An Individualized Approach to Optimize Obesity Treatment

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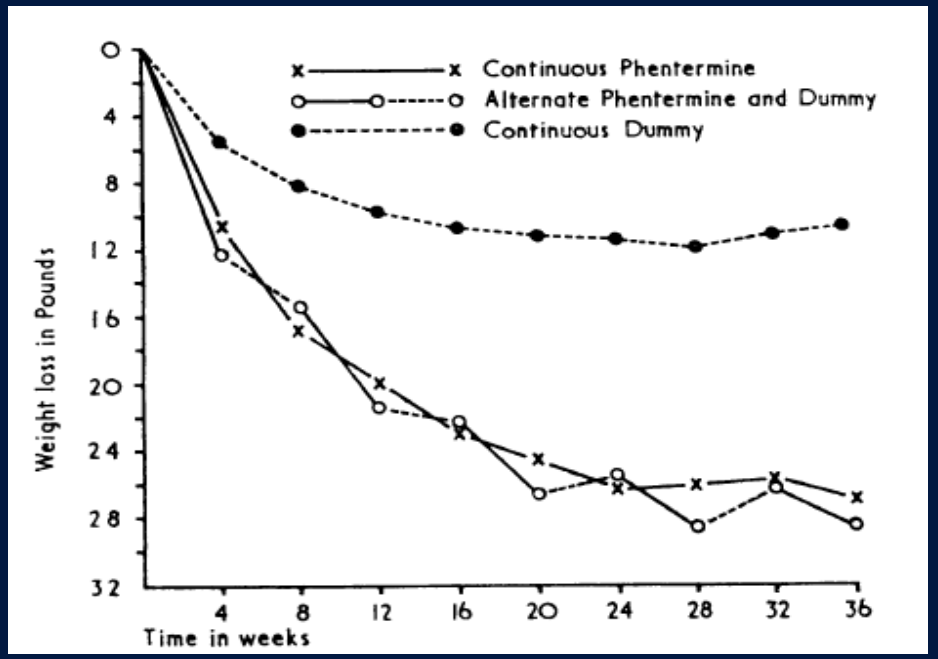
FDA-Approved Obesity Pharmacotherapy Options

- Phentermine (and other noradrenergic agents)
- Orlistat
- Lorcaserin
- Phentermine/topiramate ER
- Naltrexone SR/bupropion SR
- Liraglutide 3.0 mg

Indications: Adjunct to behavioral modification in BMI >30 kg/m^2 or 27-30 kg/m^2 with comorbidities.
All obesity medications contraindicated in pregnancy

Phentermine

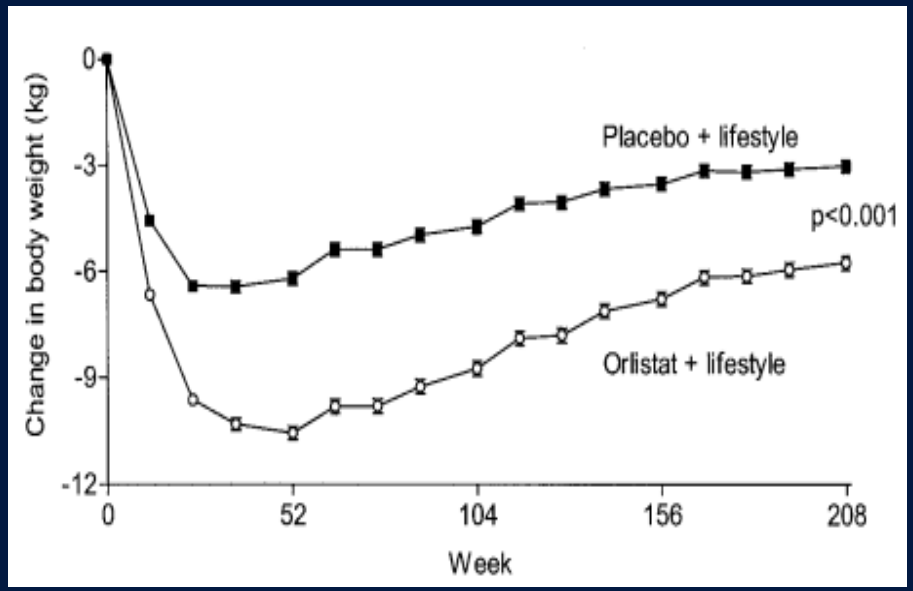
- Sympathomimetic amine; NE release
- Blunts appetite
- Approved 1959; short-term use
- Schedule IV
- Dosing: 15-37.5mg qAM
- Contraindications: Pregnancy, nursing, MAOIs, glaucoma, drug abuse history, hyperthyroidism, uncontrolled HTN, tachycardia, history of CAD, CHF, stroke



Phentermine [package insert]. Cranford, NJ: Alpex Pharma SA : 2011. Munro JF, et al. *Br Med J*. 1968;1(5588):352-354.

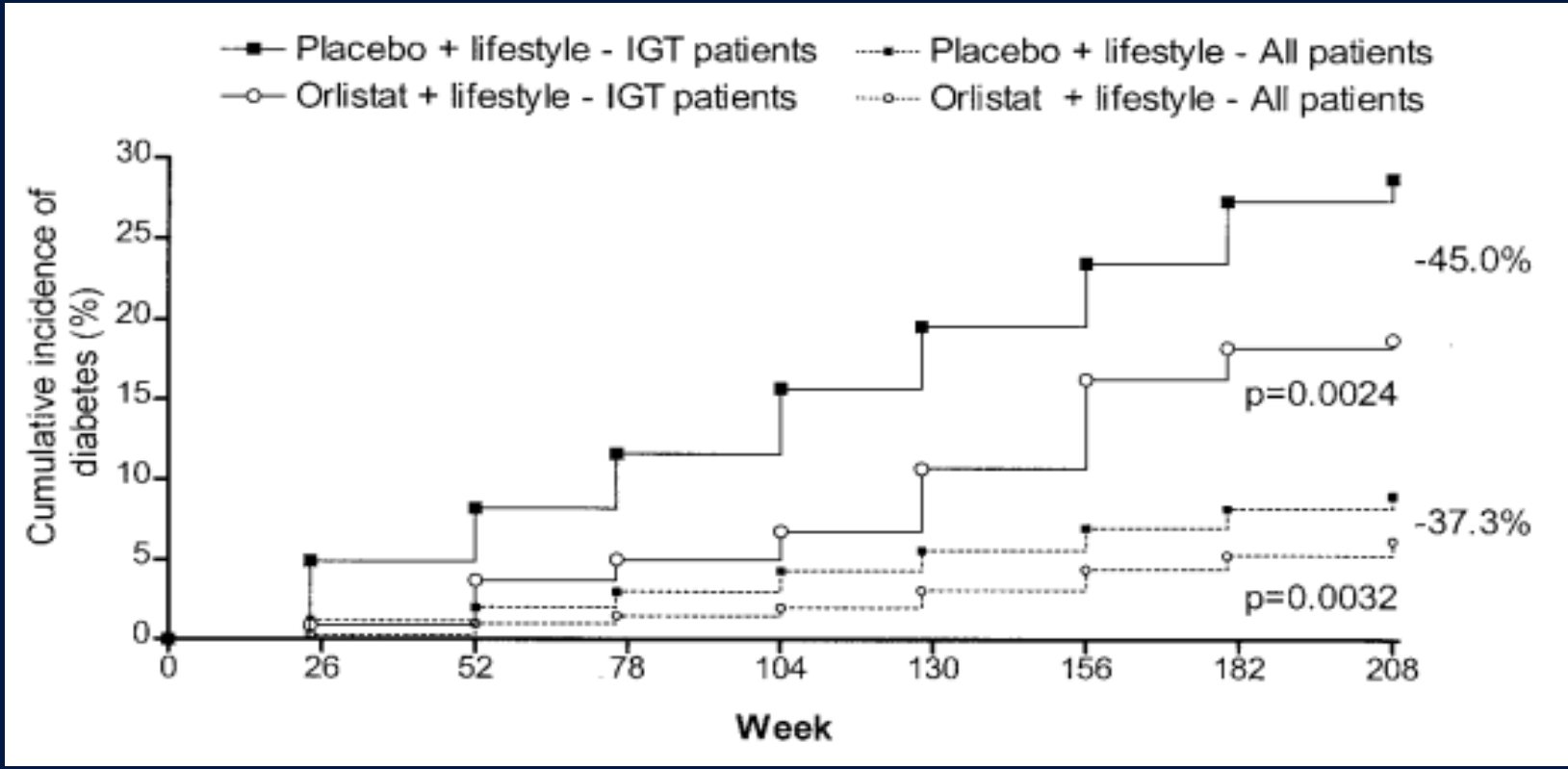
Orlistat

- Lipase inhibitor, decreases fat absorption
- Approved 1999; long-term use
- Not scheduled
- 120 mg TID with meals (Rx) or 60 mg TID (OTC)
- Use MVI with fat-soluble vitamins at bedtime
- Contraindications: pregnancy, chronic malabsorption syndrome, cholestasis
- Possible GI AEs



Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161.
Orlistat [package insert]. South San Francisco, CA : Genentech: 2012; Orlistat [package insert]. Moon Township, PA: GlaxoSmithKline: 2011.

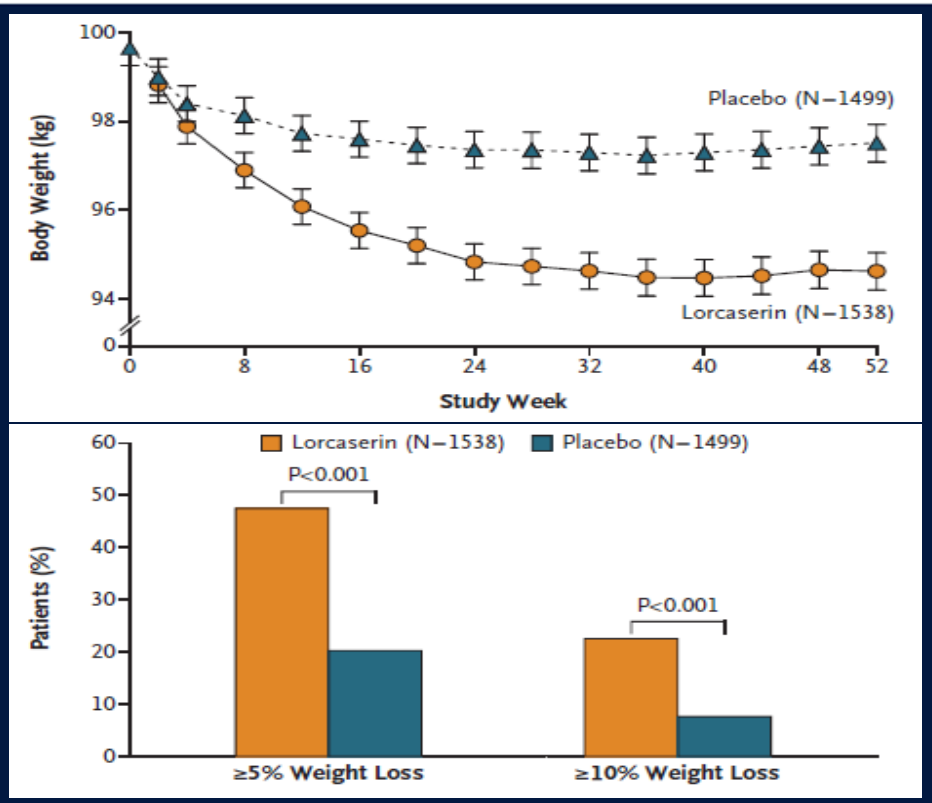
Orlistat and Prevention of Diabetes



Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161.

Lorcaserin

- Selective 5HT-2c receptor agonist
- Increases satiety
- Approved in 2012 for long-term use
- Schedule IV
- Single dose: 10 mg BID; discontinue if <5% BWL after 12 weeks
- Contraindications: pregnancy
- Warnings: coadministration with serotonergic agents; valvular heart disease; psychiatric disorders, priapism



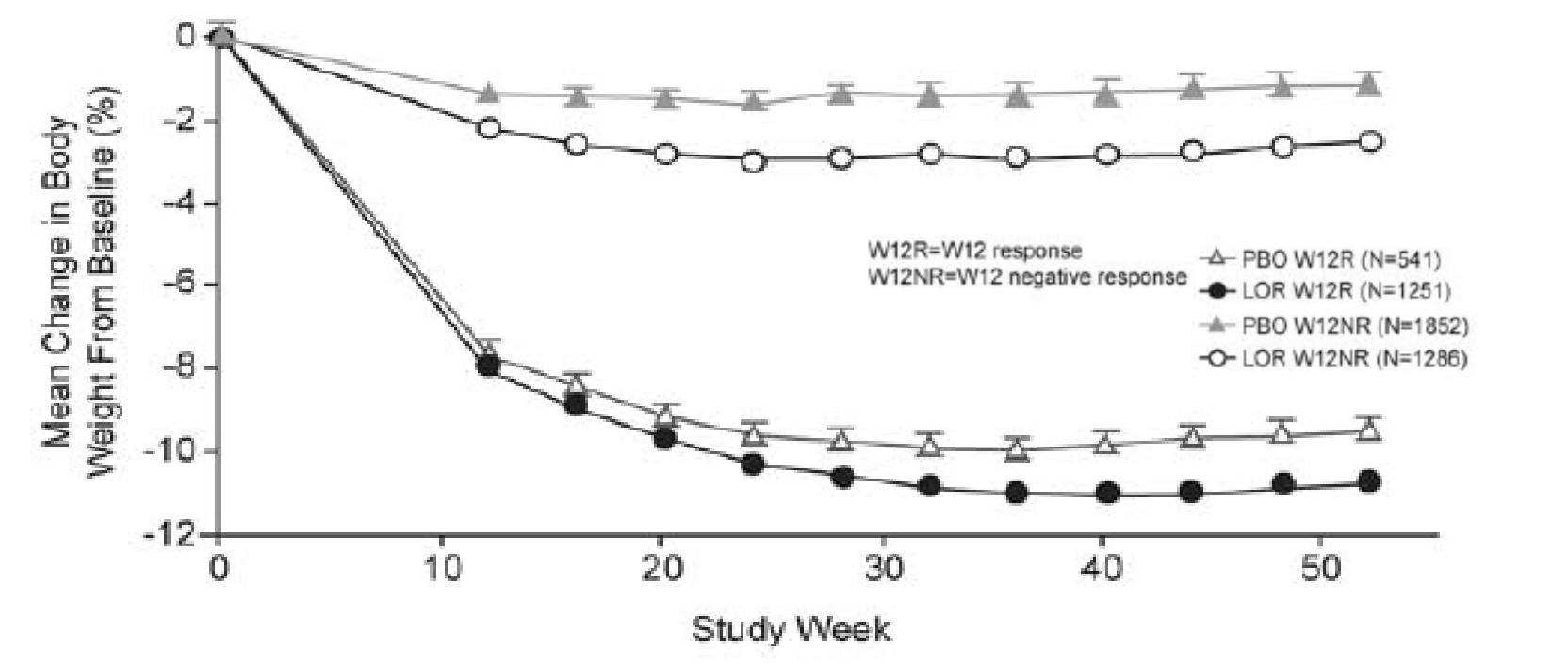
BELVIQ [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc; 2012; Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067; Smith SR, et al. *N Engl J Med.* 2010;363(3):245.

Key Secondary Endpoints

Endpoint		Lorcaserin	Placebo	*P*
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
A1c	↓	-0.9	-0.4	<0.001
Heart rate (bpm)	↓	−2.0	−1.6	0.049
Beck depression II		−1.1	−0.9	0.26

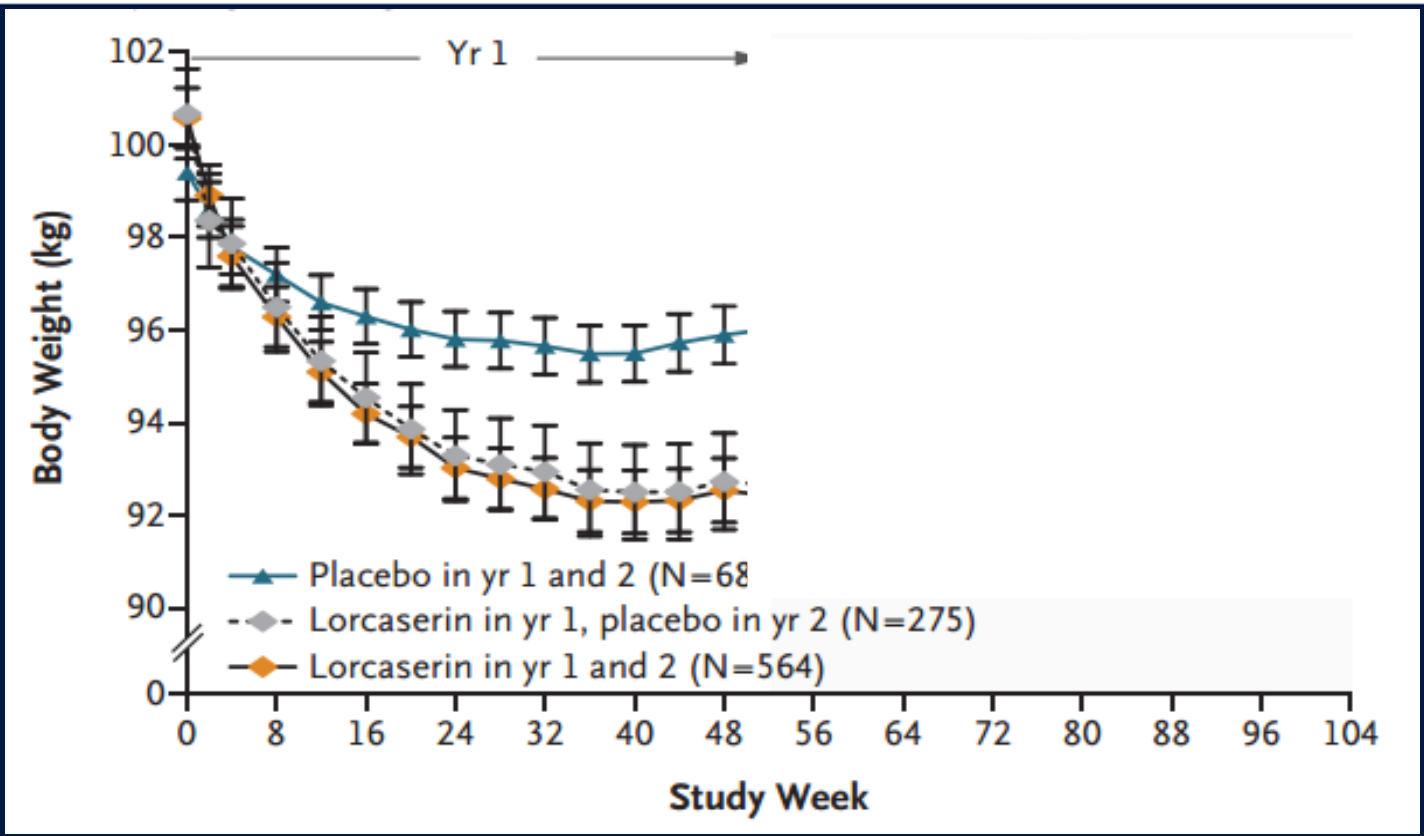
Smith SR, et al. *N Engl J Med.* 2010;363(3):245. O'Neil PM, et al. *Obesity*. 2012;20:1426-1436.

Outcomes By Responder Status



BELVIQ [Prescribing Information]. Woodcliff Lake, NJ: Eisai Inc; 2012.
Smith SR, et al. *Obesity.* 2014; Jul 18. doi: 10.1002/oby.20841.

Lorcaserin: Weight Change in 2nd Year of Treatment versus Placebo



Smith SR, et al. *N Engl J Med*. 2010;363:245-256.

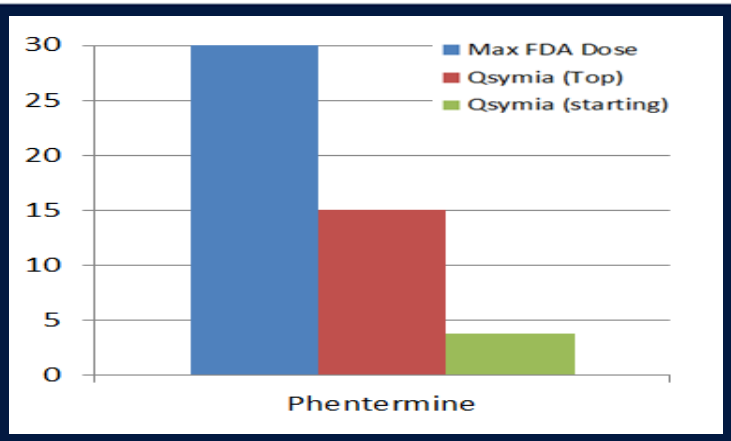
Lorcaserin: Adverse Events and Discontinuation

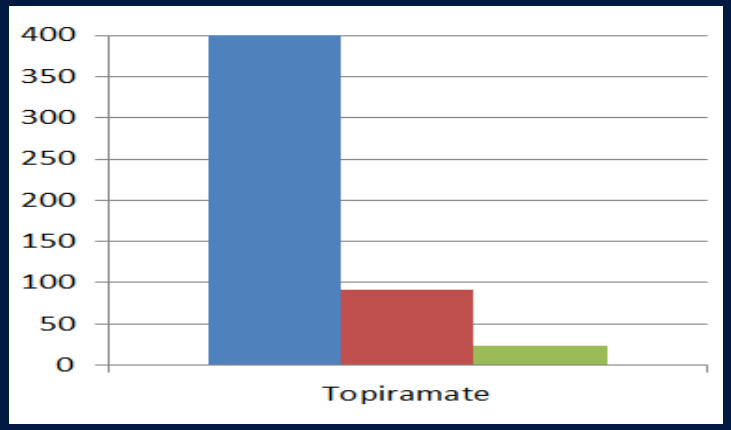
N (%)	Lorcaserin (N = 3195)	Placebo (N = 3185)	Discontinuation Lorcaserin	Discontinuation Placebo
Headache	537 (16.8)	321 (10.1)	1.3%	0.8%
Dizziness	270 (8.5)	122 (3.8)	0.7%	0.2%
Nausea	264 (8.3)	170 (5.3)		
Constipation	186 (5.8)	125 (3.9)		
Fatigue	229 (7.2)	114 (3.6)		
Dry mouth	169 (5.3)	74 (2.3)		
Hypoglycemia in T2DM	75 (29.3)	53 (21.0)	%	%
Overall			8.6%	6.7%

Smith SR, et al. *N Engl J Med*. 2010;363:245-256; O'Neil PM, et al. *Obesity*. 2012;20:1426-1436;
Lorcaserin (Prescribing Information) Woodcliff Lake, NJ Eisai Inc. 2012.

Phentermine/Topiramate ER

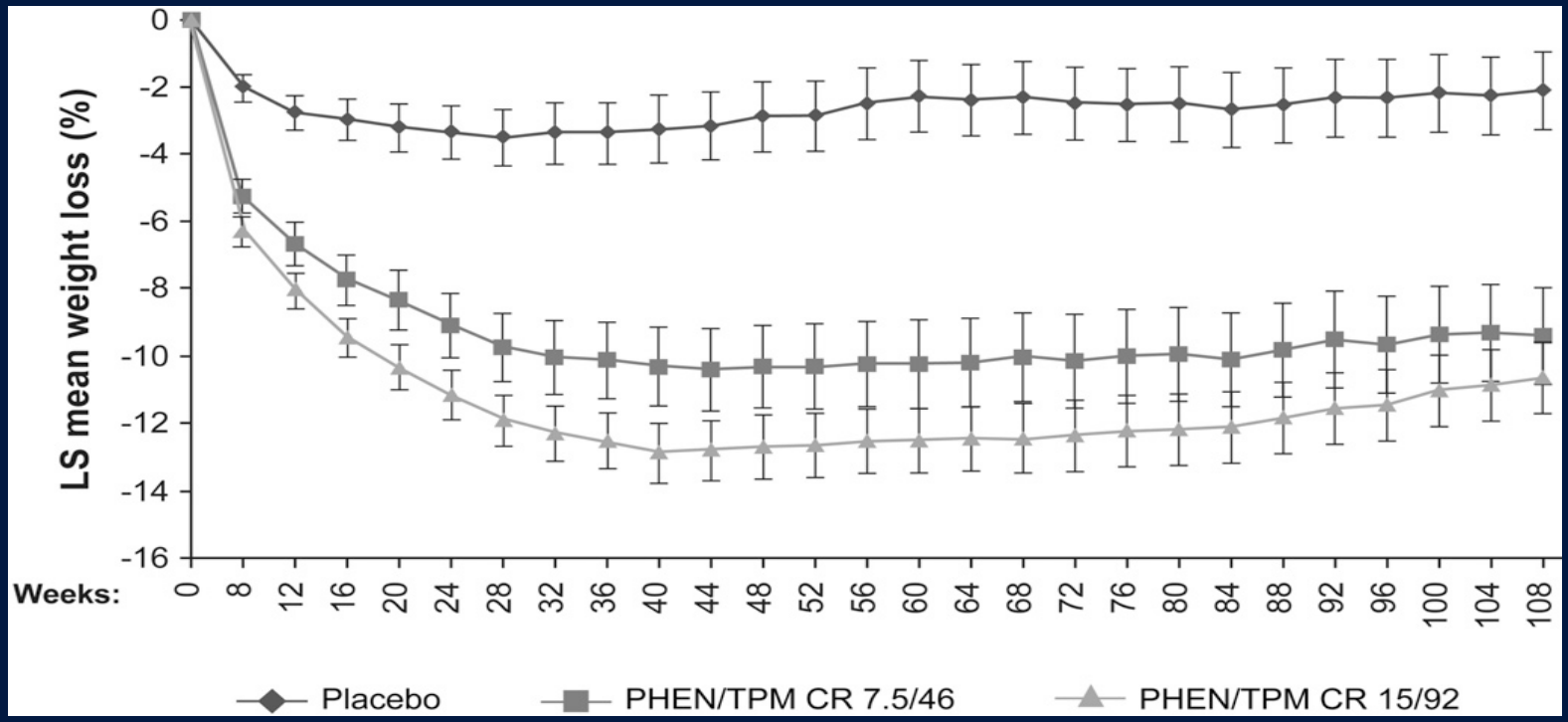
- Phentermine: blunts appetite
- Topiramate: prolongs satiety
- Approved in 2012 for long-term use
- Schedule IV
- Four fixed-dose options in 3.75 mg/23 mg increments
- Titrate or discontinue if <3% weight loss at 12 weeks
- Contraindications: pregnancy, glaucoma, MAOIs, hyperthyroidism





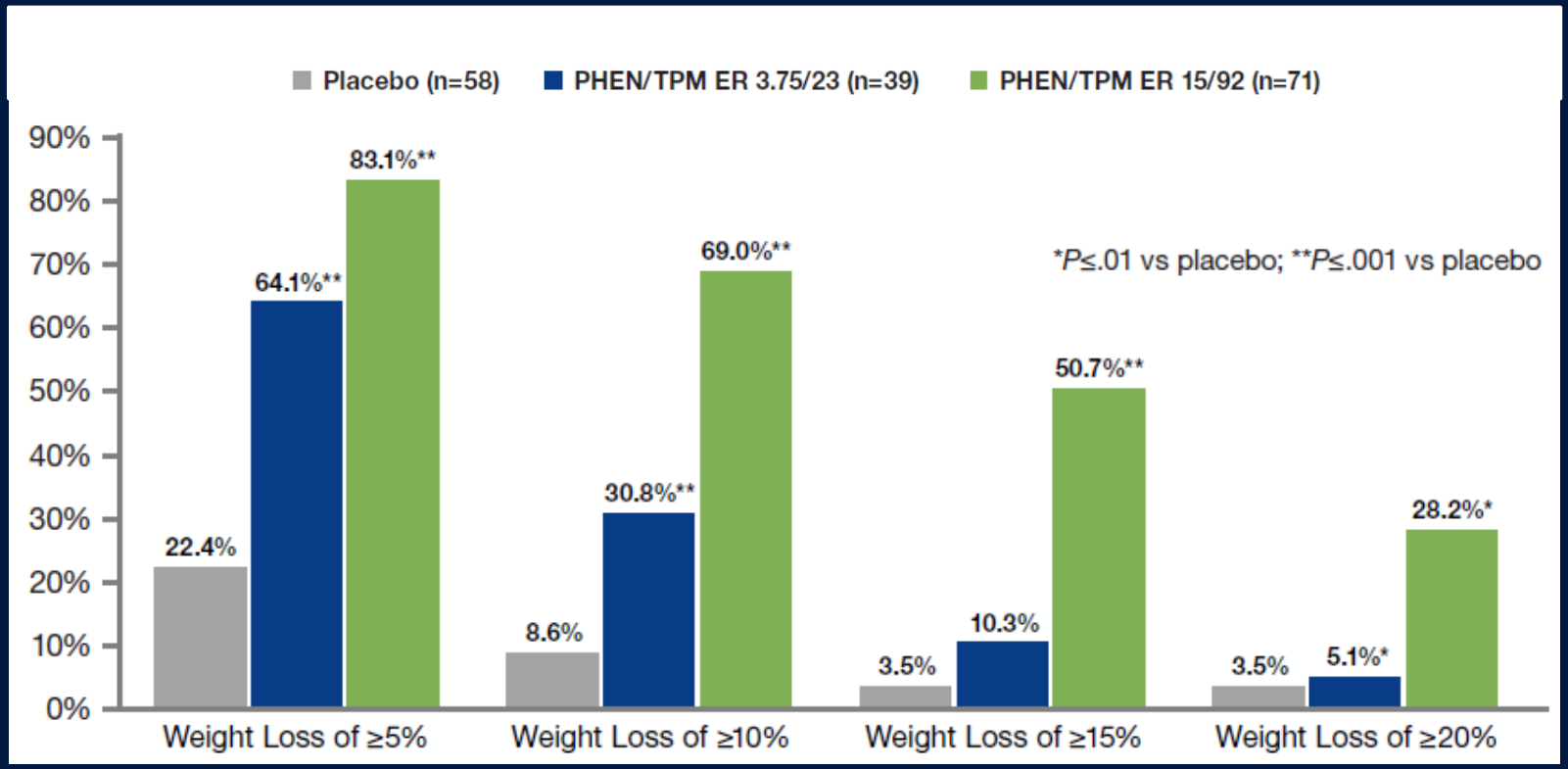
Phentermine and topiramate extended-release [package insert]. Mountain View, CA : Vivus; 2012.

Phentermine/Topiramate ER



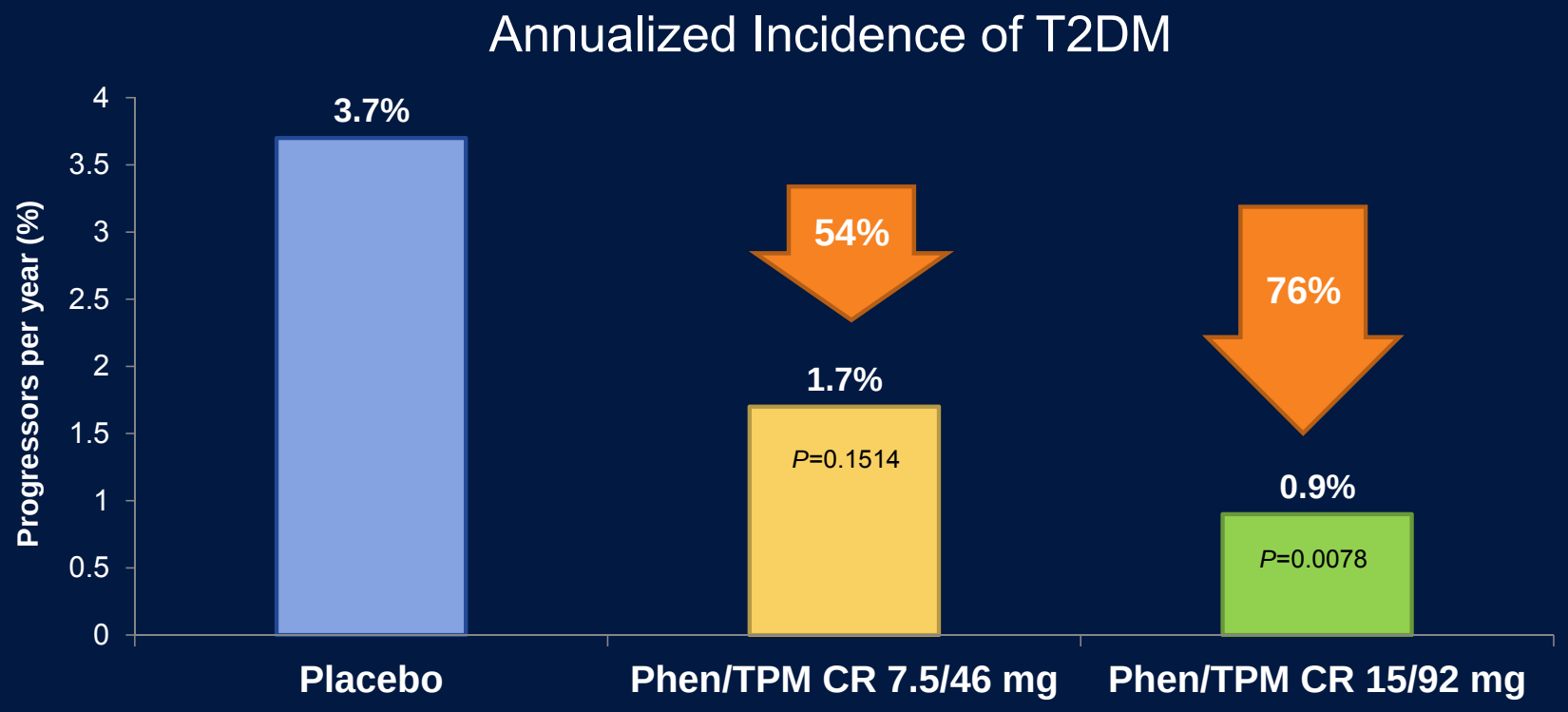
Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308.

Patients With Extreme Obesity (BMI >45)



Kahan S, et al. The Obesity Society Annual Meeting, 2015. Poster T-P-3143.

Phentermine/Topiramate ER Prevents Progression to Type 2 Diabetes Mellitus



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

Most Common 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
Dysgeusia	1.1	1.3	7.4	9.4
Insomnia	4.7	5.0	5.8	9.4
Dizziness	3.4	2.9	7.2	8.6

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

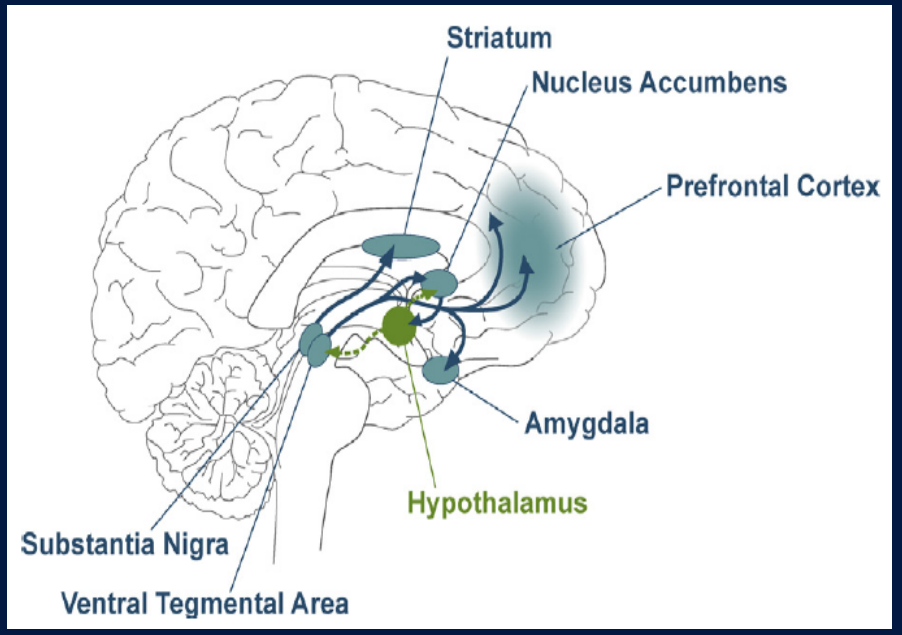
Adverse Reactions Leading to Treatment Discontinuation

	Placebo (n=1561), %	Phentermine/ Topiramate ER 3.75 mg/23 mg (n=240), %	Phentermine/ Topiramate ER 7.5 mg/46 mg (n=498), %	Phentermine/ Topiramate ER 15 mg/92 mg (n=1580), %
Vision blurred	0.5	2.1	0.8	0.7
Headache	0.6	1.7	0.2	0.8
Irritability	0.1	0.8	0.8	1.1
Dizziness	0.2	0.4	1.2	0.8
Paresthesia	0.0	0.4	1.0	1.1
Insomnia	0.4	0.0	0.4	1.6
Depression	0.2	0.0	0.8	1.3
Anxiety	0.3	0.0	0.2	1.1

Qsymia (phentermine and topiramate) capsules [package insert]. Mountain View, CA: Vivus; 2014.

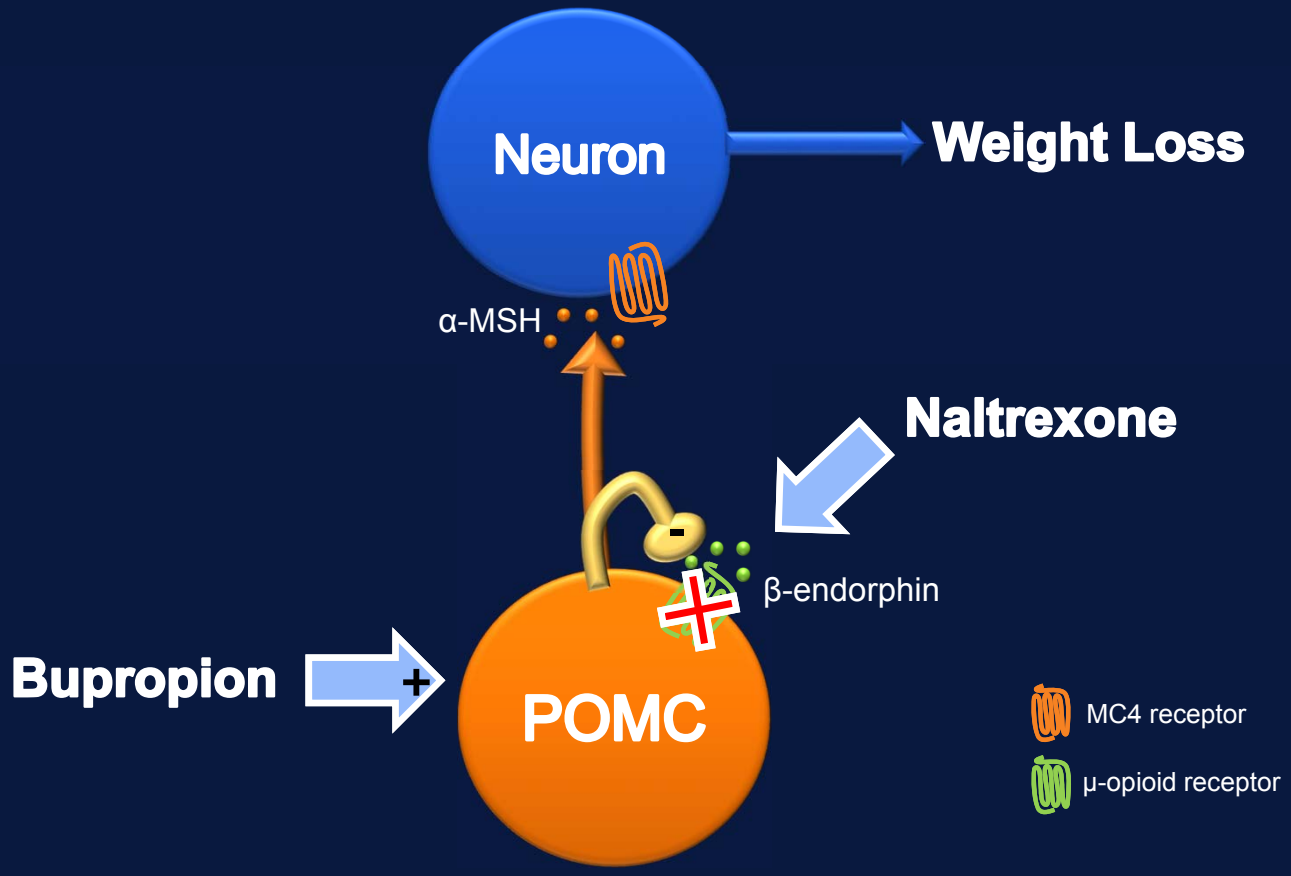
Naltrexone SR/Bupropion SR

- Bupropion: Dopamine/norepinephrine reuptake inhibitor
- Naltrexone: opioid receptor antagonist
- Approved 2014
- Long-term use; not controlled
- Dosing (8 mg/90 mg tabs): titrate weekly to 2 BID
- Consider discontinuation if <5% weight loss after 12 weeks
- Contraindications: pregnancy, seizures, uncontrolled HTN, chronic opioid use, MAOI use



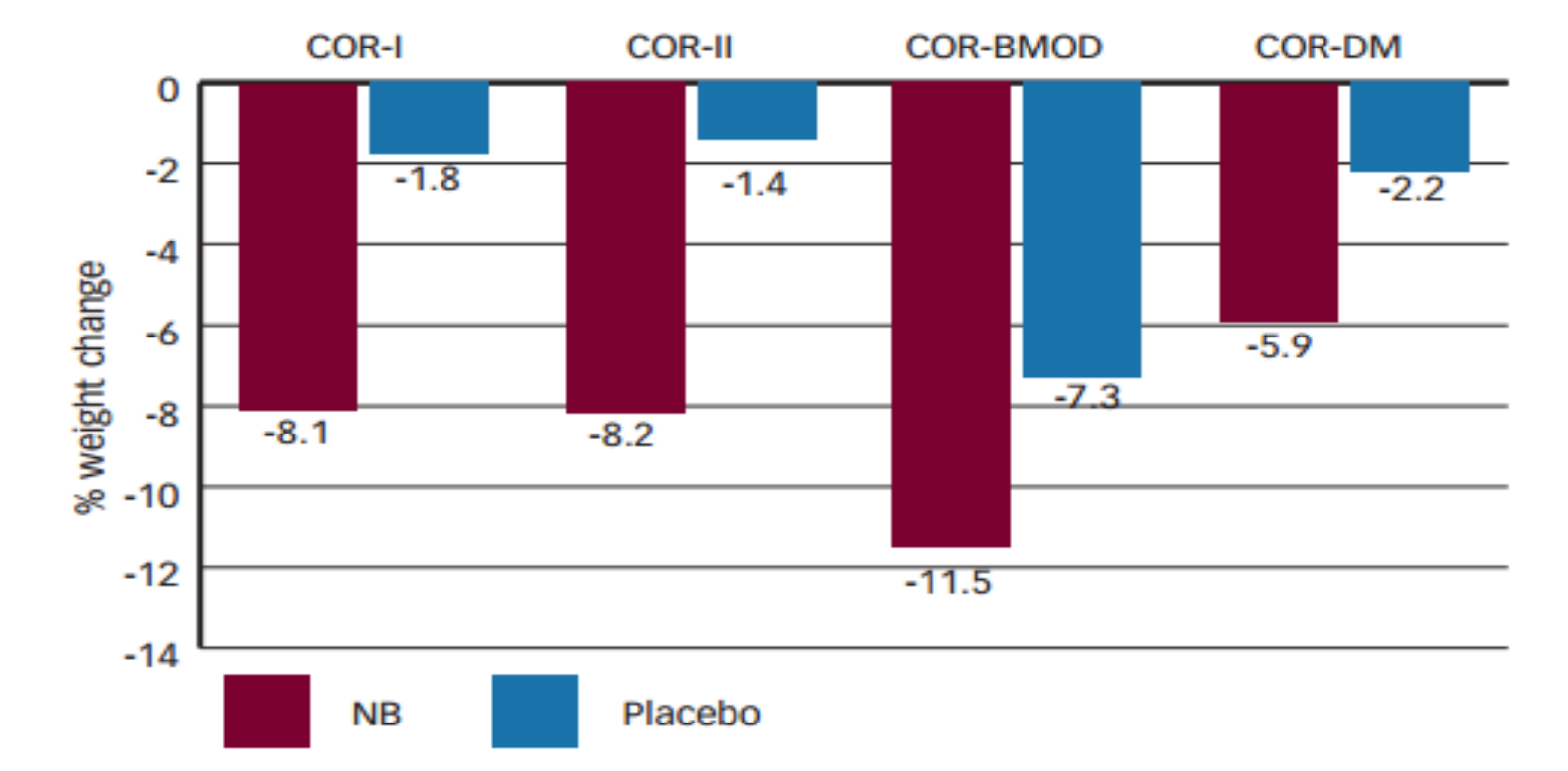
Contrave prescribing information. Takeda Pharmaceuticals. Greenway FL, et al. *Obesity*. 2009;17:30-39. Billes SK, et al. *Pharmacol Res*. 2014;84;1-11.

Naltrexone SR/Bupropion SR: Mechanism of Action



Billes SK, et al. *Pharmacol Res.* 2014;84:1-11.

Naltrexone SR/Bupropion SR: Patients Completing 1 Year of Treatment



Wadden TA, et al. *Obesity*. 2011;19:110-120. Hollander P, et al. *Diabetes Care*. 2013;36(12):4022-4029. Greenway FL, et al. *Obesity*. 2009;17:30-39. Apovian CM, et al. *Obesity.* 2013;21(5):935-943. Billes SK, et al. *Pharmacol Res*. 2014;84;1-11.

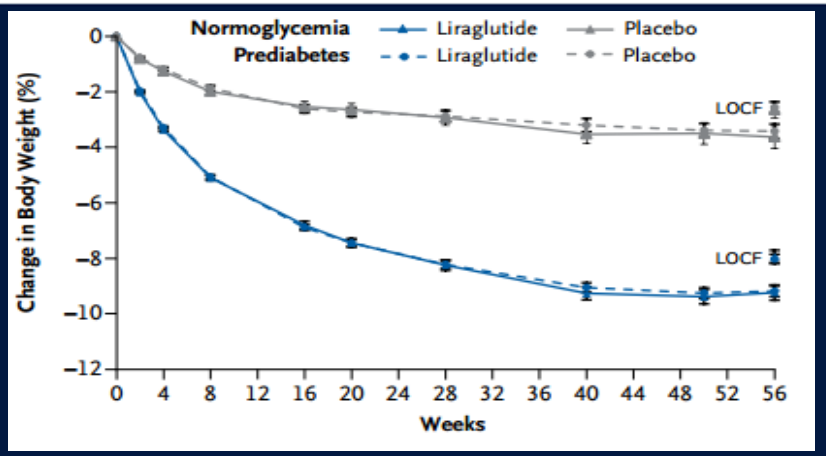
Naltrexone SR/Bupropion SR

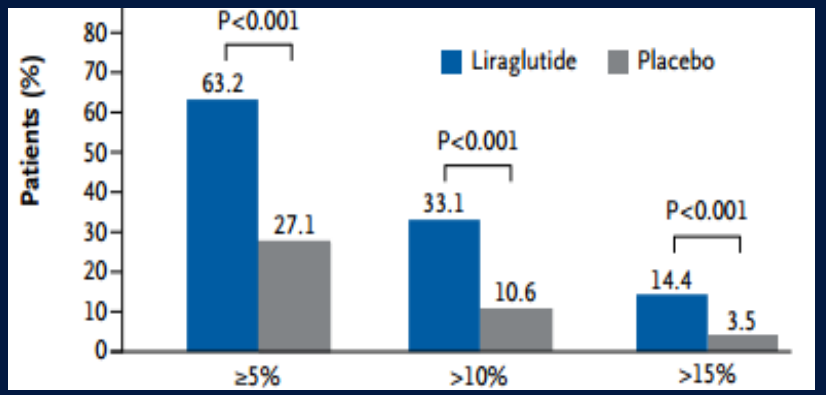
	Naltrexone SR/bupropion SR 32/360 mg	Placebo
Nausea	32.5%	6.7%
Constipation	19.2%	7.2%
Headache	17.6%	10.4%
Vomiting	10.7%	2.9%
Dizziness	9.9%	3.4%
Insomnia	9.2%	5.9%
Dry mouth	8.1%	2.3%
Subjects discontinuing due to AE:		
Overall	24%	12%
Nausea	6.3%	
Headache	1.7%	
Vomiting	1.1%	

Contrave (naltrexone HCL and bupropion HCL) extended-release tablets [package insert]. Deerfield, IL and La Jolla, CA: Takeda / Orexigen; 2014.

Liraglutide 3.0 mg

- GLP-1 receptor agonist
- Multiple actions; effect on weight is primarily via POMC neurons
- Liraglutide 1.8 mg: type 2 diabetes
- Liraglutide 3.0 mg: obesity treatment
- Long-term use; not controlled
- Dosing: SC; titrate weekly by 0.6 mg
- Discontinue if <4% loss at 16 weeks
- REMS: medullary thyroid carcinoma, acute pancreatitis

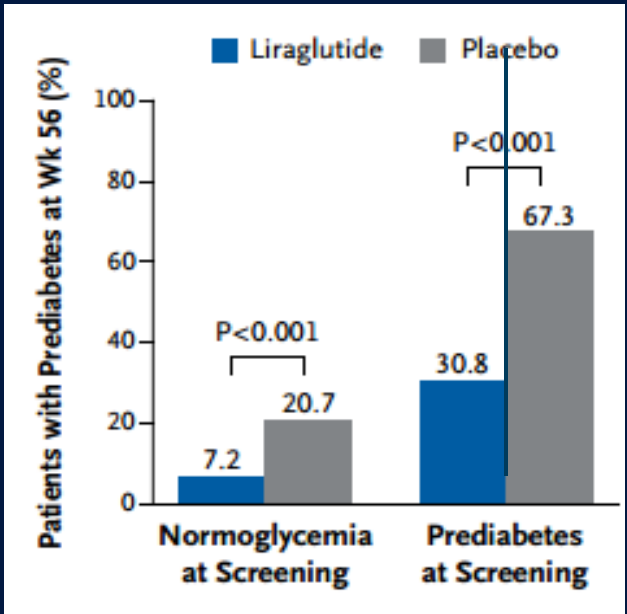




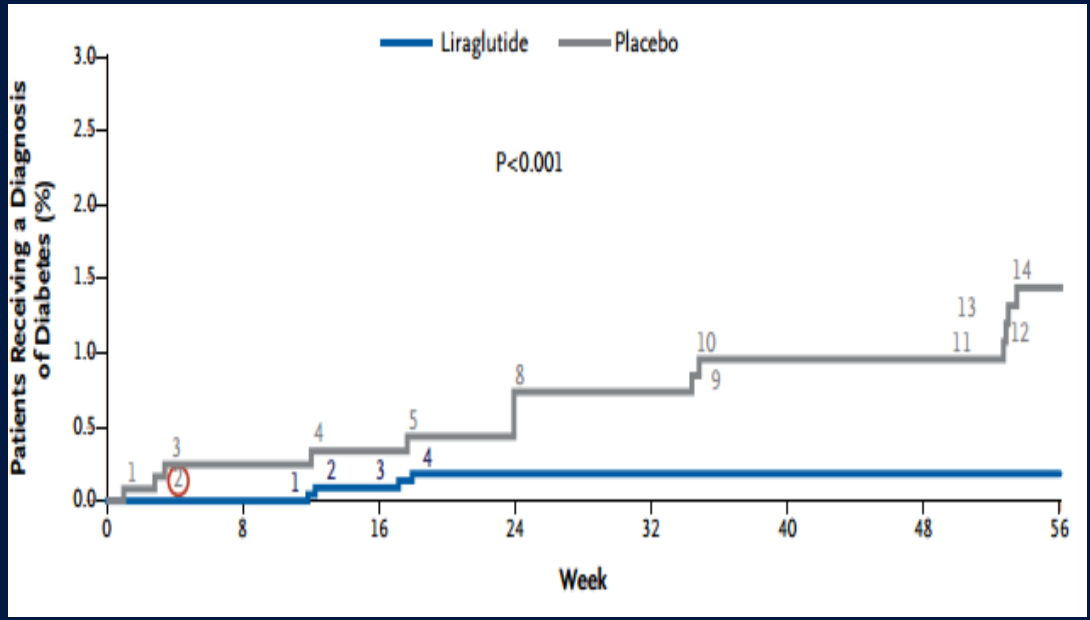
Pi-Sunyer X, et al. *N Eng J Med*. 2015;373(1):11-22. Saxenda (liraglutide) injection [package insert]. Plainsboro, NJ: Novo Nordisk, 2014

Liraglutide 3.0 mg

Prediabetes status

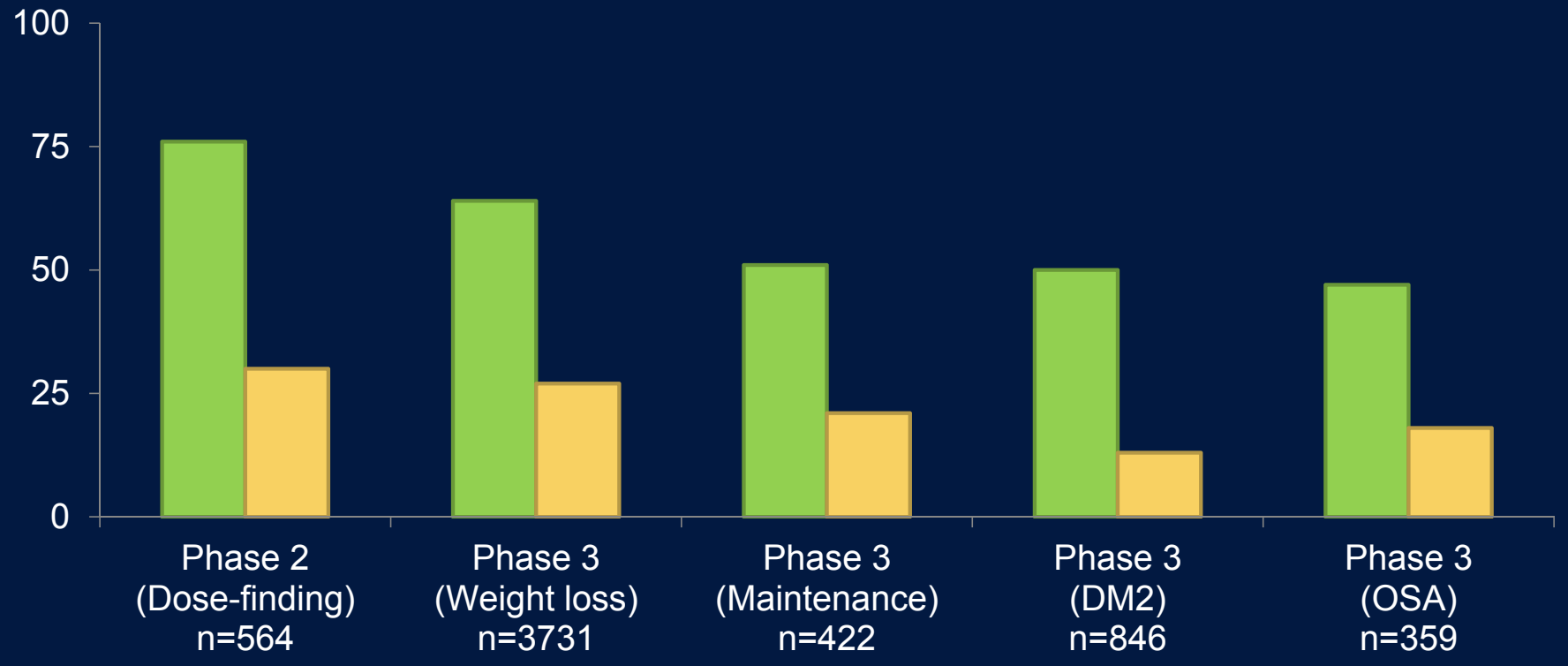


Patients receiving a diagnosis of diabetes



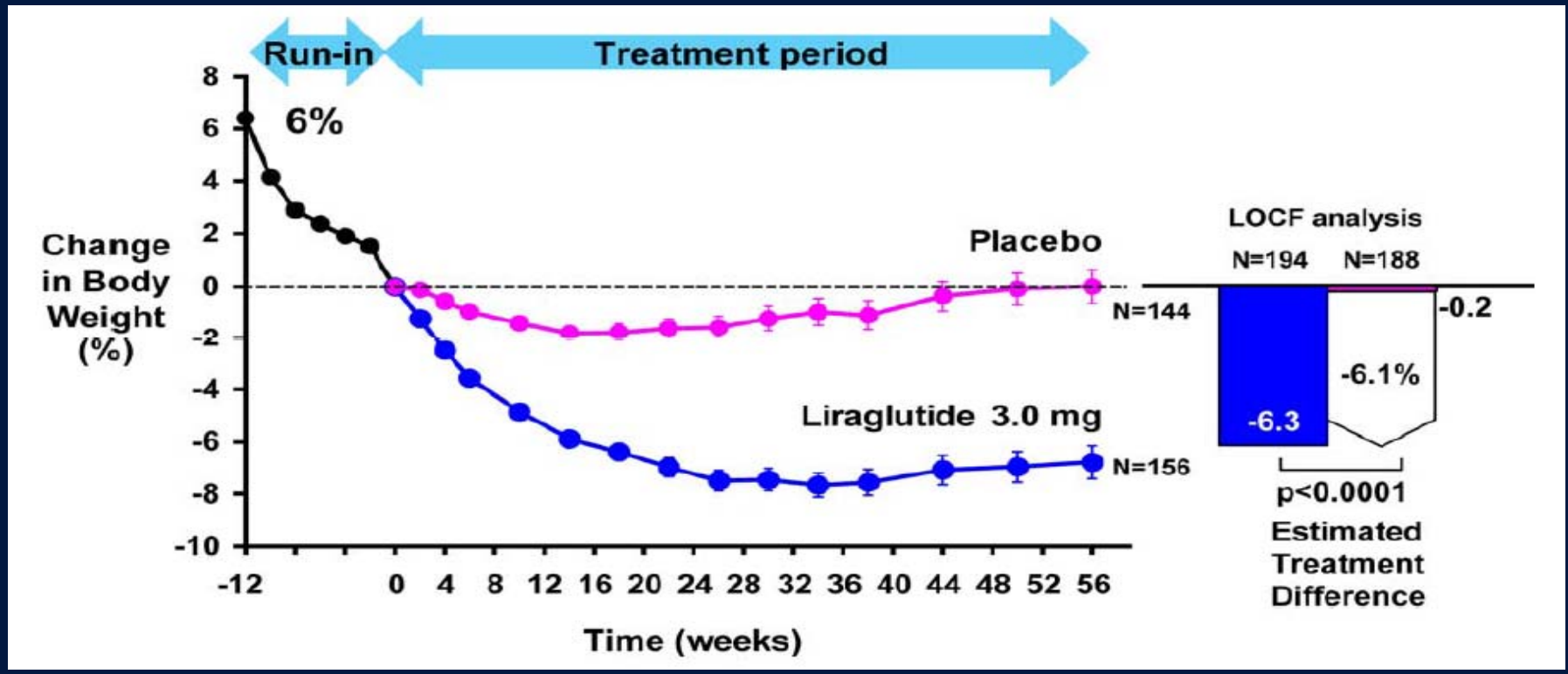
Pi-Sunyer X, et al. *N Engl J Med.* 2015;373:11-22.

Percentage of Patients Achieving >5% Weight Loss With Liraglutide 3.0 mg



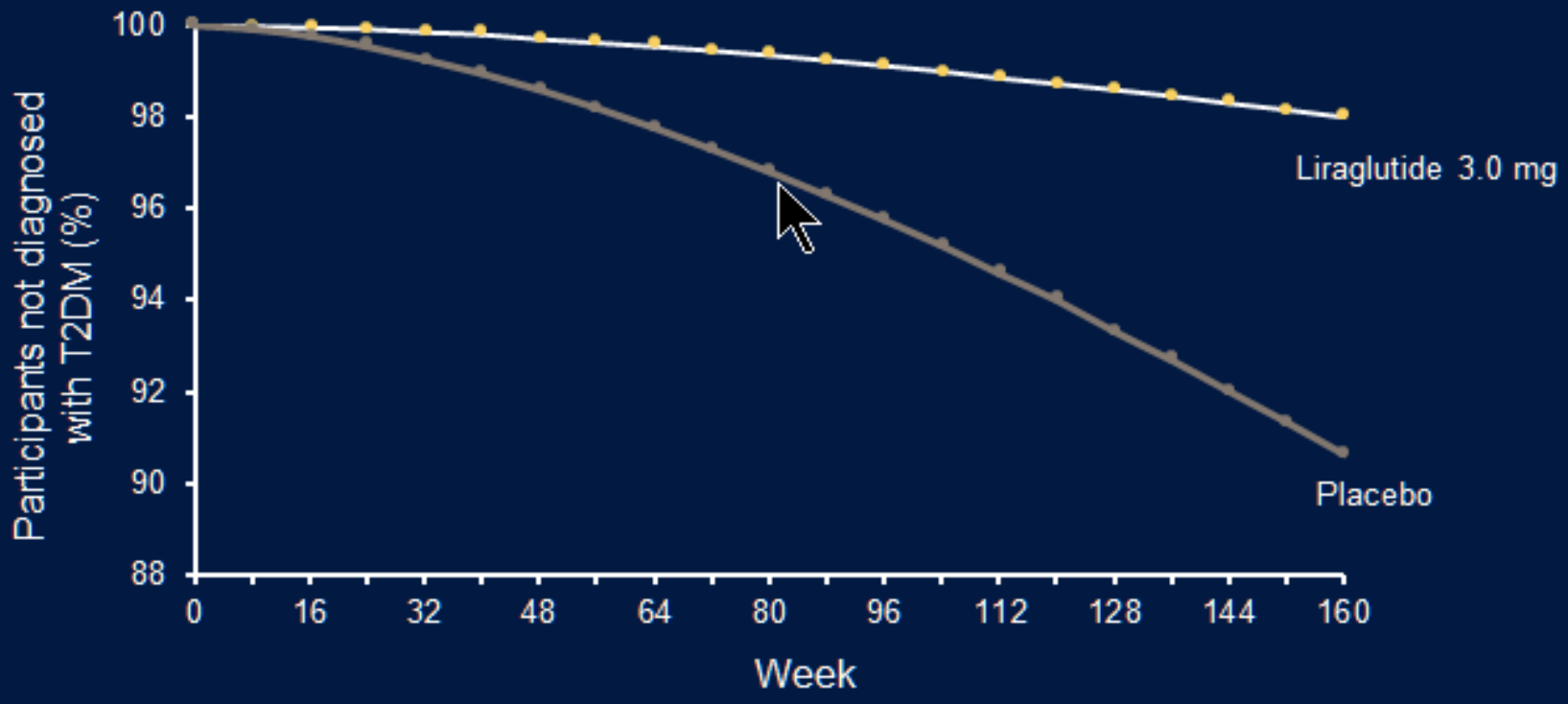
Data submitted to FDA Endocrinologic and Metabolic Drug Advisory Committee, NDA 206-321, September 11, 2014.

Liraglutide and Weight Maintenance



Data submitted to FDA Endocrinologic and Metabolic Drug Advisory Committee, NDA 206-321, September 11, 2014.

Liraglutide 3.0 mg Delayed Time to Onset of Type 2 Diabetes Mellitus



le Roux C, et al. The Obesity Society Annual Meeting, 2015. Poster T-P-LB-3843.

Liraglutide 3.0 mg

%	Liraglutide 3.0 mg	Placebo	Discontinuation
Nausea	39	14	2.9
Diarrhea	21	10	1.4
Vomiting	16	4	1.7
Constipation	19	8	
Dyspepsia	9	3	
Abdominal pain	5	3	
Hypoglycemia in T2DM	23	13	
Headache	14	13	
Dizziness	7	5	
Fatigue	7	4	
Increased lipase	5	2	
		Overall discontinuation:	9.8% vs 4.3%

Saxenda (liraglutide) injection [package insert]. Plainsboro, NJ: Novo Nordisk; 2014.

Contraindications and Cautions

Clinical Scenario	Avoid/Caution
Elevated seizure risk	Naltrexone SR / bupropion SR
History of recurrent kidney stones	Phentermine / topiramate ER, orlistat
History of glaucoma	Phentermine / topiramate ER
Uncontrolled hypertension	Naltrexone SR / bupropion SR
Coronary artery disease	Phentermine
Moderate-severe renal impairment	Do not exceed half-dose: Phentermine / topiramate ER, naltrexone SR / bupropion SR Caution: liraglutide 3.0 mg, lorcaserin
Moderate-severe hepatic impairment	Do not exceed half-dose: Phentermine / topiramate ER Do not exceed ¼ dose: naltrexone SR / bupropion SR Caution: liraglutide 3.0 mg, lorcaserin
SSRI use	Caution: lorcaserin

Dual Benefits

Obesity and…	Consider, but not explicitly approved…
Smoking	Naltrexone SR / bupropion SR
Depression	Naltrexone SR / bupropion SR
Migraines	Phentermine / topiramate ER
Diabetes	Liraglutide 3.0 mg
Chronic constipation	Orlistat
Elevated LDL	Orlistat