# Long-Term Use of Obesity Medications: How to Sustain Weight Loss

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# Obesity Pharmacotherapy

**An adjunct to lifestyle modification – not a substitute**

**Can increase chances of meaningful weight loss**

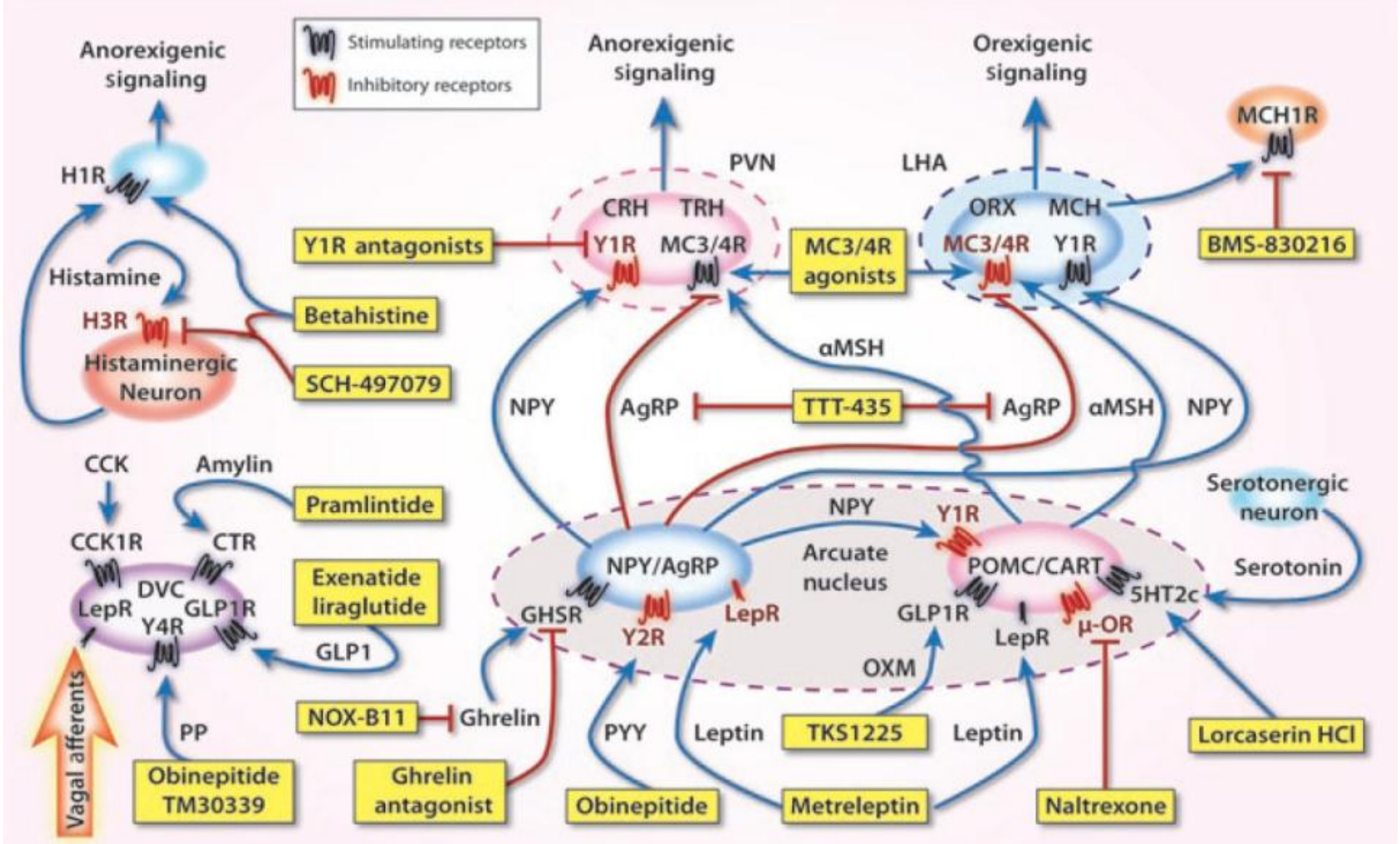
# Anti-obesity Medications

## Rationale and Criteria

- Non-drug interventions should be attempted for at least 6 months before considering pharmacotherapy*
- For patients with BMI $\geq$ 30
- For patients with BMI $\geq$ 27 or above with concomitant risk factors or diseases (hypertension, dyslipidemia, CHD, type 2 diabetes, sleep apnea)*

*NIH Clinical Guidelines Evidence Report. Sept 1998.

# Potential Anti-obesity Drugs and Their Pathways
## Complex System with Redundancy-That's Why It's Hard to Lose




Valentino et al. Clin Pharmacol Ther. 2010; 87:652–62.

# Anti-obesity Drugs Presently on the Market and Pending Approval

| FDA-Approved Drug | Company | Mechanism of Action | Comments |
|---|---|---|---|
| Benzphetamine (Didrex) | Pharmacia | Norepinephrine/dopamine releasing stimulator | Schedule III drug, approved 1960 for short-term use |
| Phendimetrazine (Bontril) | Valeant | Norepinephrine/dopamine releasing stimulator | Schedule III drug, approved 1961 for short-term use |
| Phentermine (Adipex, Suprenza) | Gates, Alpex | Noradrenaline/dopamine releasing stimulator | Schedule IV drug, approved 1973 for short-term use |
| Diethylpropion (Tenuate) | Watson Labs/ Corepharma | Norepinephrine/dopamine releasing stimulator | Schedule IV drug, approved 1973 for short-term use |
| Orlistat (Xenical) (Alli –OTC) | Roche, GSK | Pancreatic lipase inhibitor | Approved for long-term use in 1999 |
| New! Phentermine/Topiramate (Qysmia) *(formerly Qnexa)* | Vivus | Noradrenaline releasing + modulator of ɣ aminobutyric acid (GABA)/ carbonic anhydrase inhibition | Approved July 2012 |
| New! Lorcaserin (Belviq) | Arena Pharma | Selective 5-$HT_{2C}$receptor agonist | Approved June 2012 |
| New! Bupropion/Naltrexone (Contrave) | Orexigen | Inhibitor of dopamine and noradrenaline reuptake + μ opiate antagonist | FDA requested data on long-term cardiovascular risk assessment in 2011; Approved Sept 11, 2014 |
| **Pending Final FDA Approval** | **Company** | **Mechanism of Action** | **Comments** |
| PENDING Liraglutide* | Novo Nordisk | GLP-1 agonist | Approved January 2010 for treatment of Type 2 DM; phase III for anti-obesity at higher doses PDUFA Oct. 20, 2014 |

*Not FDA Approved

Modified from Zhi-yun et al. Acta Pharmacologica Sinica. 2012;33:145–47.

# Expected Weight Loss with Newly Approved and Investigational Anti-obesity Medications

| Mechanism of Action | Agent | Brand Name | Drug (kg) | Placebo (kg) | Net Weight Loss (kg) | Duration | FDA Approval |
|---|---|---|---|---|---|---|---|
| Selective serotonin 2C receptor agonist | Lorcaserin | Belviq | 8.2 | 3.4 | 4.8 | 52 weeks | June 2012 |
| Combination-Sympathomimetic /gaba-ergic migraine med | Topiramate/ phentermine | Qsymia | 10.2 | 1.4 | 8.8 | 56 weeks | July 2012 |
| Combination Antidepressant/ Opiate antagonist | Bupropion/ naltrexone | Contrave | 8.2 | 1.9 | 6.2 | 48 weeks | Approved Sept.11, 2014 |
| Glucagon-like peptide 1 (GLP-1) | Liraglutide* 3.0 mg | Victoza | 10.3±7.1 | 4.1 | 6.2 | 104 weeks | Pending for obesity PDUFA date: October 20, 2014 |

*Not FDA Approved

Modified from Powell et al. Clin Pharmacol Ther. 2011;90:40-51.

# Phentermine/Topiramate ER


## Mechanism of Action
### Phentermine

- Sympathomimetic amine, NE release
- Blunts appetite

### Topiramate

- Increases GABA activity, antagonize AMPA/ kainate glutamate receptor, carbonic anhydrase inhibitor
- Prolongs satiety

## Indications and Dose

- Approved by FDA, July 2012, schedule IV
- **Indication**
  Weight loss in pts with BMI ≥30 kg/m$^2$ or BMI ≥27 kg/m$^2$ with weight-related co-morbid condition(s)
- **Treatment Dose Daily**
  phentermine 7.5 mg
  topiramate ER 46 mg
- **Max Dose Daily**
  phentermine 15 mg
  topiramate ER 92 mg

## Contraindications and Warnings

**Contraindications**

ü Pregnancy, glaucoma, hyperthyroidism, MAOIs

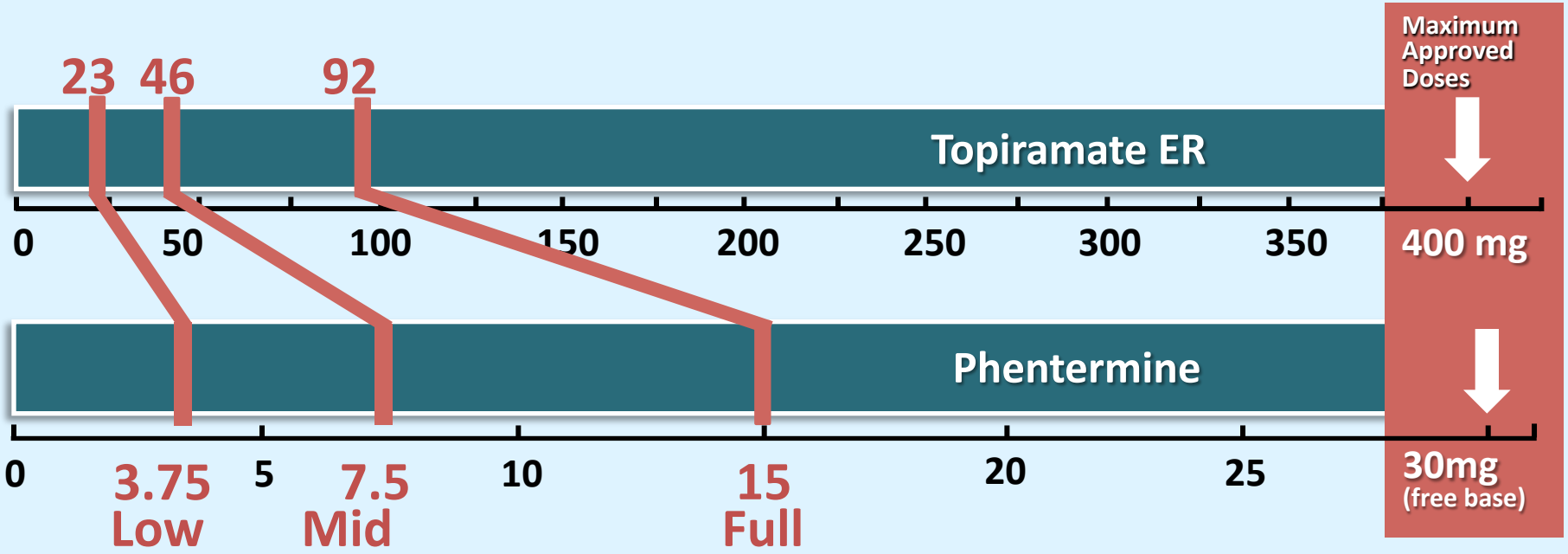
**Warnings**

- Fetal toxicity
- Increased heart rate
- Suicide and mood and sleep disorders
- Acute myopia and glaucoma
- Cognitive impairment
- Metabolic acidosis
- Creatinine elevations
- Hypoglycemia with diabetes meds

Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

# Phentermine/Topiramate ER

- Once-a-day, oral, extended-release topiramate
- Low doses of previously approved medications to minimize side effects

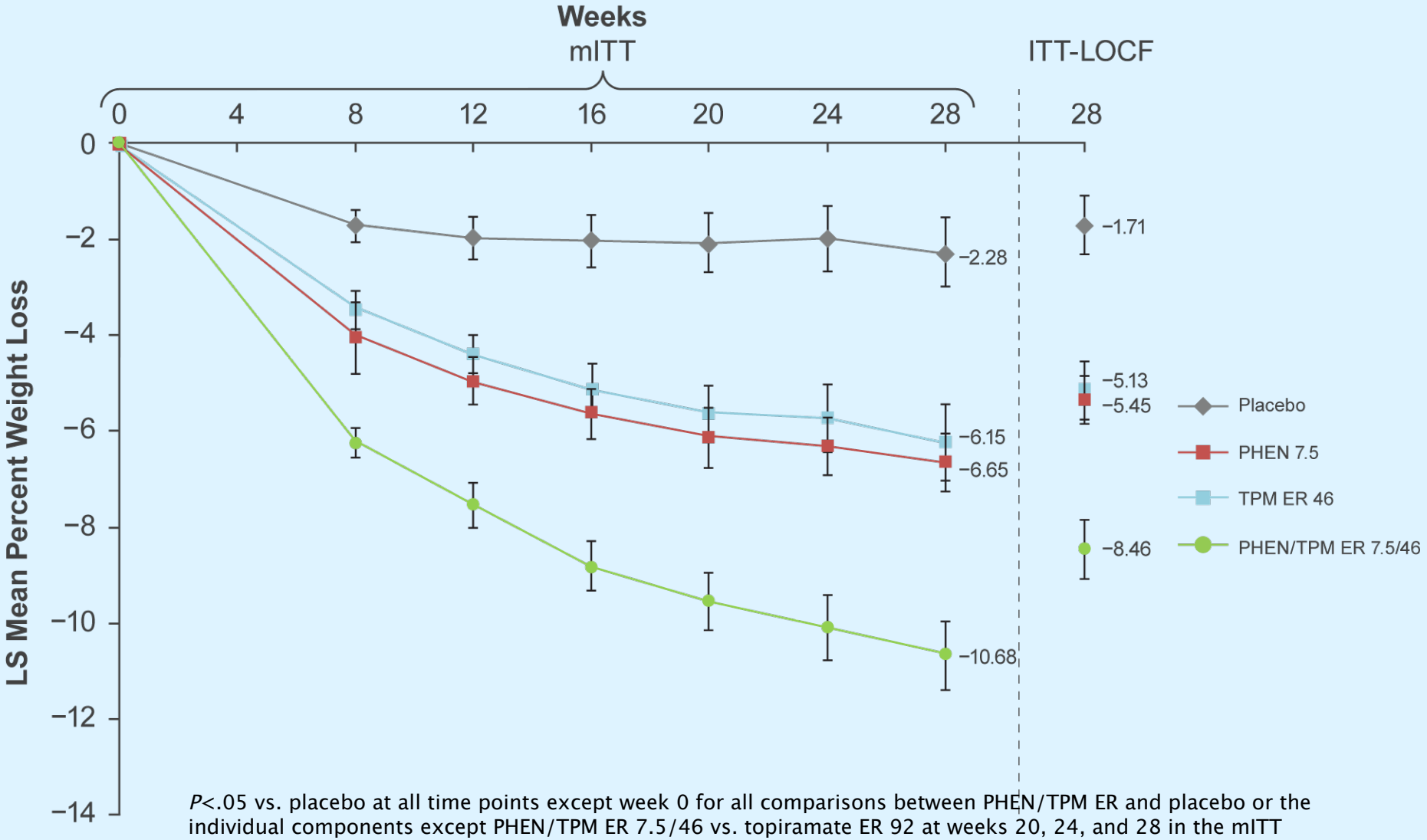



**DOSING**

- Begin with low dose for 2 wks phentermine 3.75/ topiramate ER 23
- Advance to treatment dose phentermine 7.5/ topiramate ER 46
- If <3% weight loss after 12 wks, either discontinue or advance to full dose phentermine 15/ topiramate ER 92 (transition dose phentermine 11.25/ topiramate ER 69 for 2 wks)
- If <5% weight loss after 12 wks on full dose, discontinue (take every other day for 1 wk)

Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

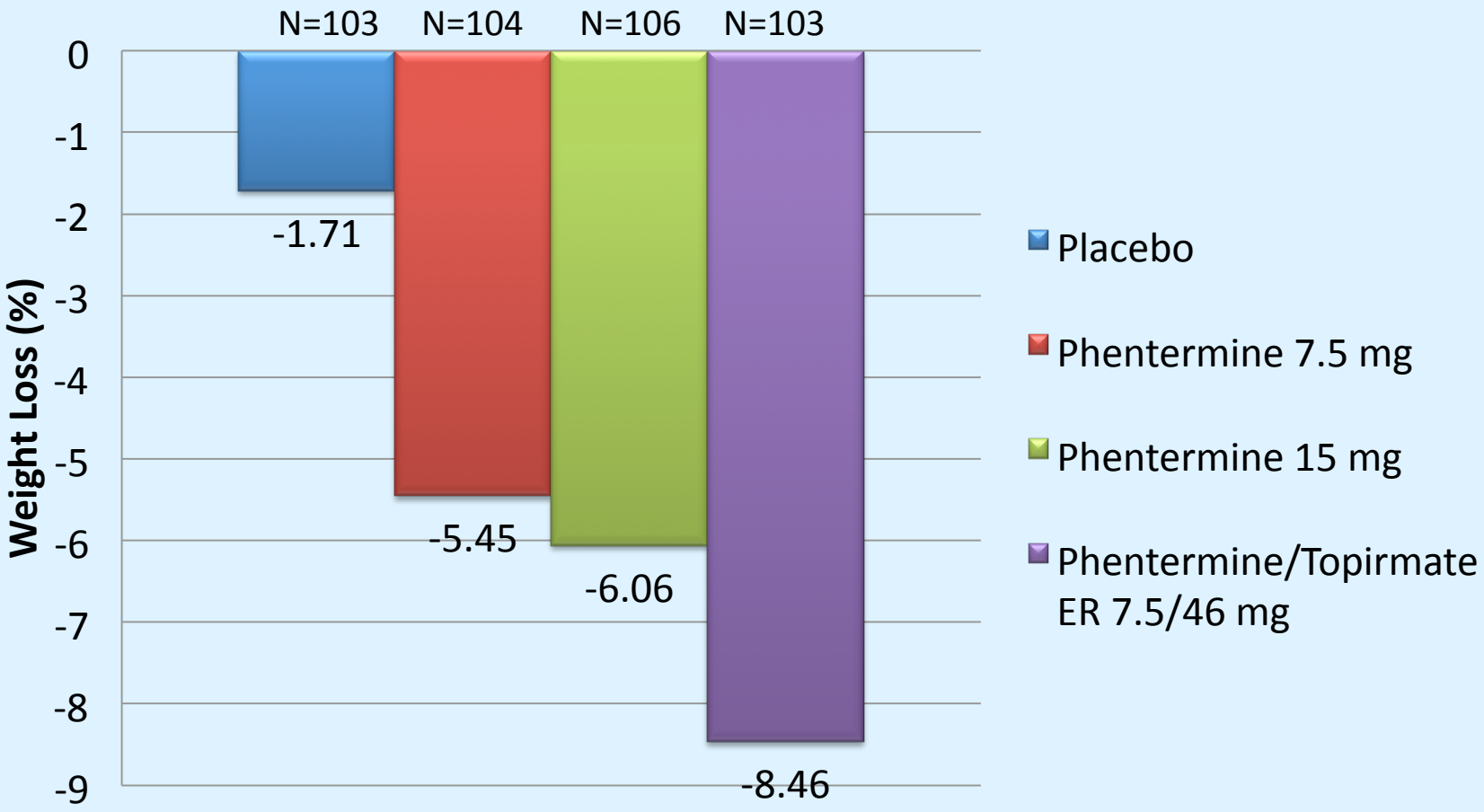
# Percent Weight Loss with PHEN/TPM ER 7.5/46 and the Individual Components




*P*<.05 vs. placebo at all time points except week 0 for all comparisons between PHEN/TPM ER and placebo or the individual components except PHEN/TPM ER 7.5/46 vs. topiramate ER 92 at weeks 20, 24, and 28 in the mITT population

Aronne et al. Obesity. 2013 Oct 17. doi: 10.1002/oby.20584.

# Weight loss at 28 weeks with lifestyle intervention and placebo, phentermine, and phentermine/topiramate ER



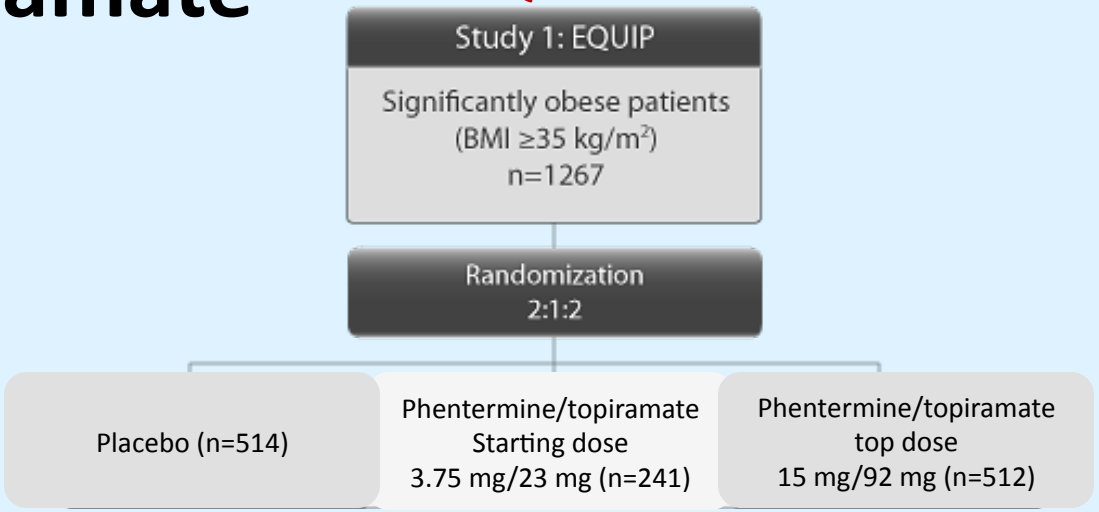

Data shown are LS mean and all comparisons are statistically significant.
Treatment arms not shown are topiramate 46 mg, topiramate 92 mg and phentermine/topiramate ER 15/92 mg.
Aronne et al. Obesity. 2013;21:1-9.

# Phentermine/Topiramate
## 3 Trials

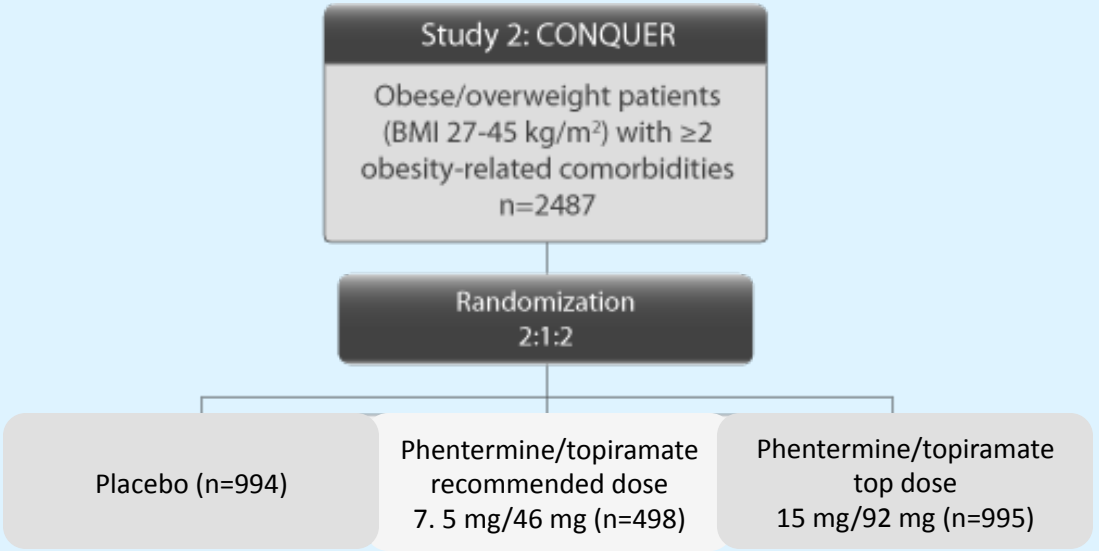
## SEQUEL

- **Double-blind, placebo-controlled, three-arm, prospective study**
- **Extension of CONQUER Trial**
- **Same treatment as CONQUER study in a blinded fashion: either once-a-day treatment with 15 mg phentermine/topiramate (n=295), 7.5 mg phentermine/topiramate (n=153), or placebo (n=227)**
- **108-week treatment period, all patients were advised to follow a simple lifestyle modification program including reduction of food intake by 500 calories per day**

## EQUIP



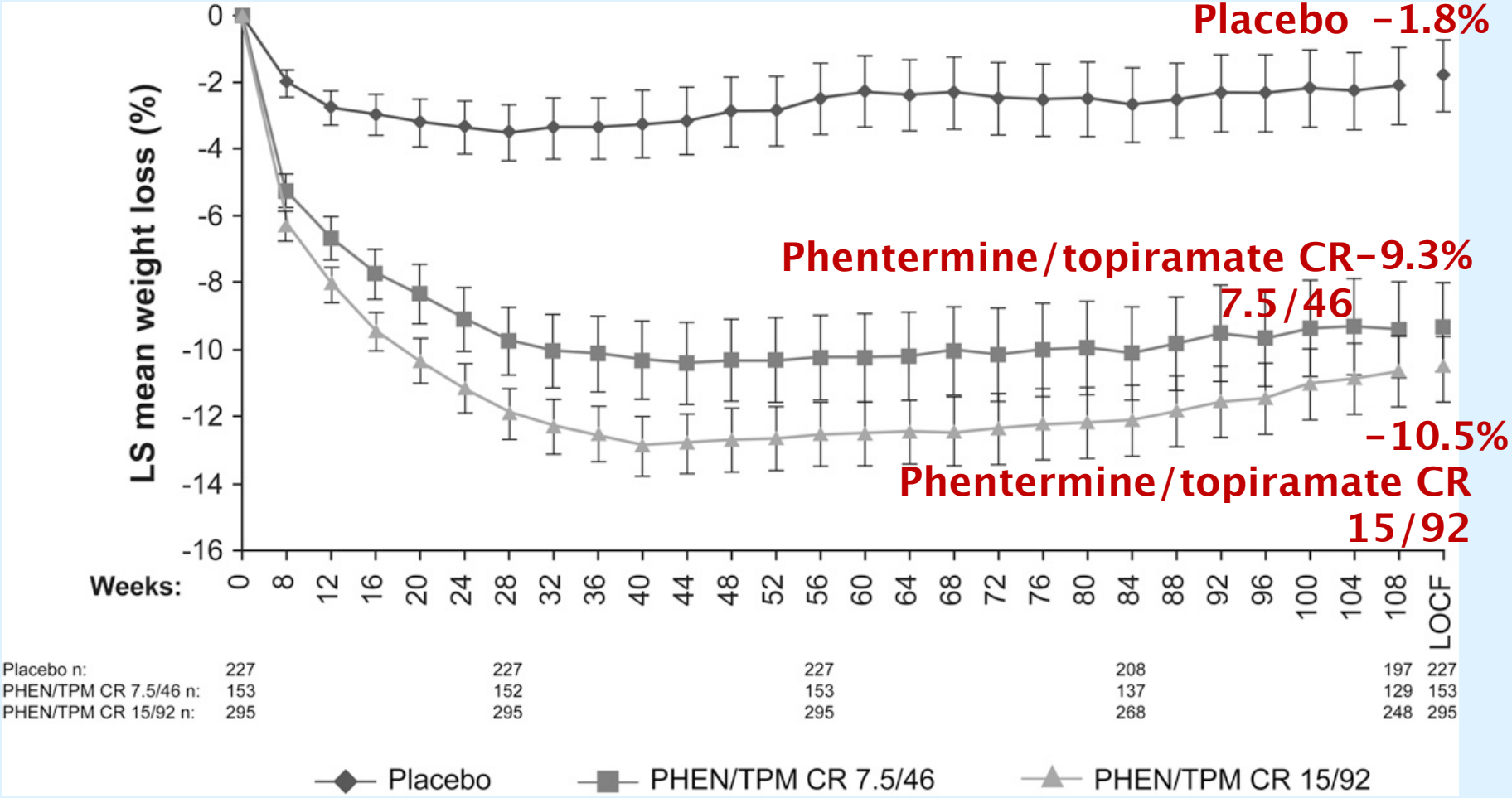

## CONQUER




www.qsymia.com/hcp/conquer-trial.aspx

# Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years

## SEQUEL Study




Data are shown with least squares mean (95% CI).

Garvey et al. Am J Clin Nutr. 2012;95:297-308.

# Phentermine/Topiramate ER Improves Risk Factors and Manifestations of Cardiometabolic Disease CONQUER Study

## Changes from baseline to week 56 in secondary endpoints

| Variable | | Phentermine 7.5mg/ Topiramate 46 mg ER | Placebo | *P* value |
|---|---|---|---|---|
| Waist circumference (cm) | | −7.6 | −2.4 | <0.0001 |
| Systolic BP (mm Hg) | | −4.7 | −2.4 | 0.0008 |
| Diastolic BP (mm Hg) | | −3.4 | −2.7 | 0.1281 |
| Triglycerides (%) | | −8.6 | 4.7 | <0.0001 |
| LDL–C (%) | | −3.7 | −4.1 | 0.7391 |
| HDL–C (%) | | 5.2 | 1.2 | <0.0001 |
| CRP (mg/L) | | −2.49 | −0.79 | <0.0001 |
| Adiponectin (µg/mL) | | 1.40 | 0.33 | <0.0001 |

Gadde et al. Lancet. 2011;377:1341-52.

# Phentermine/Topiramate ER: EQUIP and CONQUER

## Most Commonly Reported Treatment-Emergent Adverse Events

| Adverse Event (%) (N=3749) | Placebo | PHEN/TPM ER 3.75/23 | PHEN/TPM ER 7.5/46 | PHEN/TPM ER 15/92 |
|---|---|---|---|---|
| **Paresthesia** | **1.9** | **4.2** | **13.7** | **19.9** |
| **Dry mouth** | **2.8** | **6.7** | **13.5** | **19.1** |
| **Constipation** | **6.1** | **7.9** | **15.1** | **16.1** |
| **Upper respiratory tract infection** | 12.8 | 15.8 | 12.2 | 13.5 |
| **Headache** | 9.3 | 10.4 | 7.0 | 10.6 |
| **Dysgeusia** | **1.1** | **1.3** | **7.4** | **9.4** |
| **Nasopharyngitis** | 8.0 | 12.5 | 10.6 | 9.4 |
| **Insomnia** | **4.7** | **5.0** | **5.8** | **9.4** |
| **Dizziness** | **3.4** | **2.9** | **7.2** | **8.6** |
| **Sinusitis** | 6.3 | 7.5 | 6.8 | 7.8 |
| **Nausea** | 4.4 | 5.8 | 3.6 | 7.2 |
| **Back pain** | 5.1 | 5.4 | 5.6 | 6.6 |
| **Fatigue** | 4.3 | 5.0 | 4.4 | 5.9 |
| **Blurred vision** | 3.5 | 6.3 | 4.0 | 5.4 |
| **Diarrhea** | 4.9 | 5.0 | 6.4 | 5.6 |

Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

# Phentermine/Topiramate

- IR phentermine HCl/ER topiramate approved for weight management in 2012 (titrated in AM up to 7.5/46 mg/d; max 15/92 mg/d)
- Phentermine: decreases short-term appetite
- Topiramate: decreases longer-term appetite and may have glycemic effects
- Most common AEs: paresthesia, dizziness, cognitive dysfunction, dysgeusia (change in taste), insomnia, constipation, dry mouth, metabolic acidosis, elevated creatinine
- Significant improvements in multiple CV and DM risk factors

IR = immediate release.

Bays et al. Drugs Today. 2011;47:903-14; Bays. Expert Rev Cardiovasc Ther. 2010;8:1777-1801; Qsymia [prescribing Information]. Mountain View, CA: Vivus, Inc.; 2012; Qsymia. http://www.qsymiarems.com.

# Summary of Phentermine and Topiramate Neuropsychiatric Safety

- No serious AEs related to depression, anxiety or cognition
- No increase in the risk of suicidality (C-SSRS*, PHQ-9**, and AE reporting) in a population where 20% had a prior history of depression
- Can be prescribed in patients with stable depression and patients on SSRIs

*Columbia Suicide Severity Rating Scale
** Patient Health Questionnaire 9-item depression scale

Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

# Lorcaserin


## Mechanism of Action

- Selective 5-HT2C receptor agonist
- Stimulates α-MSH production from POMC neurons resulting in activation of MC4R
- Increases satiety

## Indications and Dose

- Approved by FDA June 2012
- Indication: Weight loss in patients with BMI ≥30 kg/m2 or BMI ≥27 kg/m2 with weight-related co-morbid condition(s)
- 10 mg po bid
- Schedule IV
- Discontinue if 5% weight loss is not achieved in 12 wks

## Contraindications and Warnings

**Contraindications**

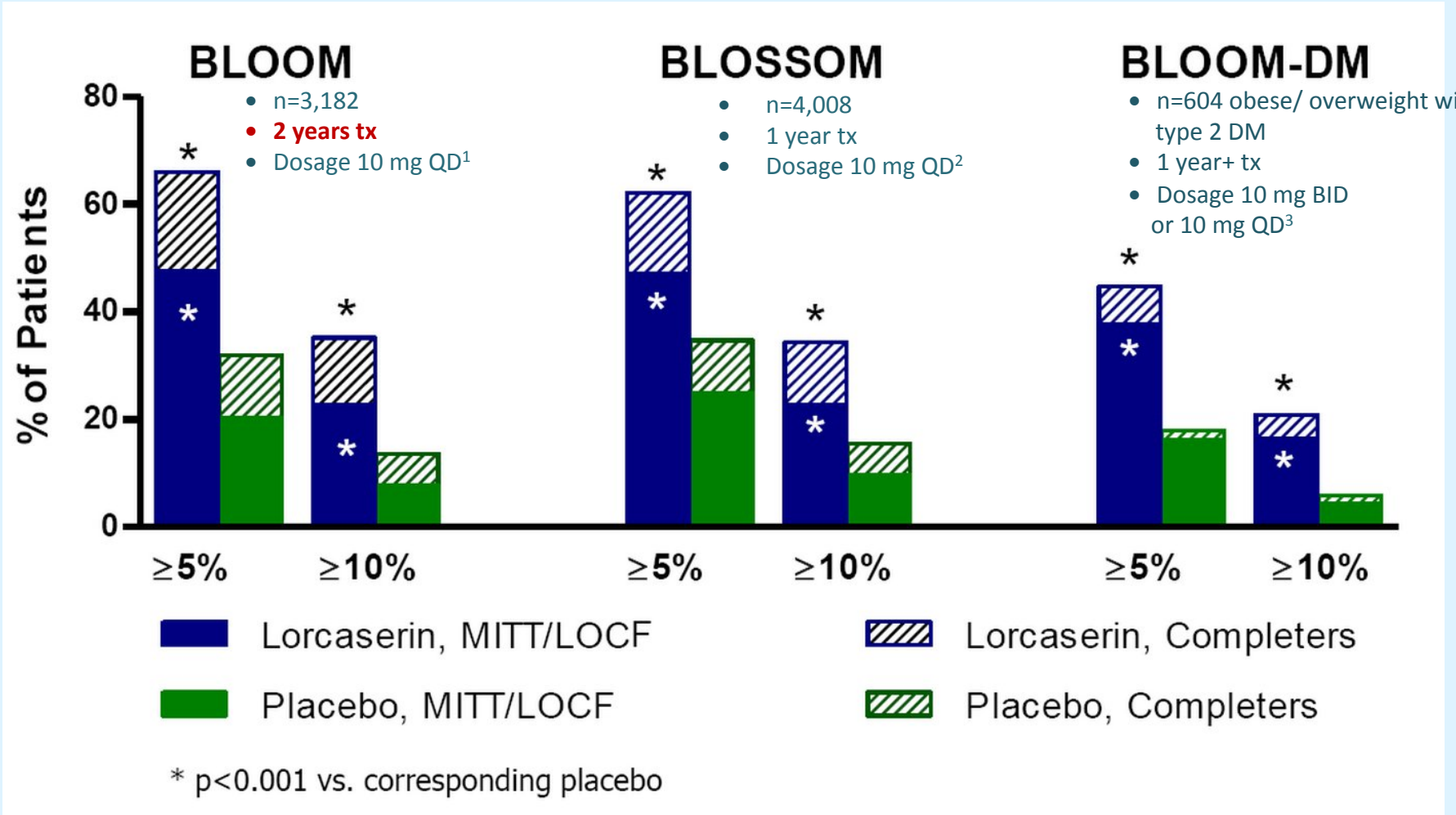
- Pregnancy

**Warnings**

- Co-administration with other serotonergic or anti-dopaminergic agents
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders (euphoria, suicidal thoughts, depression)
- Priapism
- Risk of hypoglycemia with diabetes meds

Lorcaserin hydrochloride [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2012.

# Lorcaserin Phase 3 Trials

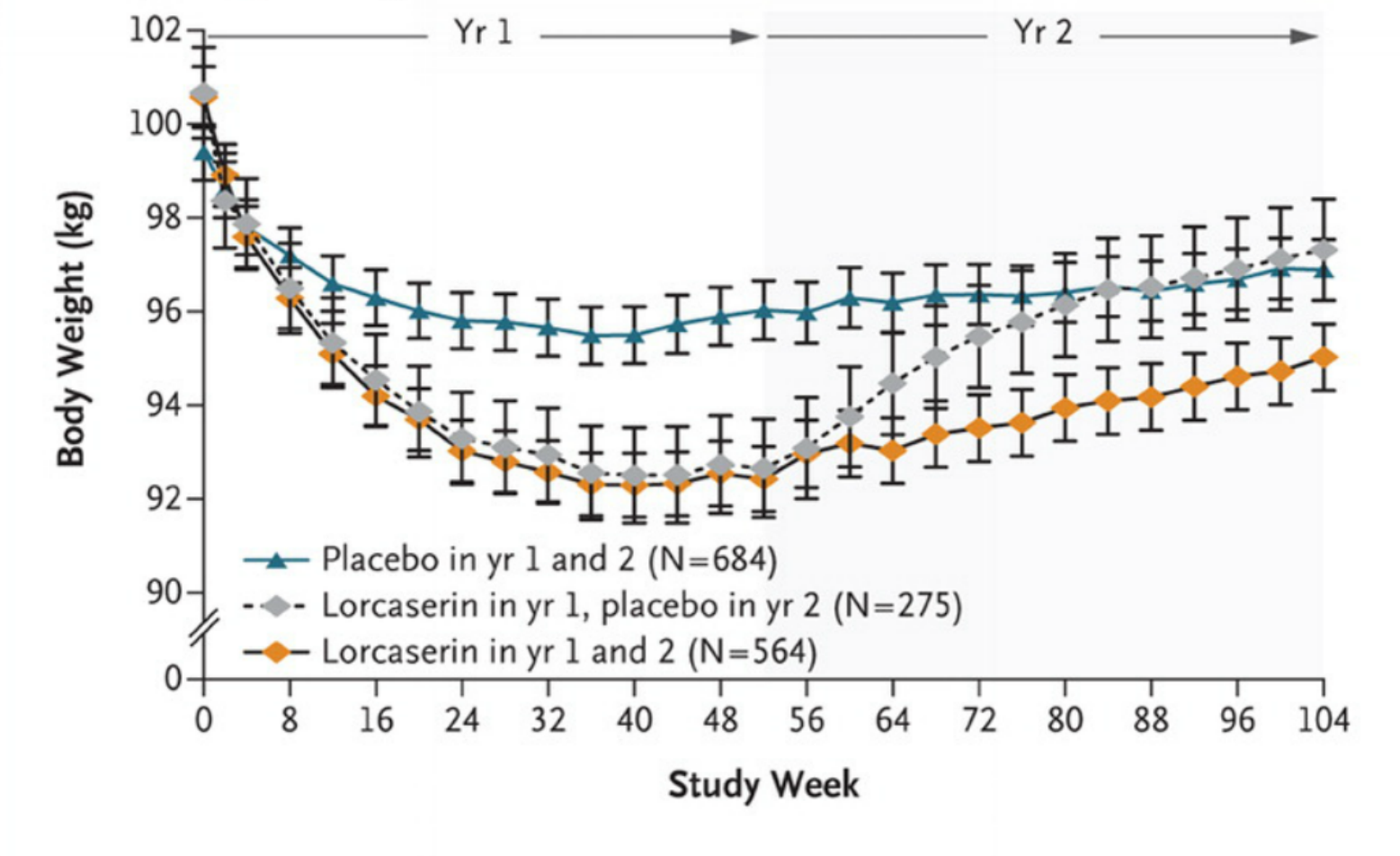




1. Smith et al. N Engl J Med 2010;363:245-56.
2. Fidler et al. J Clin Endocrinol Metab. 2011;96:3067–77.
3. O'Neil et al. Obesity. doi:10.1038/oby.2012.66.

# Lorcaserin: Body Weight at Year 1 and 2

**Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial:** 2-year, randomized, placebo-controlled, double-blind clinical trial




Effects of lorcaserin on body weight during years 1 and 2 among only those patients who continued the study past year 1

Smith et al. N Engl J Med 2010; 363:245-56.

# Lorcaserin: Adverse Events Reported by ≥5% in Any Group

| N (%) | Lorcaserin (N = 3195) | Placebo (N = 3185) |
|---|---|---|
| Headache | 537 (16.8) | 321 (10.1) |
| Dizziness | 270 (8.5) | 122 (3.8) |
| Nausea | 264 (8.3) | 170 (5.3) |
| Constipation | 186 (5.8) | 125 (3.9) |
| Fatigue | 229 (7.2) | 114 (3.6) |
| Dry mouth | 169 (5.3) | 74 (2.3) |

Intention-to-Treat Analysis with LOCF Imputation

Smith et al. N Engl J Med 2010; 363:245-56.

# Lorcaserin — BLOOM Study: Key Secondary Endpoints

| Endpoint | | Lorcaserin | Placebo | *P* value |
|---|---|---|---|---|
| Waist circumference (cm) | ✓ | −6.8 | −3.9 | <0.001 |
| SBP/DBP (mm Hg) | ✓ | −1.4 / −1.1 | −0.8 / −0.6 | 0.04/0.01 |
| Cholesterol (% Δ) | | | | |
| Total | ✓ | −0.90 | 0.57 | 0.001 |
| LDL | ✓ | 2.87 | 4.03 | 0.049 |
| HDL | | 0.05 | −0.21 | 0.72 |
| Triglycerides (%) | ✓ | −6.15 | −0.14 | <0.001 |
| Safety | | | | |
| HR (beats/min) | ✓ | −2.0 | −1.6 | 0.049 |
| Beck depression II | | −1.1 | −0.9 | 0.26 |

Intention-to-Treat Analysis with LOCF Imputation

Smith et al. N Engl J Med 2010; 363:245-56.

# Liraglutide*

- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Appetite effect mediated by both the activation of GLP-1 receptors expressed in the hypothalamus
- Affects appetite, food preference, and cardiovascular biomarkers in patients with type 2 diabetes
- Phase III trials assessing effects of doses as high as 3.0 mg/day submitted to FDA

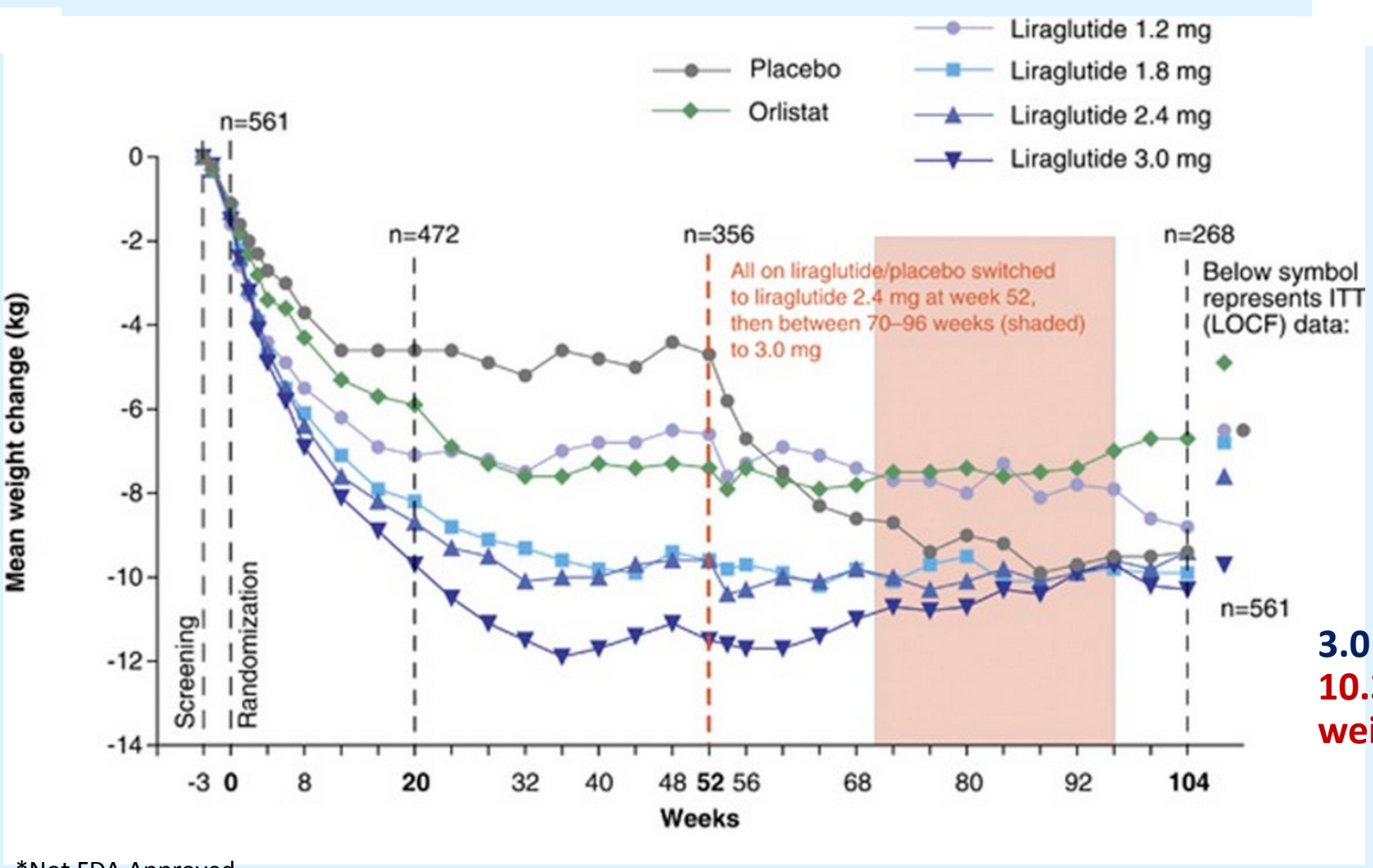


**PDUFA goal date:**
**October 20, 2014**
**for anti-obesity**

*Not FDA Approved

# Liraglutide* Weight Loss: Two Years

**Liraglutide 3.0 mg for 1 year (and then maintained on 2.4/3.0 mg for the second year) maintained a mean weight loss of 10.3±7.1 kg from screening over 2 years**




**3.0 mg**
**10.3±7.1 kg weight loss**

*Not FDA Approved

Astrup et al. Int J Obes. 2012;36: 843–54.

# Liraglutide*: Adverse Events

- Generally well tolerated and improved quality of life
- Adverse events mostly mild or moderate
- Gastrointestinal events (particularly nausea and vomiting), consistent with the known physiological effects of GLP-1, were more frequent than with placebo
- At year 1, nausea and/or vomiting was associated with greater weight loss with liraglutide 3.0 mg, but even those who did not experience these events lost more weight than those on placebo or orlistat
- Injection regimen did not impair adherence or cause significant withdrawal during treatment or run-in

*Not FDA Approved

Astrup et al. Int J Obes.2012;36: 843–54.

# Naltrexone/Bupropion

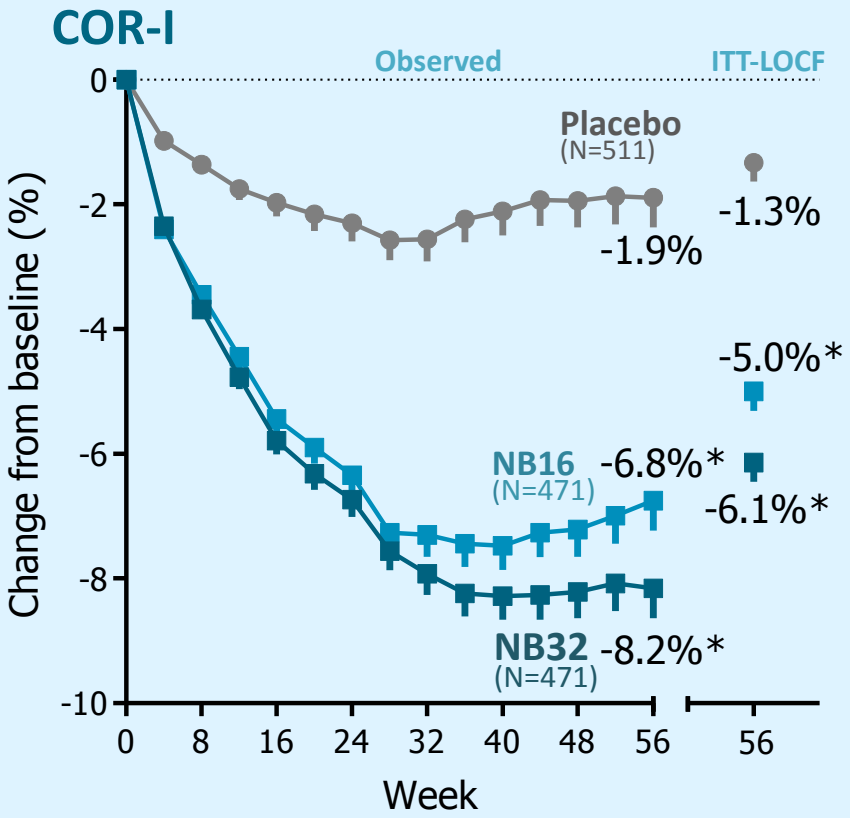
Approved
Sept. 11, 2014

- **Mechanism of Action**
  - Naltrexone — Opioid receptor antagonist
  - Bupropion — Dopamine/noradrenaline reuptake inhibitor
- **Approved by FDA committee but FDA would not approve until a CVD outcome study is performed due to concerns about blood pressure and pulse in some patients**
- **The Light Study (CVD outcomes) is under way; estimated completion: July 2017**

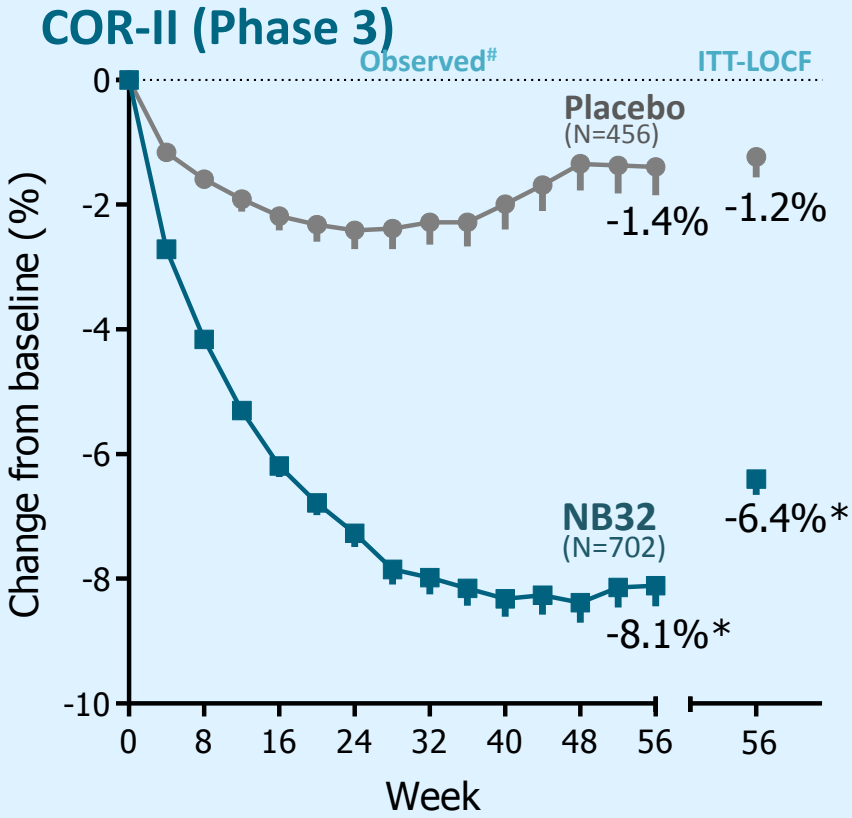
Apovian C, et al. *Obesity.* 2013.
Clinicaltrials.gov. Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study). 2012. http://clinicaltrials.gov/show/NCT01601704

# Naltrexone/Bupropion

## COR-I and COR-II: Body Weight, Percent Change from Baseline




**Completers**
Placebo (N=290): -1.8%
NB16 (N=284): -6.7%*
NB32 (N=296): -8.1%*

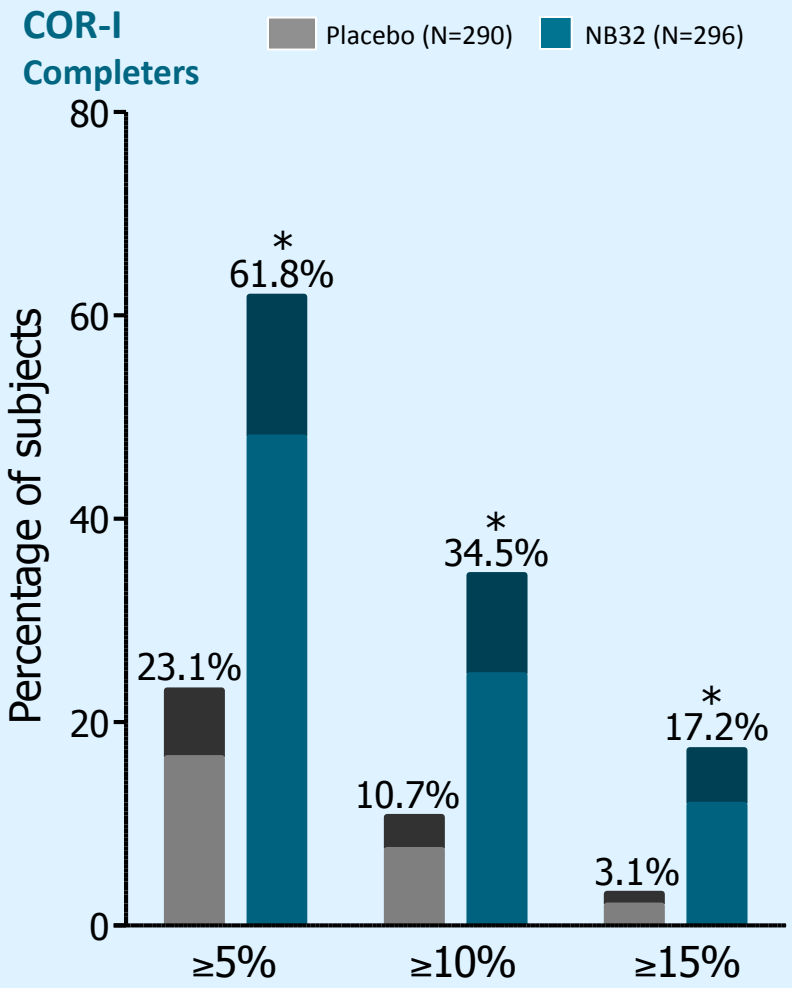


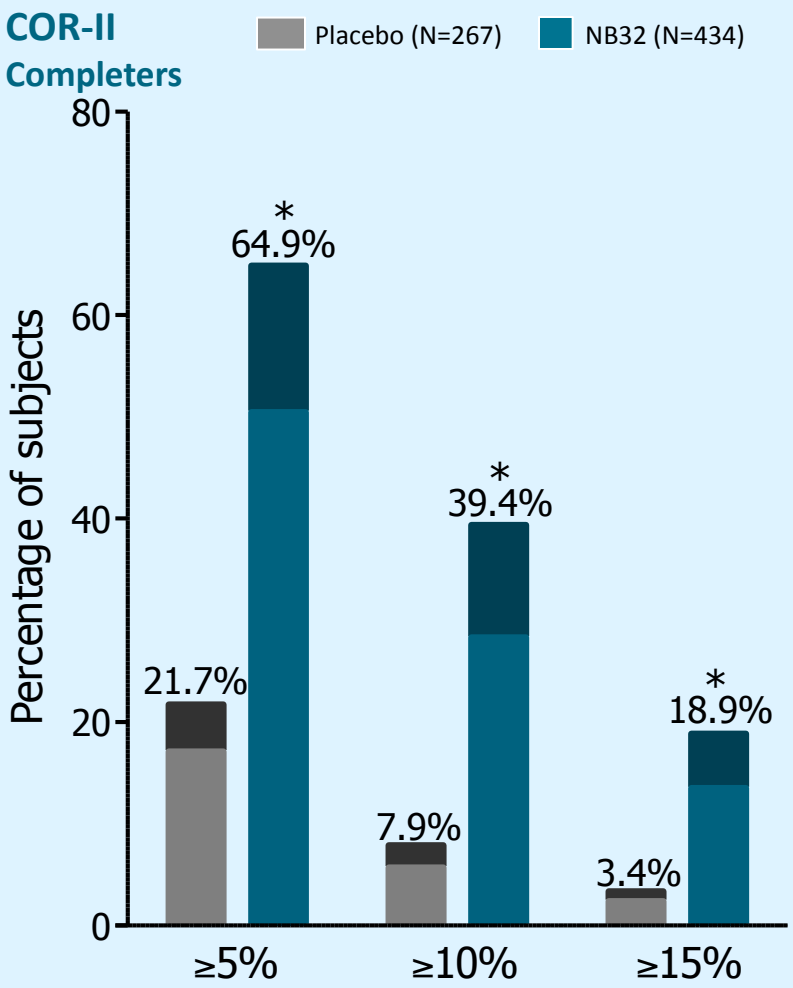

**Completers**
Placebo (N=267): -1.4%
NB32 (N=434): -8.2%*

#COR-II: NB observed data are NB32/NB48 pooled (N=825), no differences were observed for subjects re-randomized to NB32 vs. NB48. LS mean ± SE; *P<0.001 vs Placebo at all time points. COR-II: Week 56 data from subjects re-randomized to NB32 is double-weighted to account for the pre-specified exclusion of subjects re-randomized to NB48. ITT-LOCF: Subjects with a baseline and ≥1 post-baseline weight measurement while on study drug. Data on file at Orexigen Therapeutics, Inc.

# Naltrexone/Bupropion

## COR-I and COR-II: Categorical Weight Loss at Week 56, Completers




Data are for the completer population. *P<0.001 vs Placebo. Data on file at Orexigen Therapeutics, Inc.
COR-II: Week 56 data from subjects re-randomized to NB32 is double-weighted to account for the pre-specified exclusion of subjects re-randomized to NB48.

# Naltrexone SR / Bupropion SR

## Improvement in Risk Factors

| Measure | Week 56 | | |
|---|---|---|---|
| | Placebo *N* = 456 | NB32 *N* = 702 | *P*-value |
| **Waist circumference, cm** | | | |
| Baseline | 108.6 ± 11.8 | 109.0 ± 11.8 | |
| Change | −2.1 ± 0.5 | −6.7 ± 0.3 | <0.001 |
| **Triglycerides, mg/dL** | | | |
| Baseline | 112.8 ± 1.6 | 118.9 ± 1.6 | |
| Percent change (95% CI) | −0.5% (−4.5%, +3.7%) | −9.8% (−12.4%, −7.1%) | <0.001 |
| **HDL-cholesterol, mg/dL** | | | |
| Baseline | 51.6 ± 12.9 | 51.8 ± 13.6 | |
| Change | −0.9 ± 0.5 | +3.6 ± 0.4 | <0.001 |
| **LDL-cholesterol, mg/dL** | | | |
| Baseline | 116.8 ± 32.9 | 120.5 ± 30.2 | |
| Change | −2.1 ± 1.3 | −6.2 ± 0.9 | 0.008 |
| **Fasting blood glucose, mg/dL** | | | |
| Baseline | 94.2 ± 10.4 | 95.0 ± 11.3 | |
| Change | −1.3 ± 0.6 | −2.8 ± 0.5 | 0.051 |
| **Fasting insulin, µIU/mL** | | | |
| Baseline | 10.7 ± 1.9 | 11.4 ± 1.9 | |
| Percent change (95% CI) | +3.5% (−3.8%, +11.2%) | −11.4% (−15.9%, −6.6%) | <0.001 |
| **Systolic blood pressure, mm Hg** | | | |
| Baseline | 118.2 ± 10.5 | 117.9 ± 10.0 | |
| Change | −0.5 ± 0.4 | +0.6 ± 0.3 | 0.039 |
| **Diastolic blood pressure, mm Hg** | | | |
| Baseline | 76.8 ± 7.0 | 76.7 ± 7.0 | |
| Change | +0.3 ± 0.3 | +0.4 ± 0.2 | 0.847 |

Apovian et al. Obesity. 2013;21:935-43.

# Naltrexone/Bupropion: Side Effects

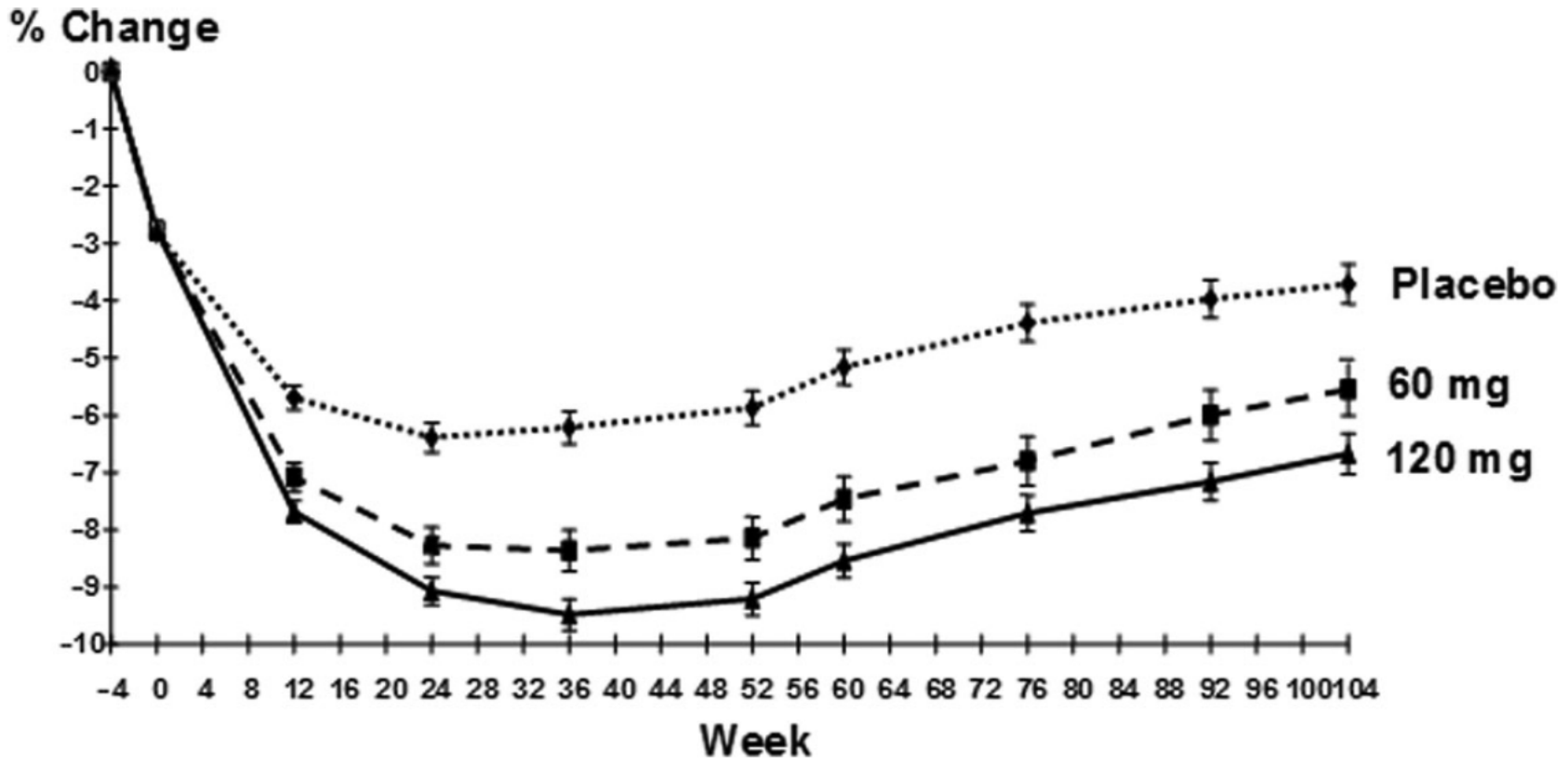
## Most frequent events:

- Nausea
  - N=171 (29.8%) naltrexone 32 mg plus bupropion
  - N=155 (27.2%) naltrexone 16 mg plus bupropion
  - N=30 (5.3%) placebo
- Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups vs. placebo
- Transient increase of ~1.5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mm Hg below baseline in the naltrexone plus bupropion groups
- Combination treatment was not associated with increased depression or suicides vs. placebo

Greenway et al. Lancet. 2010;376:595-605.

# Orlistat, 2-Year Data

**60 or 120 mg TID**

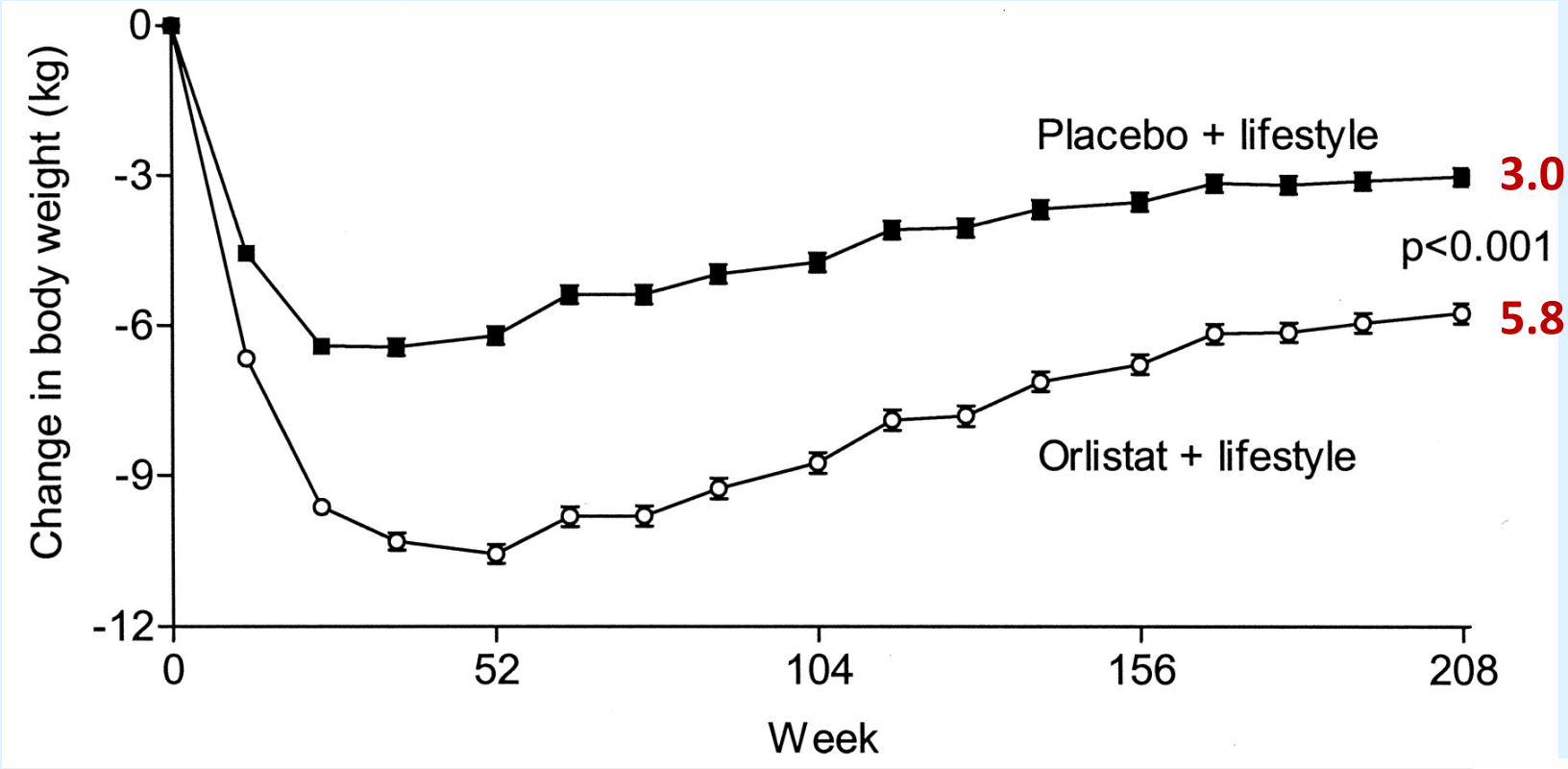



- **Selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat**
- **Side Effects: Initial gastrointestinal symptoms**

Bray et al. Ann N Y Acad Sci. 2014;1311:1-13.

# Orlistat, 4-Year Data

**Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data)**




Torgerson et al. Dia Care. 2004;27:155-61.

# Summary of Randomized Placebo-Controlled Antiobesity Drug Trials

| Drug | Reference | *N* (T2D) | BMI (mean) | Age (mean) | 1-year Δ %WL (mean) | % with >5% WL (*vs* placebo) | Frequent Side Effects | Uncommon Side Effects |
|---|---|---|---|---|---|---|---|---|
| Lorcaserin | [Smith *et al.* 2010] (BLOOM) | 3182 (0) | 36.2 | 44.1 | 3.7% | 45% *vs* 20% | Dry mouth<br>Fatigue | Nausea<br>Urinary tract infection |
| Lorcaserin | [Fidler *et al.* 2011] (BLOSSOM) | 4008 (0) | 35.9 | 43.8 | 3.0% | 47% *vs* 25% | Dizziness<br>Headache | Constipation /diarrhea<br>Hypoglycemia (in pts with T2D) |
| Lorcaserin | [O'Neil *et al.* 2012] (BLOOM-DM) | 604 (604) | 36.0 | 52.4 | 3.5% | 45% *vs* 16% | | |
| Phentermine/ topiramate | [Allison *et al.* 2012] (EQUIP) | 1267 (0) | 42.2 | 42.6 | 9.4% | 67% *vs* 17% | Paresthesia<br>Dry mouth | Palpitations<br>Disturbances in attention |
| Phentermine/ topiramate | [Gadde *et al.* 2011] (CONQUER) | 2487 (393) | 36.6 | 51.1 | 8.6% | 70% *vs* 21% | Constipation<br>Headache<br>Dysgeusia<br>Insomnia<br>Dizziness | Alopecia<br>Diarrhea<br>Anxiety and irritability<br>Depression/fatigue<br>Blurred vision<br>Glaucoma |
| Liraglutide | [Astrup *et al.* 2012] | 398 (21) | 34.8 | 45.9 | 4.9% | 73% vs 28% | Nausea<br>Vomiting | Pancreatitis |
| Liraglutide* | [Wadden *et al.* 2013] | 422 (0) | 35.6 | 46.2 | 6.1% | 51% *vs* 21% | Constipation<br>Diarrhea<br>Headache | |

*Patients in this study were randomized after a run-in on a low calorie diet during which mean weight loss was 6%.
BMI, body mass index; T2D, type 2 diabetes mellitus; WL, weight loss.

Manning et al. Ther Adv Chronic Dis. 2014;5:135-48.

# Weaning Weight Loss Medications

**For patients who do not want to remain on daily medication**

*Suggested Plan for:*

**Accelerated wean over one month using 28 pills**

T = take that day  S = skip that day

Week 1 - 2
T T S T T S T T S T T S
(take two days, skip a day)

Week 3 - 4
T S T S T S T S T S T S
(take one day, skip a day)

Week 5 +
T S S T S S T S S T S S
(Take one day, skip two days and continue until out of pills)

# Summary

- Few choices of anti-obesity medications
- Two new medications approved in 2012
- One new medication approved and one more pending approval in 2014
- Medications can enhance long-term weight loss for select candidates despite adverse effects
- Medications are always only adjunct to diet and exercise

RESOURCE

# Anti-obesity Medications in Development

| Target | Drug | Company | Mechanism of action | Status |
|---|---|---|---|---|
| Central neuropeptide signaling | | | | |
| Melanocortin receptor | MK-0493 | Merck | Selective MC4R agonist, increases MC3R/4R signaling | Phase II completed |
| | RM-493 | Rhythm | Selective MC4R agonist, increases MC3/4R signaling | Phase II |
| NPY | MK-0557 | Merck | Y5 receptor antagonist, NPY blocker | Phase II completed |
| | Velneperit (S-2367) | Shionogi USA | Y5 receptor antagonist, NPY blocker | Phase III |
| Monoamine neurotransmission | | | | |
| Dopamine/norepinephrine/serotonin | Contrave (bupropion/ naltrexone) | Orexigen | Norepinephrine/dopamine reuptake inhibitor | Phase III completed; NDA submission |
| Intestinal peptide hormone signaling | | | | |
| GLP-1 | Liraglutide (Victoza) | Novo Nordisk | GLP-1R agonist, GLP-1 mimicking | Phase III completed; NDA submission |
| | Byetta (Exenatide) | Amylin | GLP-1R agonist, GLP-1 mimicking | Phase III |
| OXM | Oxyntomodulin (OXY-RPEG) | Prolor | GLP-1R agonist, OXM mimicking | Phase I recruiting |
| | TKS1225 | Thiakis/Wyeth/ Pfizer | GLP-1R agonist, OXM mimicking | Phase I |
| Pancreatic hormone signaling | | | | |
| PP | PP1420 | Wellcome Trust | Pancreatic polypeptide analog | Phase I completed |
| Amylin | Davalintide (AC2307) | Amylin | Amylin mimicking | Phase II |
| Adipose tissue hormone signaling | | | | |
| Leptin | Metreleptin | Amylin/Takeda | Leptin receptor agonist | Phase III recruiting |
| Inhibition of lipase | | | | |
| Pancreatic lipase | Cetilistat (ATL-962) | Alizyme/Takeda/ Norgine | Pancreatic lipase inhibitor, inhibits intestinal lipid absorption | Phase III completed |

GLP-1, glucagon-like peptide 1; MC3R/4R, melanocortin 3 and melanocortin 4 receptors; NDA, New Drug Application; NPY, neuropeptide Y; OXM, oxyntomodulin; PP, pancreatic polypeptide.

Kim et al. Clin Pharmacol Ther. 2014;95:53-66.

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