td>Resolution among subjects discontinuing drug</td>
<td>3/3 (100%)</td>
<td>2/2 (100%)</td>
<td>NA</td>
<td>21/21 (100%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are number (%) or n/N (%), unless otherwise indicated. p values are for comparisons of phentermine plus topiramate with placebo. NA= not applicable. "Psychiatric and cognitive adverse events arising at a frequency of 2% or more, and other adverse events arising at a frequency of 5% or more with any treatment are shown. (Including the preferred terms in the psychiatric class, except sleep-related adverse events, from the Medical Dictionary for Regulatory Activities (MedDRA). Included in the psychiatric adverse events category although it is classified as a general disorder in MedDRA. Including the preferred terms from MedDRA: disturbance in attention, memory impairment, amnesia, confusion, bradypsia, disorientation, mental impairment, aphasia, and dysarthria.

Table 3: Adverse events in the safety population (n=2485)"
Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study\textsuperscript{1–3}

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden

Disposition of Subjects from OB-303 into OB-305

OB-303
2487 (100\%) randomized

OB-303
1542 (62\%) completed study on drug

676 (27.2\%) not eligible to participate
866 (34.8\%) eligible to participate from selected sites

190 (7.6\%) did not enroll in OB-305
676 (27.2\%) enrolled in OB-305

568 (22.8\%) completed all study visits on drug

Conclusion: PHEN/TPM CR in conjunction with lifestyle modification may provide a well-tolerated and effective option for the sustained treatment of obesity complicated by cardiometabolic disease. This trial was registered at clinicaltrials.gov as NCT00796367. Am J Clin Nutr 2012;95:297–308.
SEQUEL STUDY
Am J Clin Nutr 2012; 95:297-308

Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study

W Timothy Garvey, Donna H Ryan, Michelle Look, Kishore M Gadde, David B Allison, Craig A Peterson, Michael Schwiers, Wesley W Day, and Charles H Bowden
Safety Events of Interest: Two-year Cohort

- **Psychiatric disorders**
  - Placebo: 18.5%
  - Mid-dose PHEN/TPM: 21.6%
  - High-dose PHEN/TPM: 23.7%

- **Cognitive disorders**
  - Placebo: 6.5%
  - Mid-dose PHEN/TPM: 5.8%
  - High-dose PHEN/TPM: 2.2%

- **Cardiovascular disorders**
  - Placebo: 5.3%
  - Mid-dose PHEN/TPM: 7.8%
  - High-dose PHEN/TPM: 5.1%

- **Bicarb <21 mEq/L**
  - Placebo: 4.0%
  - Mid-dose PHEN/TPM: 22.9%
  - High-dose PHEN/TPM: 30.5%

Topiramato inibisce anidrasi carbonica
General Safety: OB-305

- Safety data from 52-week extension study, OB-305, consistent with safety profile observed in 1-year safety cohort

- PHEN/TPM-treated subjects experienced higher incidence of the targeted medical events related to psychiatric, cognitive, cardiac disorders, and reductions in serum bicarbonate
Mean (SD) Change in BP and HR
2-year Cohort at Week 108 from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=227</th>
<th>Mid-dose PHEN/TPM N=153</th>
<th>High-dose PHEN/TPM N=295</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>197</td>
<td>129</td>
<td>248</td>
</tr>
<tr>
<td>SBP</td>
<td>-4.2 (15.1)</td>
<td>-5.0 (14.3)</td>
<td>-3.9 (14.0)</td>
</tr>
<tr>
<td>DBP</td>
<td>-3.6 (10.3)</td>
<td>-3.5 (9.6)</td>
<td>-2.9 (9.4)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+0.4 (9.9)</td>
<td>+1.3 (10.2)</td>
<td>+1.7 (10.6)</td>
</tr>
<tr>
<td>RPP</td>
<td>-0.22</td>
<td>-0.20</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

n is the number of subjects with measurements at both Baseline and Week 108
MACE

- MACE: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke
- HR 0.84 (95% 0.26, 2.64)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Sponsor adjudication</th>
<th>Placebo N=1742</th>
<th>PHEN/TPM N=2581</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio-respiratory arrest</td>
<td>CV death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction/Acute MI</td>
<td>Myocardial infarction/coronary revascularization</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cerebrovascular accident Intracranial hemorrhage</td>
<td>Stroke</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Brain stem infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total subjects</td>
<td></td>
<td>5 (0.29%)</td>
<td>7 (0.27%)</td>
</tr>
</tbody>
</table>
Cardiovascular Safety

- Palpitations and tachycardia were the most common terms reported in cardiac arrhythmia subclass
- Ischemic events were too few in number to draw definitive conclusions regarding PHEN/TPM and its effect on major cardiovascular events
- Long term effects of decrease blood pressure and increase heart rate change in an at-risk obese population uncertain
- PHEN/TPM cardiovascular outcomes trial proposed
Teratogenicity

Conclusions

- No evidence for an increased risk of overall MCMs
- First-trimester TPM exposure is associated with an increased risk of oral clefts
- The estimated relative risks of OCs were unstable
  - Could range from 2 fold up to 5 fold based on currently available point estimates
Risk Management Options for Phentermine/Topiramate

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
February 22, 2012

Joyce Weaver, Pharm.D.
Senior Drug Risk Management Analyst
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Risk Management
What is a REMS?

- Risk Evaluation and Mitigation Strategy (REMS)
  - A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.

  - Designed to achieve specific goals to mitigate reported risks with a drug.

  - The Agency has authority to require a REMS in the pre-approval of a drug or post-approval.
What are the REMS Elements?

A REMS may include:
- Medication Guide - directed to patients
- Communication plan - directed to healthcare providers
- Elements to Assure Safe Use (ETASU)
  A. Certification and training of prescribers
  B. Certification of dispensers
  C. Requirement that a drug be dispensed to patients only in certain health care settings
  D. Documentation of safe use prior to dispensing a drug
  E. Requirement for certain monitoring of a patient to receive a drug
  F. Requirement that a patient enroll in a registry

A REMS for an NDA or BLA must include a timetable for submission of assessments of the REMS
Qsymia, il controllo REMS si attenua

I recenti studi clinici, ad un anno dall’approvazione della Qsymia, hanno dimostrato che in media i pazienti hanno perso il 5,8% del loro peso corporeo iniziale, con una diminuzione della pressione sanguigna ed un abbassamento dei livelli di colesterolo.

L’anno scorso la pillola, in commercio solamente negli Stati Uniti, veniva venduta esclusivamente attraverso farmacie certificate online, ora invece è disponibile anche in farmacie appositamente specializzate e non più via Web.
Febbraio 2013 : per il momento EMA non autorizza in Europa Qsiva (Qyrmia)

VIVUS Receives Decision Regarding Qsiva Appeal

MOUNTAIN VIEW, Calif., Feb. 21, 2013 (GLOBE NEWSWIRE) -- VIVUS, Inc. (Nasdaq:VVUS) announced today that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) confirmed its October 18, 2012 decision to decline the Marketing Authorization Application (MAA) for Qsiva™ (phentermine/topiramate ER) for the treatment of obesity in the European Union.

VIVUS had requested a re-examination of the opinion. After considering the grounds for this request, CHMP again declined the marketing authorization on February 21, 2013. In its consideration of the Qsiva MAA, CHMP indicated that a pre-approval cardiovascular outcomes trial would be necessary to establish long-term safety.
In data 27 giugno 2012 la FDA ha autorizzato l’immissione in commercio di lorcaserina per il trattamento di soggetti obesi o con BMI $\geq$ di 27 in presenza di comorbilità.

Questo parere favorevole è stato preso dopo l’iniziale rifiuto del 2010 e costituisce una svolta nell’atteggiamento dell’agenzia nei confronti dell’obesità.

L’Azienda titolare del brevetto dovrà condurre degli studi post marketing sulla sicurezza CV e sul rischio di tumori.
Lorcaserina

- E’ un potente e selettivo agonista dei recettori serotoninergici $5-HT_{2C}$

- I recettori $5-HT_{2C}$ sono localizzati in numerose aree cerebralì deputate al controllo dell’assunzione alimentare e sono virtualmente assenti in periferia.

- E’ 15 e 100 volte più potente nello stimolare i recettori $5-HT_{2C}$ rispetto a quelli $5-HT_{2A}$ e $5-HT_{2B}$ a livello periferico.

- I recettori e $5-HT_{2B}$ sono quelli implicati nell’insorgenza di valvulopatia nei soggetti che assumevano fenfluramine.
<table>
<thead>
<tr>
<th>5HT2 subtype</th>
<th>Distribution/Function</th>
<th>CNS</th>
<th>Periphery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A</td>
<td>Drug-induced hallucinogenic responses</td>
<td>Anxiety, behavior, locomotion</td>
<td>Liver, renal mesangium mitogenesis Vasoactive (pulmonary/coronary vessels) Adipocyte differentiation, Platelet aggregation, enteric neurotransmitter</td>
</tr>
<tr>
<td>2B</td>
<td>Motor behavior, Anxiety, cerebrovascular tone</td>
<td>Drug-induced valvulopathy</td>
<td>Pulmonary vascular remodeling/hypertension Hepatocellular mitogen</td>
</tr>
<tr>
<td>2C</td>
<td>Appetite suppression</td>
<td>Locomotion, Anxiety DA output, stress response</td>
<td>Limited expression</td>
</tr>
</tbody>
</table>
Lorcaserina

Sarà commercializzata negli USA con il nome di Belviq

Sarà disponibile in capsule da 10 mg da assumere due volte al giorno

La FDA sconsiglia di proseguire il trattamento con lorcaserina se il calo ponderale dopo 12 settimane è inferiore al 5%.

Arena's marketing authorization application was accepted in the EU on March 26, 2012. Day 120 questions are set to occur in July, and depending on how quickly ARNA addresses any concerns, approval may occur as early as 1H 2013.
Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management


3182 pz obesi (BMI 30 – 45)
   o sovrappeso/obesi (BMI 27–45) con almeno una comorbilità
   (ipertensione, dislipidemia, malattia CV, IGT, OSAS)

Criteri di esclusione
   insufficienza mitralica moderata, insufficienza aortica lieve
   diabete mellito, PAS > 140 PAD > 90
   Depressione fino a 2 anni prima con necessità di terapia farmac.
   Gravidanza e lattazione
Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Perdita di peso dopo 1 anno

Completers placebo 45,1%

Completers lorcaserina 55,4%
Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management

Perdita di peso dopo 2 anni
<table>
<thead>
<tr>
<th>End Point</th>
<th>Intention-to-Treat Analysis with LOCF Imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lorcan (N=1538)</td>
</tr>
<tr>
<td><strong>Coprimary end points</strong></td>
<td></td>
</tr>
<tr>
<td>Loss of $\geq$5% of body weight</td>
<td></td>
</tr>
<tr>
<td>Patients (%)</td>
<td>47.5</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>$-5.8\pm0.2$</td>
</tr>
<tr>
<td>Loss of $\geq$10% of body weight (%)</td>
<td>22.6</td>
</tr>
<tr>
<td><strong>Key secondary end points</strong></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>$-6.8\pm0.2$</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>$-2.09\pm0.06$</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>$-1.4\pm0.3$</td>
</tr>
<tr>
<td>Diastolic</td>
<td>$-1.1\pm0.2$</td>
</tr>
<tr>
<td>Cholesterol (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$-0.90\pm0.33$</td>
</tr>
<tr>
<td>LDL</td>
<td>2.87\pm0.56</td>
</tr>
<tr>
<td>HDL</td>
<td>0.05\pm0.33</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>$-0.8\pm0.3$</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>$-3.33\pm0.38$</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>$-0.41\pm0.03$</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>$-0.04\pm0.01$</td>
</tr>
<tr>
<td>High-sensitivity CRP (mg/liter)</td>
<td>$-1.19\pm0.18$</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>$-21.5\pm2.2$</td>
</tr>
<tr>
<td>IWQOL-Lite score</td>
<td>12.4\pm0.4</td>
</tr>
</tbody>
</table>
Overall Summary

- Lorcaserin is a non-genotoxic carcinogen inducing multiple tumor types in rats.
- Mammary neoplasms occur near clinical exposure and the tumorigenic MOA remains unresolved.
- Brain neoplasm occur at uncertain multiple of clinical exposure.
- Schwannoma and skin/subcutis neoplasms occur at a 17-fold multiple of clinical exposure.
- Differences in survival and drug exposure may explain the apparent gender- and species-specificity of the tumor response.
Lorcaserina

Richieste di studi post marketing da parte di FDA

Serie di studi per valutare la sicurezza e l'efficacia di BELVIQ per la gestione del peso in pazienti obesi in età pediatrica.

Uno studio per valutare il trattamento di lunga durata con BELVIQ sull'incidenza di MACE (Major Adverse Cardiovascular Events) in pazienti obesi e in sovrappeso con malattie cardiovascolari o più fattori di rischio cardiovascolare.
BELVIQ®
(lorcaserin HCl)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BELVIQ safely and effectively. See full prescribing information for BELVIQ.

BELVIQ (lorcaserin hydrochloride) tablets, for oral use, CIV
Initial U.S. Approval: 2012

INDICATIONS AND USAGE
BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
• 30 kg/m² or greater (obese) (1)
• 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes) (1)

Limitations of Use:
• The safety and efficacy of coadministration with other products for weight loss have not been established (1)
• The effect of BELVIQ on cardiovascular morbidity and mortality has not been established (1)

DOSAGE AND ADMINISTRATION
• One tablet of 10 mg twice daily (2)
• Discontinue if 5% weight loss is not achieved by week 12 (2)

DOSAGE FORMS AND STRENGTHS
10 mg film-coated tablets (3)

CONTRAINDICATIONS
Pregnancy (4)

WARNINGS AND PRECAUTIONS
• Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. Manage with immediate BELVIQ discontinuation and provide supportive treatment. (5.1)
• Valvular heart disease: If signs or symptoms develop consider BELVIQ discontinuation and evaluate the patient for possible valvulopathy. (5.2)
• Cognitive Impairment: May cause disturbances in attention or memory. Caution with use of hazardous machinery when starting BELVIQ treatment. (5.3)
• Psychiatric Disorders, including euphoria and dissociation: Do not exceed recommended dose of 10 mg twice daily. (5.4)
• Monitor for depression or suicidal thoughts. Discontinue if symptoms develop. (5.4)
• Use of Antidiabetic Medications: weight loss may cause hypoglycemia. Monitor blood glucose. BELVIQ has not been studied in patients taking insulin. (5.5)
• Priapism: Patients should seek emergency treatment if an erection lasts >4 hours. Use BELVIQ with caution in patients predisposed to priapism. (5.6)

ADVERSE REACTIONS
Most common adverse reactions (greater than 5%) in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients are hypoglycemia, headache, back pain, cough, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378, or FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch.

DRUG INTERACTIONS
Serotonergic drugs (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, St. John’s Wort): use with extreme caution due to the risk of serotonin syndrome. (7.1)

USE IN SPECIFIC POPULATIONS
• Nursing Mothers: Discontinue drug or nursing. (8.3)
• Pediatric Use: Safety and effectiveness not established and use not recommended. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2012
Questions and answers
Withdrawal of the marketing authorisation application for Belviq (lorcaserin)

On 3 May 2013, Arena Pharmaceuticals officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Belviq, a medicine intended for helping to achieve weight control in obese and overweight patients.
Bupropione - Naltrexone

**Bupropione**
- Farmaco dopaminergico e noradrenergico che stimola i neuroni POMC nel NA
- In commercio dagli anni '85 e '89 come SR
- AIC depressione, disassuefazione al fumo
- Dose massima giornaliera 450 mg

**Naltrexone**
- Farmaco antagonista oppiacei
- In commercio dal 1984
- AIC: disintossicazione da dipendenze (alcool, oppiacei)
- Dose massima giornaliera 50 mg

Somministrazione due volte al giorno di bupropione SR e naltrexone SR

---

![Graph showing dosages of Bupropione and Naltrexone](image)
Bupropione - Naltrexone

Il razionale dell'associazione

Il bupropione stimola i neuroni POMC che rilasciano alfa MSH

L'alfa-MSH, a sua volta, legandosi ai recettori MC4, induce a cascata un aumento della spesa energetica e una riduzione dell'introduzione di cibo

I neuroni POMC rilasciano simultaneamente beta-endorfina che svolge un feed-back negativo sui neuroni POMC stessi

Il naltrexone blocca questo feed-back negativo consentendo una più protratta stimolazione dei neuroni POMC
Bupropione + Naltrexone: azione sinergica

Figure 2  Effect of Naltrexone and Bupropion Administration Alone and in Combination on Food Intake

Systemic Administration
Obese mice – High Fat Diet

Intra-VTA Administration
Lean mice – Normal Diet

** p<0.01 and *** p<0.001 vs. vehicle. Data are mean + SE.
Systemic administration data based on Greenway et al., 2009. Intra-VTA administration based on Sinnayah et al., 2007.
Abbreviations: Bup=bupropion; Nal=naltrexone; NB=Nal+Bup combination dosing; SE=standard error; VTA=ventral tegmental area.
Comparison of Combined Bupropion and Naltrexone Therapy for Obesity with Monotherapy and Placebo

Frank L. Greenway, Eduardo Dunayevich, Gary Tollefson,* Janelle Erickson, Maria Guttadauria, Ken Fujioka, and Michael A. Cowley for the NB-201 Study Group
Percent change in body weight.

# P < 0.05 for NB16 vs. placebo, Nal 48 and Bup
* P < 0.05 for NB32 vs. placebo, Nal 48 and Bup
† P < 0.05 for NB48 vs. placebo, Nal 48 and Bup
Statistical significance indicated for Week 24 and Week 48 only. Dashed line indicates primary endpoint (Week 24).
Abbreviations: Nal = naltrexone; Bup = bupropion; NB=naltrexone/bupropion, ITT= intent-to-treat, LOCF = last observation carried forward

Greenway F L et al. JCEM 2009;94:4898-4906
Contrave® Produced Rapid and Sustained Weight Loss Up to 56 Weeks

***p<0.001 vs placebo; 303 based on weighted ANCOVA; completers at endpoint
Contrave Obesity Research Program (COR)
COR-I (NB-301) In October 2007, Orexigen initiated enrollment in its third Phase III clinical trial, a 58-week study designed to assess the safety and efficacy of Contrave in healthy, nondiabetic, obese patients. The trial took place at 34 centers nationwide and enrolled 1,742 patients. In April 2008, Orexigen completed enrollment of this trial.
COR-II (NB-303) In December 2007, Orexigen initiated enrollment in its fourth Phase III clinical trial, a 56-week study designed to assess the safety and efficacy of Contrave in healthy, nondiabetic, obese patients. The trial took place at 36 centers nationwide and enrolled 1,496 patients. In May 2008, Orexigen completed enrollment of this trial.
COR-Diabetes (NB-304) In May 2007, Orexigen initiated enrollment in its second Phase III clinical trial, a 56-week study designed to assess the safety and efficacy of Contrave in obese subjects who also have been diagnosed with Type II diabetes. The trial took place at 51 centers nationwide and enrolled 505 patients. In May 2008, Orexigen completed enrollment of this trial.
COR-BMOD (NB-302) In April 2007, Orexigen initiated enrollment in its first Phase III clinical trial, a 56-week study designed to evaluate the safety and efficacy of Contrave alone or when combined with intense diet, exercise and behavior modification. This trial took place at nine centers nationwide and enrolled approximately 800 patients. In November 2007, Orexigen completed enrollment of this trial.
Bupropione - Naltrexone

Contrave Obesity Research Program (COR)

COR-I (NB-301) In October 2007, Orexigen initiated enrollment in its third Phase III clinical trial, a 58-week study designed to assess the safety and efficacy of Contrave in healthy, nondiabetic, obese patients. The trial took place at 34 centers nationwide and enrolled 1,742 patients. In April 2008, Orexigen completed enrollment of this trial.

COR-II (NB-303) In December 2007, Orexigen initiated enrollment in its fourth Phase III clinical trial, a 56-week study designed to assess the safety and efficacy of Contrave in healthy, nondiabetic, obese patients. The trial took place at 36 centers nationwide and enrolled 1,496 patients. In May 2008, Orexigen completed enrollment of this trial.

COR-Diabetes (NB-304) In May 2007, Orexigen initiated enrollment in its second Phase III clinical trial, a 56-week study designed to assess the safety and efficacy of Contrave in obese subjects who also have been diagnosed with Type II diabetes. The trial took place at 51 centers nationwide and enrolled 505 patients. In May 2008, Orexigen completed enrollment of this trial.

COR-BMOD (NB-302) In April 2007, Orexigen initiated enrollment in its first Phase III clinical trial, a 56-week study designed to evaluate the safety and efficacy of Contrave alone or when combined with intense diet, exercise and behavior modification. This trial took place at nine centers nationwide and enrolled approximately 800 patients. In November 2007, Orexigen completed enrollment of this trial.
Significantly More Subjects Achieved Meaningful Weight Loss with Contrave®

≥5% Weight Loss

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>NB32</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>303</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>302 BMOD</td>
<td>42</td>
<td>66</td>
</tr>
<tr>
<td>304 T2DM</td>
<td>19</td>
<td>45</td>
</tr>
</tbody>
</table>

≥10% Weight Loss

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>NB32</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>303</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>302 BMOD</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>304 T2DM</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>

mITT-LOCF; ***p<0.001 vs placebo
ContraVe® Phase 3 Safety Conclusions

- Safety profile consistent with well-established profile for approved components (naltrexone and bupropion)

- Most common side effects include:
  - Nausea
  - Dizziness
  - Constipation
  - Insomnia
  - Headache
  - Dry mouth
  - Vomiting
  - Diarrhea

Side effects were generally mild in severity and transient

- A low incidence (<0.1%) of seizure was observed, consistent with that seen in patients that take bupropion SR (300 mg/day)

- Blood pressure (BP) and heart rate observations with ContraVe are consistent with the changes seen in patients who take bupropion SR

- No evidence of increased depression or suicidality
Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial

Thomas A. Wadden¹, John P. Foreyt², Gary D. Foster³, James O. Hill⁴, Samuel Klein⁵, Patrick M. O’Neil⁶, Michael G. Perri⁷, F. Xavier Pi-Sunyer⁸, Cheryl L. Rock⁹, Janelle S. Erickson¹⁰, Holly N. Maier¹¹, Dennis D. Kim¹¹ and Eduardo Dunayevich¹¹
Table 1 Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo + BMOD</th>
<th>NB32 + BMOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>91.6</td>
<td>89.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.6 ± 11.4</td>
<td>45.9 ± 10.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37.0 ± 4.2</td>
<td>36.3 ± 4.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>101.9 ± 15.0</td>
<td>100.2 ± 15.4</td>
</tr>
</tbody>
</table>
L’ approvazione di Contrave da parte della FDA dipende dai risultati di uno studio di sicurezza, concentrato soprattutto sul rischio cardiovascolare.

Lo studio arruolerà circa 10.000 soggetti
Età > 45 maschi; > 50 femmine
Con patologia cardiaca nota e/o diabete
Durata: dal 2012 al 2014 : è in corso

Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study)
Eisai Announces Availability of BELVIQ® (lorcaserin HCl) CIV Tablets for Chronic Weight Management in Adults who are Overweight with a Comorbidity or Obese

BELVIQ Available in U.S. Pharmacies within One Week

WOODCLIFF LAKE, N.J., June 7, 2013 /PRNewswire/ -- Eisai Inc. announced today that BELVIQ (pronounced BEL-VEEK) will be available to eligible patients by prescription in the United States beginning June 11.

Arena and its partner Eisai announced plans to conduct a 12-week pilot study combining Belviq with phentermine, a currently approved weight-loss medicine. Details about the design of the study were not disclosed, although patient enrollment is expected to begin late this year or early in 2014, Arena said.

They believe Bel-Phen will be the next Fen-Phen weight-loss blockbuster therapy -- minus the pesky problem of melting heart valves, of course. Belviq (lorcaserin) is chemically similar to fenfluramine, except the former is not supposed to cause the serious heart defects.

Given 12 weeks of treatment, a rough guess would be top-line results announced in the second half of 2014.
VIVUS Announces FDA Approval of Qsymia REMS Modification Allowing Access Through Certified Retail Pharmacies
Retail Availability Expected Within 90 Days

MOUNTAIN VIEW, Calif., April 16, 2013 /PRNewswire/ -- VIVUS, Inc. (Nasdaq: VVUS) today announced that the U.S. Food and Drug Administration (FDA) has approved its amendment and modification to the Risk Evaluation and Mitigation Strategy (REMS) for Qsymia® (phentermine and topiramate extended-release) capsules CIV. "With FDA approval of the REMS modification, today we begin the process of increasing the availability of Qsymia, simplifying prescribing and dispensing and resolving the challenges associated with the mail-order-only system," said Peter Tam, president of VIVUS.

New Guidelines From American Association of Clinical Endocrinologists Recommend Medical Treatment of Obesity
First Guidelines to Incorporate Anti-Obesity Medications as Recommended Treatment for Cardiometabolic Diseases

MOUNTAIN VIEW, Calif., May 1, 2013 (GLOBE NEWSWIRE) -- A new comprehensive treatment algorithm for diabetes from the American Association of Clinical Endocrinologists (AACE) is the first to recommend active obesity management, which includes lifestyle modification and, if appropriate, the use of FDA-approved anti-obesity medications, as first-line therapy in the management of chronic cardiometabolic diseases, including prediabetes, diabetes, dyslipidemia and hypertension.
# Weight Beneficial Treatments for Type 2 Diabetes


## TABLE 3. Summary of treatment effects on HbA1c, weight, PPG, and FPG (1, 49, 68, 103)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Expected reduction in HbA1c with monotherapy (%)</th>
<th>Expected weight Δ over 6 months (kg)</th>
<th>Impact on PPG</th>
<th>Impact on FPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5–0.8</td>
<td>Weight neutral</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>(acarbose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>0.5–1.0</td>
<td>Weight neutral or loss 0 to −1.5 kg</td>
<td>++ to +++</td>
<td>+</td>
</tr>
<tr>
<td>Basal insulin Detemir</td>
<td>1.5–3.5</td>
<td>Weight neutral or gain 0 to +1.5 kg</td>
<td>+</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Glargine</td>
<td>1.5–3.5</td>
<td>Weight gain up to +4 kg</td>
<td>+</td>
<td>++ to +++</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>0.5–1.0</td>
<td>Weight loss −1.0 to −3.0 kg</td>
<td>++ to +++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5–0.8</td>
<td>Weight neutral</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0–2.0</td>
<td>Weight neutral or loss 0 to −1.5 kg</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>SU</td>
<td>1.0–2.0</td>
<td>Weight gain +1 to +5 kg</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>TZD</td>
<td>0.5–1.4</td>
<td>Weight gain: +3 kg</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE™ - Obesity and Pre-diabetes

This study is ongoing, but not recruiting participants.

Sponsor:
Novo Nordisk

Information provided by (Responsible Party):
Novo Nordisk

ClinicalTrials.gov Identifier:
NCT01272219

First received: January 6, 2011
Last updated: September 17, 2013
Last verified: September 2013

Purpose

This trial is conducted in Africa, Asia, Europe, Oceania, North America and South America.

The aim of this clinical trial is to evaluate the potential of liraglutide to induce and maintain weight loss over 56 weeks in obese subjects or overweight subjects with co-morbidities. Furthermore, the aim is to investigate the long term potential of liraglutide to delay the onset of type 2 diabetes in subjects diagnosed with pre-diabetes at baseline.

Based on body mass index (BMI) and pre-diabetes status, subjects will be randomised to either 68 weeks (56 weeks of randomised treatment followed by a 12 week re-randomised treatment period) or 160 weeks of treatment (160 week treatment will only be applicable to subjects with pre-diabetes status at baseline).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorder</td>
<td>Drug: liraglutide</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Drug: placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
Benefits of Liraglutide Treatment in Overweight and Obese Older Individuals With Prediabetes

Sung H. Kim, MD1
Farid Abbasi, MD1
Cindy Lamendola, MSN1
Alice Liu, MD1
Danya Arel, MD1
Patricia Schaaf, MS, RD3
Kaylene Grove, BS1
Vanessa Tomasso, BS1
Hector Ochoa, BS3
Yiyeng V. Liu, BS, MPH1,2
Yi-Deh Ida Chen, PhD1,3
Gerald Reaven, MD1

associated with weight loss in individuals with T2DM (9). Only a few studies have evaluated the effect of GLP-1 action in individuals without diabetes (10–12), and none has focused on individuals with prediabetes. The purpose of this study was to evaluate the effect of liraglutide treatment.

Figure 1—Proportion of individuals who lost at least 5, 7, and 10% of baseline weight. Liraglutide treatment was associated with greater degree of weight loss compared with placebo.

Figure 2—Insulin resistance (SSPG) at baseline and after 14 weeks of liraglutide or placebo treatment. Insulin resistance significantly improved following liraglutide treatment but not placebo.
Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

Fig 2 Meta-analysis of change in body weight (kg) in included trials after at least 20 weeks of treatment, using random effects model

Vilsbøll T et al. BMJ 2012;344:d7771
**Trial profile**

564 patients
BMI 30 – 40
stable bodyweight
FPG<7mmol/l

**LIRAGLUTIDE**

733 screened
117 not eligible

616 entered run-in
52 failed run-in

564 randomly allocated to receive treatment

98 placebo
19 withdrawn
3 adverse events
3 non-compliance
2 lack of efficacy
11 other reasons
79 completed
20 weeks
98 included in ITT analyses

95 liraglutide 1.2 mg per day
5 withdrawn
5 adverse events
non-compliance
lack of efficacy
other reasons
85 completed
20 weeks
94 included in ITT analyses

90 liraglutide 1.8 mg per day
16 withdrawn
5 adverse events
2 non-compliance
1 lack of efficacy
8 other reasons
74 completed
20 weeks
90 included in ITT analyses

93 liraglutide 2.4 mg per day
20 withdrawn
9 adverse events
2 non-compliance
3 lack of efficacy
8 other reasons
73 completed
20 weeks
92 included in ITT analyses

93 liraglutide 3.0 mg per day
11 withdrawn
5 adverse events
2 non-compliance
0 lack of efficacy
4 other reasons
82 completed
20 weeks
92 included in ITT analyses

95 orlistat three times a day
16 withdrawn
3 adverse events
2 non-compliance
8 lack of efficacy
0 other reasons
79 completed
20 weeks
95 included in ITT analyses

**Placebo**

**Liraglutide**

**Orlistat**
Figure 1: Change in bodyweight. Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.
LIRAGLUTIDE

Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, Liraglutide


LIRAGLUTIDE

Safety and weight loss with diet and liraglutide
A Astrup et al

Inclusion criteria:
BMI ≥30 and ≤40 kg/m²
Age 18–65 years
Stable body weight
FPG <7.0 mmol/L at Wk -2

Screening: Wk -3
Placebo run-in: Wk -2

Liraglutide 3.0 mg s.c.
Liraglutide 2.4 mg s.c.
Liraglutide 1.8 mg s.c.
Liraglutide 1.2 mg s.c.
Placebo s.c.
Orlistat 120 mg x3

Double blind
Extension* n=398
Randomization n=564
20 weeks 472 completed
year 1 356 completed
year 2 268 completed

Lifestyle intervention: -500 kcal/day deficit diet + increased physical activity

Switch was when approved locally (between 70–96 weeks)
Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Pre-Diabetes


Figure 1—Changes in body weight over 24 weeks in nondiabetic obese subjects treated with lifestyle intervention and randomized to exenatide or placebo. ○, Placebo (n = 78); ▲, exenatide (n = 73). Results derived from mixed-model repeated-measures analysis and presented as least squares means ± SE. Change from baseline: *P < 0.001, †P < 0.05.
Tesoefensine

Obesity

Tesoefensine is a drug candidate that acts on several sites and thereby increase the neurotransmission of three monoaminergic neurotransmitters, dopamine, noradrenaline and serotonin simultaneously (triple mode of action). Each of these transmitters exerts an important function on appetite and metabolism at different locations in the brain. Dopamine acts in the nucleus accumbens of the forebrain to modulate reward and "pleasure"-feeling of food. The two other transmitters act in the hypothalamus to increase metabolism and reduce appetite.

Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial

Arne Astrup, Sten Madsbad, Leif Breum, Thomas J. Jensen, Jens Peter Kroustrup, Thomas Meinert Larsen

Summary

Weight-loss drugs produce an additional mean weight loss of only 3–5 kg above that of diet and placebo over 6 months, and more effective pharmacotherapy of obesity is needed. We assessed the efficacy and safety of tesofensine—an inhibitor of the presynaptic uptake of noradrenaline, dopamine, and serotonin—in patients with obesity.
Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial

A Astrup, S Madsbad, L Breum, T J Jensen, J P Kroustrup, T Meinert Larsen

The Lancet Early Online Publication, 23 October 2008
DOI:10.1016/S0140 6736(08)61525-1
La tesofensina è un inibitore presinaptico del reuptake di noradrenalina, serotonina e dopamina.

Questi neurotrasmettitori giocano un ruolo fondamentale nella regolazione dell’assunzione di cibo e nel bilancio energetico.
Figure 1: Trial profile
Study duration was 34 weeks, consisting of a run-in period of 2 weeks, a 24-week treatment period, and 8 weeks of follow-up. Some patients were excluded from the per-protocol population because of concomitant medication. ITT=intention to treat. PP=per protocol.
New and Emerging Pharmacologic Therapies for Type 2 Diabetes, Dyslipidemia, and Obesity

James R. Taylor, PharmD, CDE\textsuperscript{1,2}; Eric Dietrich, PharmD, BCPS\textsuperscript{1,2}; and Jason G. Powell, PharmD\textsuperscript{1,2}

\textsuperscript{1}University of Florida College of Pharmacy, Gainesville, Florida; and \textsuperscript{2}Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, Florida

Table V. Comparative Medication Costs.

<table>
<thead>
<tr>
<th>Medication</th>
<th>WAC Cost, $ (30-Day Supply\textsuperscript{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Metformin 500 mg</td>
<td>10.00</td>
</tr>
<tr>
<td>Glyburide 10 mg</td>
<td>15.00</td>
</tr>
<tr>
<td>Glipizide XL 20 mg</td>
<td>75.00</td>
</tr>
<tr>
<td>Pioglitazone 45 mg</td>
<td>209.27</td>
</tr>
<tr>
<td>Exenatide\textsuperscript{b} 10 mg</td>
<td>315.25</td>
</tr>
<tr>
<td>Liraglutide\textsuperscript{c} 1.8 mg</td>
<td>303.34</td>
</tr>
<tr>
<td>Sitagliptin\textsuperscript{d} 100 mg</td>
<td>223.81</td>
</tr>
<tr>
<td>Saxagliptin\textsuperscript{e} 5 mg</td>
<td>223.79</td>
</tr>
<tr>
<td>Linagliptin\textsuperscript{f} 5 mg</td>
<td>223.81</td>
</tr>
<tr>
<td>Exenatide (extended release)\textsuperscript{g} 2 mg</td>
<td>349.32</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
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<tr>
<td>Lovastatin 40 mg</td>
<td>19.60</td>
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<tr>
<td>Simvastatin 40 mg</td>
<td>11.13</td>
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<tr>
<td>Atorvastatin 40 mg</td>
<td>18.30</td>
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<tr>
<td>Rosuvastatin\textsuperscript{h} 40 mg</td>
<td>152.40</td>
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<tr>
<td>Niacin 500 mg</td>
<td>1.44</td>
</tr>
<tr>
<td>Niacinpan 1000 mg</td>
<td>156.6</td>
</tr>
<tr>
<td>Fenofibrate 145 mg</td>
<td>135.00</td>
</tr>
<tr>
<td>Omega-3 Fatty acid ethyl esters\textsuperscript{i} 1 g</td>
<td>184.10</td>
</tr>
<tr>
<td>\textsuperscript{i} ω3-fish oils 2 g</td>
<td>40.75</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg</td>
<td>15.00</td>
</tr>
<tr>
<td>Colestelamine 4 g</td>
<td>18.00</td>
</tr>
<tr>
<td>Ezetimibe\textsuperscript{j} 10 mg</td>
<td>141.60</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
</tr>
<tr>
<td>Ozivstat\textsuperscript{k} (orlistat) 120 mg</td>
<td>395.45</td>
</tr>
<tr>
<td>Phentermine 37.5 mg</td>
<td>18.60</td>
</tr>
<tr>
<td>Diethylpropion ER 25 mg</td>
<td>19.80</td>
</tr>
<tr>
<td>Diethylpropion ER 75 mg</td>
<td>25.20</td>
</tr>
<tr>
<td>Phendimetrazine IR 35 mg</td>
<td>11.703</td>
</tr>
<tr>
<td>Phendimetrazine ER 105 mg</td>
<td>22.20</td>
</tr>
<tr>
<td>Phentermine and Topiramate</td>
<td>183.90</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Extended-release 15 mg/92 mg

Table IV. Obesity Clinical Trials Summary.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Design and Intervention</th>
<th>Results</th>
<th>(P)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks</td>
<td>At 52 weeks weight loss of &gt;5% of baseline weight occurred in 47.2% of lor 10 BID, 40.2% of lor 10 QD, and in 25% of pcb patients</td>
<td>&lt;0.001 for both doses vs pcb</td>
<td>24</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>R, DB, PC; lor 10 mg BID or pcb for 52 weeks; pcb continued for 52 weeks, lor randomized in 2:1 ratio to continue lor 10 mg BID or pcb for 52 weeks</td>
<td>At 52 weeks weight loss of &gt;5% of baseline weight occurred in 47.5% of lor 10 BID and 20.3% of pcb patients</td>
<td>&lt;0.001</td>
<td>25</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks</td>
<td>At 52 weeks weight loss of &gt;5% of baseline weight occurred in 37.5% of lor 10 BID, 44.1% of lor 10 QD, and 16.1% of pcb patients</td>
<td>&lt;0.001 for both doses vs pcb</td>
<td>26</td>
</tr>
<tr>
<td>Phentermine-topiramate</td>
<td>R, DB, PC; P/T 15/92, P/T 3.75/23, or pcb for 52 weeks</td>
<td>Percentage of baseline weight lost at 52 weeks was 10.9% for P/T 15 mg/92 mg, 5.1% for P/T 3.75 mg/23 mg, and 1.6% for pcb</td>
<td>&lt;0.001 for both doses compared to pcb</td>
<td>30</td>
</tr>
<tr>
<td>Phentermine-topiramate</td>
<td>R, DB, PC; P/T 7.5 mg/46 mg, P/T 15 mg/92 mg, or pcb for 52 weeks</td>
<td>Percentage of baseline weight lost at 52 weeks was 9.8% for P/T 15 mg/92 mg, 7.8% for P/T 7.5 mg/46 mg, and 1.2% for pcb</td>
<td>&lt;0.001 for both doses compared to pcb</td>
<td>31</td>
</tr>
<tr>
<td>Phentermine-topiramate</td>
<td>R, DB, PC extension of Gadde et al\textsuperscript{16}, continued same treatment for 52 weeks</td>
<td>Percentage of baseline weight lost at 104 weeks was 10.5% for P/T 15 mg/92 mg, 9.3% for P/T 7.5 mg/46 mg, and 1.8% for pcb</td>
<td>&lt;0.001 for both doses vs pcb</td>
<td>32</td>
</tr>
</tbody>
</table>

\textsuperscript{b} BID = twice daily; DB = double blind; lor = lorcaserin; PC = placebo controlled; pcb = placebo; P/T = phentermine-topiramate extended-release; QD = once daily; R = randomized.
Grazie per l’attenzione!