How Do We Treat Obesity?

Weight Loss Medications

AACE OBESITY RESOURCE CENTER

AACE ONLINE ENDOCRINE ACADEMY

WEIGHT-LOSS MEDICATIONS APPROVED BY THE FDA FOR LONG-TERM TREATMENT OF OBESITY

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments

Orlistat
 	
(Xenical™)
(Alli™) – OTC
 	
1999
	Lipase inhibitor
	
	XENDOS
	
	1 yr: 4.0%
	4 yr: 2.6%
		120 mg PO TID (before meals)
		
		OTC: 60 mg PO TID (before meals)
			• Steatorrhea
			• Fecal urgency
			• Incontinence
			• Flatulence
			• Oily spotting
			• Frequent bowel movements
			• Abdominal pain
			• Headache
				✓ Pregnancy and breastfeeding
				✓ Chronic malabsorption syndrome
				✓ Cholestasis
				✓ Oxalate nephrolithiasis
				• Rare severe liver injury
				• Cholelithiasis
				• Malabsorption of fat-soluble vitamins
				• Effects on other medications:
				  • Warfarin (enhance)
				  • Antiepileptics (decrease)
				  • Levothyroxine (decrease)
				  • Cyclosporine (decrease)
					Monitor for:
					• Cholelithiasis
					• Nephrolithiasis
					
					- Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose
					- Eating >30% kcal from fat results in greater GI side effects
					- FDA-approved for children ≥12 years old
					- Administer levothyroxine and orlistat 4 hours apart

Lorcaserin (Belviq®) 2012	Serotonin (5HT2c) receptor agonist BLOSSOM BLOOM **1 yr: 3.0%-3.6%** **2 yr: 3.1%**	10 mg PO BID	• Headache • Nausea • Dizziness • Fatigue • Xerostomia • Dry eye • Constipation • Diarrhea • Back pain • Nasopharyngitis • Hyperprolactinemia	✓ Pregnancy and breastfeeding ✓ Serotonin syndrome or neuroleptic malignant syndrome • Safety data lacking in patients who have depression • Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John's wort as may increase risk of developing serotonin syndrome • Uncontrolled mood disorder • Cognitive impairment • Avoid in patients with severe liver injury or renal insufficiency • Caution with patients with bradycardia, heart block, or heart failure • Unproven concern for potential cardiac valvulopathy • Leukopenia	**Monitor for:** • Symptoms of cardiac valve disease • Bradycardia • Serotonin syndrome • Neuroleptic malignant syndrome • Depression • Severe mood alteration, euphoria, dissociative state • Confusion/somnolence • Priapism • Leukopenia • Euphoria at high doses could predispose to abuse • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas
Phentermine/ Topiramate ER (Qsymia®) 2012	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose** **2 yr: 8.7% on high dose; 7.5% on treatment dose**	**Starting dose:** 3.75/23 mg PO QD for 2 weeks **Recommended dose:** 7.5/46 mg PO QD **Escalation dose:** 11.25/69 mg PO QD **Maximum dose:** 15/92 mg PO QD	• Headache • Paresthesia • Insomnia • Decreased bicarbonate • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia	✓ Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) • Tachyarrhythmias • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic and renal impairment • Concern for abuse potential • Combined use with alcohol or depressant drugs can worsen cognitive impairment	**Monitor for:** • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check ßHCG before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments
Naltrexone ER/ Bupropion ER (Contrave®) 2014	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 yr: 4.2%-5.2%**	**Titrate dose:** **Week 1:** 1 tab (8/90 mg) PO QAM **Week 2:** 1 tab (8/90 mg) PO BID **Week 3:** 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS **Week 4:** 2 tabs (total 16/180 mg) PO QHS	• Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhea • Dizziness • Anxiety • Xerostomia	✓ Pregnancy and breastfeeding ✓ Uncontrolled hypertension ✓ Seizure disorder ✓ Anorexia nervosa ✓ Bulimia nervosa ✓ Severe depression ✓ Drug or alcohol withdrawal ✓ Concomitant MAOI (within 14 days) ✓ Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver and kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalized anxiety disorder • Bipolar disorder • Safety data lacking in patients who have depression • Seizures (bupropion lowers seizure threshold)	**Monitor for:** • Increased heart rate and blood pressure • Worsening depression and suicidal ideation • Worsening of migraines • Liver injury (naltrexone) • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between discontinuation) - Dose adjustment for patients with renal and hepatic impairment - Avoid taking medication with a high-fat meal - Can cause false positive urine test for amphetamine - Bupropion inhibits CYP2D6
Liraglutide 3 mg (Saxenda®) 2014	GLP-1 analog SCALE Obesity & Prediabetes **1 yr: 5.6%**	**Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):** 0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and Cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Abbreviations: BID = twice daily; DA = dopamine; FDA = US Food and Drug Administration; GI = gastrointestinal; HCTZ = hydrochlorothiazide; MAOI = monoxidase inhibitor; MEN2 = multiple endocrine neoplasia type 2; NE = norepinephrine; OTC = over-the-counter medication; % TBWL = percent total body weight loss from baseline over that observed in the placebo group; PO = oral; QAM = every morning; QD = daily; QHS = every bedtime; SC = subcutaneous; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TID = 3 times a day; T2DM = type 2 diabetes mellitus.

FDA indication for all medications: BMI >30 kg/m² or BMI ≥27kg/m² with significant comorbidity.

After 3 to 4 months of treatment with antiobesity medication:

- **For naltrexone ER/bupropion ER and lorcaserin:**
  If the patient has not lost at least 5% of their baseline body weight at 12 weeks on the maintenance dose, the medication should be discontinued.
- **For phentermine/topiramate ER:**
  Continue medication if the patient has lost >5% body weight after 12 weeks on recommended dose (7.5 mg/42 mg); if the patient has not lost at least 3% of body weight after being on the recommended dose for 12 weeks then the medication should be discontinued, or the patient can be transitioned to maximum dose (15 mg/92 mg); if patient has not lost at least 5% after 12 additional weeks on the maximum dose, the medication should be discontinued.
- **For liraglutide 3 mg:**
  If the patient has not lost at least 4% of body weight 16 weeks after initiation, the medication should be discontinued.

References:
1–4 and package inserts for each medication

1. Wyatt HR. Update on treatment strategies for obesity. *J Clin Endocrinol Metab*. 2013;98(4):1299-1306.
2. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20(9):977-989.
3. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.
4. Fujioka K. Current and emerging medications for overweight and obesity in people with comorbidities. *Diabetes Obes Metab*. 2015;17(11):1021-1032.

Phentermine

Mechanism of Action

- Sympathomimetic amine anorectic

Dosing

- 15, 30, or 37.5 mg once daily before breakfast or 1-2 hours after breakfast

Indications

- Short-term adjunct to diet and exercise in patients with
  - Treatment duration ≤12 weeks
  - BMI ≥30 kg/m^2
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Hyperlipidemia
- DEA Schedule IV Controlled Substance

See prescribing information for specific instructions

DEA = Drug Enforcement Agency; T2D = type 2 diabetes.

Adipex-P prescribing information. Sellersville, PA: Teva Pharmaceuticals.; 2013.

Phentermine: Summary of Warnings and Contraindications

Contraindications

- Cardiovascular disease
- MAO inhibitor use
- Hyperthyroidism
- Glaucoma
- Agitation
- History of drug abuse
- Pregnant or nursing

Adverse Effects

- Dry mouth
- Restlessness
- Insomnia
- Increase in pulse
- Increase in blood pressure

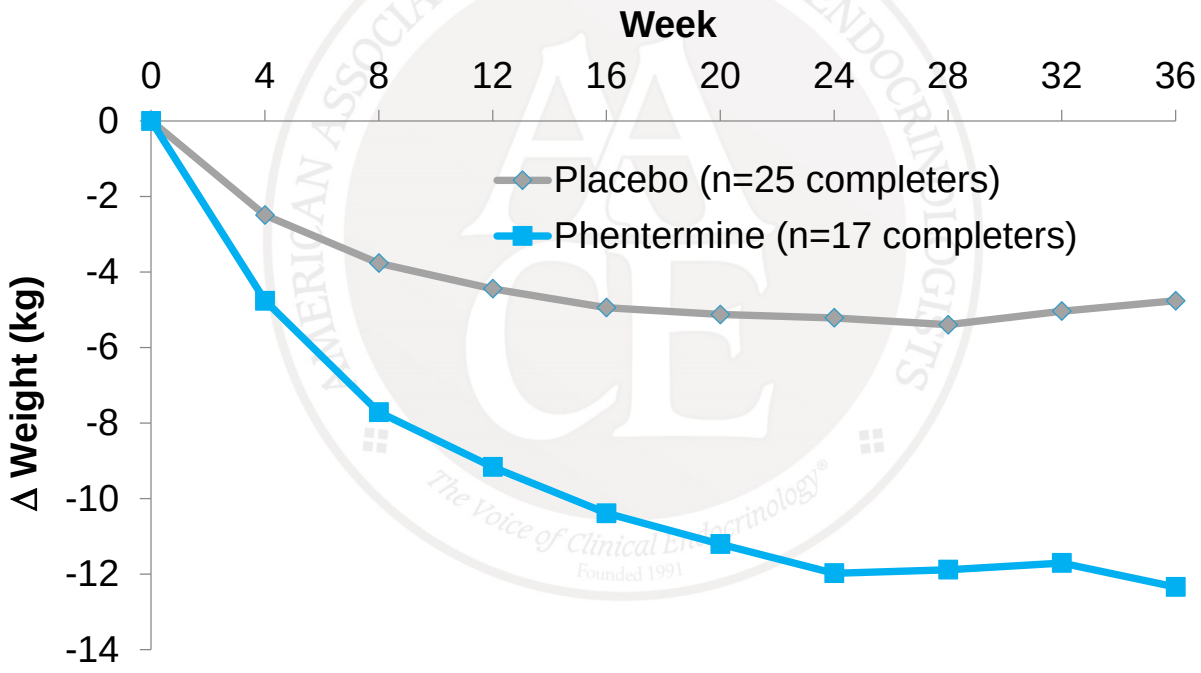
Warnings

- Indicated for ≤12 weeks treatment duration
- Coadministration with other weight loss drugs, including OTC products, and SSRIs not recommended
- Primary pulmonary hypertension
- Valvular heart disease
- Drug tolerance and abuse/dependence risk
- Impaired use of machinery/vehicles
- Adverse drug reaction when used with alcohol
- Increased blood pressure
- Possible need for dose reduction of insulin or oral hypoglycemic agents in patients with diabetes

MAO = monoamine oxidase; OTC = over the counter; SSRI = serotonin reuptake inhibitor.

Adipex-P prescribing information. Sellersville, PA: Teva Pharmaceuticals.; 2013.

Phentermine: Clinical Efficacy



Munro JF, et al. *Br Med J*. 1968;1:352-354.

Phentermine Adverse Events

Cardiovascular	Primary pulmonary hypertension and/or regurgitant valvular disease, palpitation, tachycardia, BP elevations, ischemic events
Central nervous system	Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis
Gastrointestinal	Dryness of the mouth, unpleasant taste, diarrhea, constipation
Allergic	Urticaria
Endocrine	Impotence, changes in libido

Adipex-P prescribing information. Sellersville, PA: Teva Pharmaceuticals.; 2013.

Orlistat

Mechanism of Action

- Reversible gastrointestinal lipase inhibitor

Dosing

- 120 mg thrice daily with each main meal containing fat, taken during or up to 1 hour after eating

Indications

- Weight loss and weight maintenance in conjunction with a reduced calorie diet
  - BMI ≥30 kg/m^2
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

See prescribing information for specific instructions

T2D = type 2 diabetes.

Xenical prescribing information. South San Francisco, CA: Genentech USA, Inc.; 2013.

Orlistat: Summary of Warnings and Contraindications

Contraindications

- Pregnancy
- Chronic malabsorption syndrome
- Cholestasis

Adverse Effects

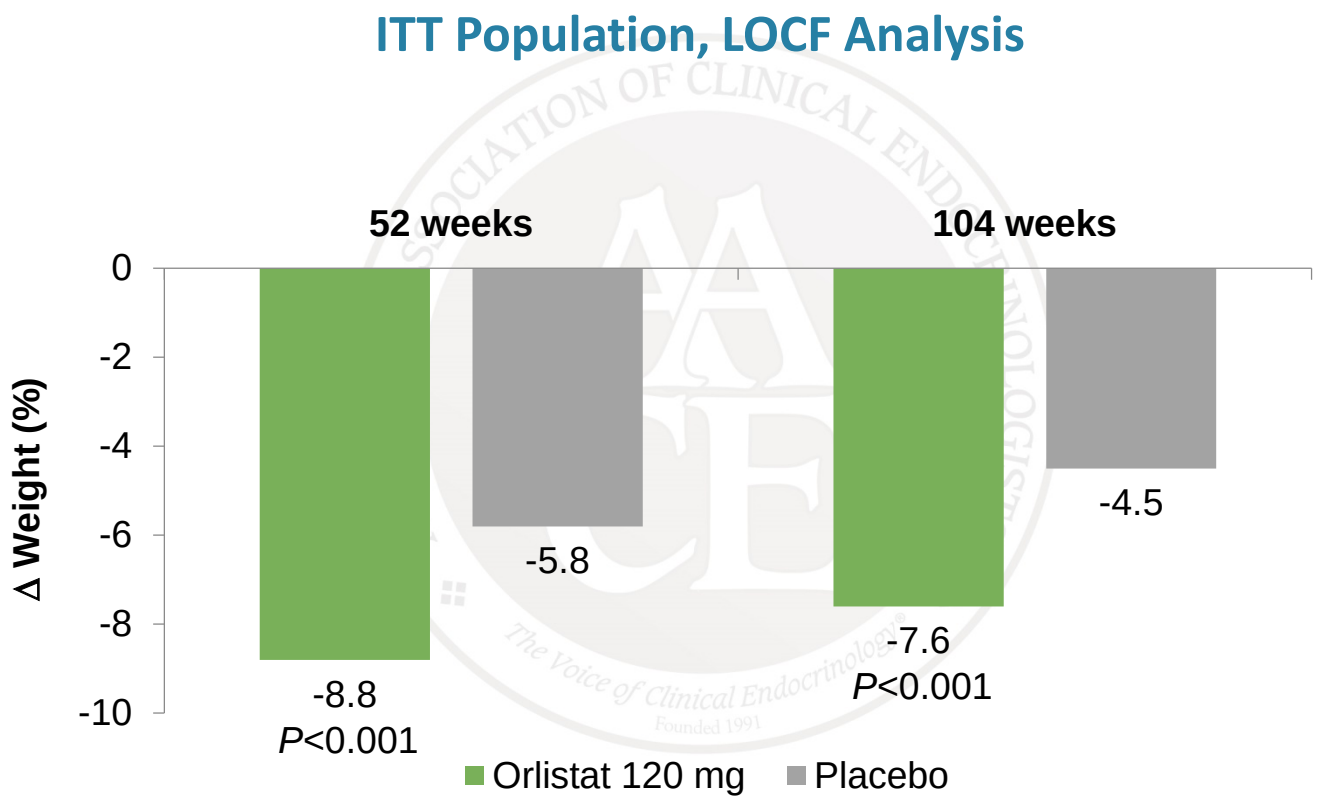
- Oily spotting
- Flatus with discharge
- Fecal urgency and incontinence

Warnings

- Decreased cyclosporine exposure
- Multivitamin supplement containing fat-soluble vitamins recommended to ensure adequate nutrition
- Hepatocellular necrosis, acute hepatic failure
- Increased urinary oxalate; monitor renal function
- Cholelithiasis
- Increased GI events with high-fat diets (fat >30% of total daily calories)

Xenical prescribing information. South San Francisco, CA: Genentech USA, Inc.; 2013.

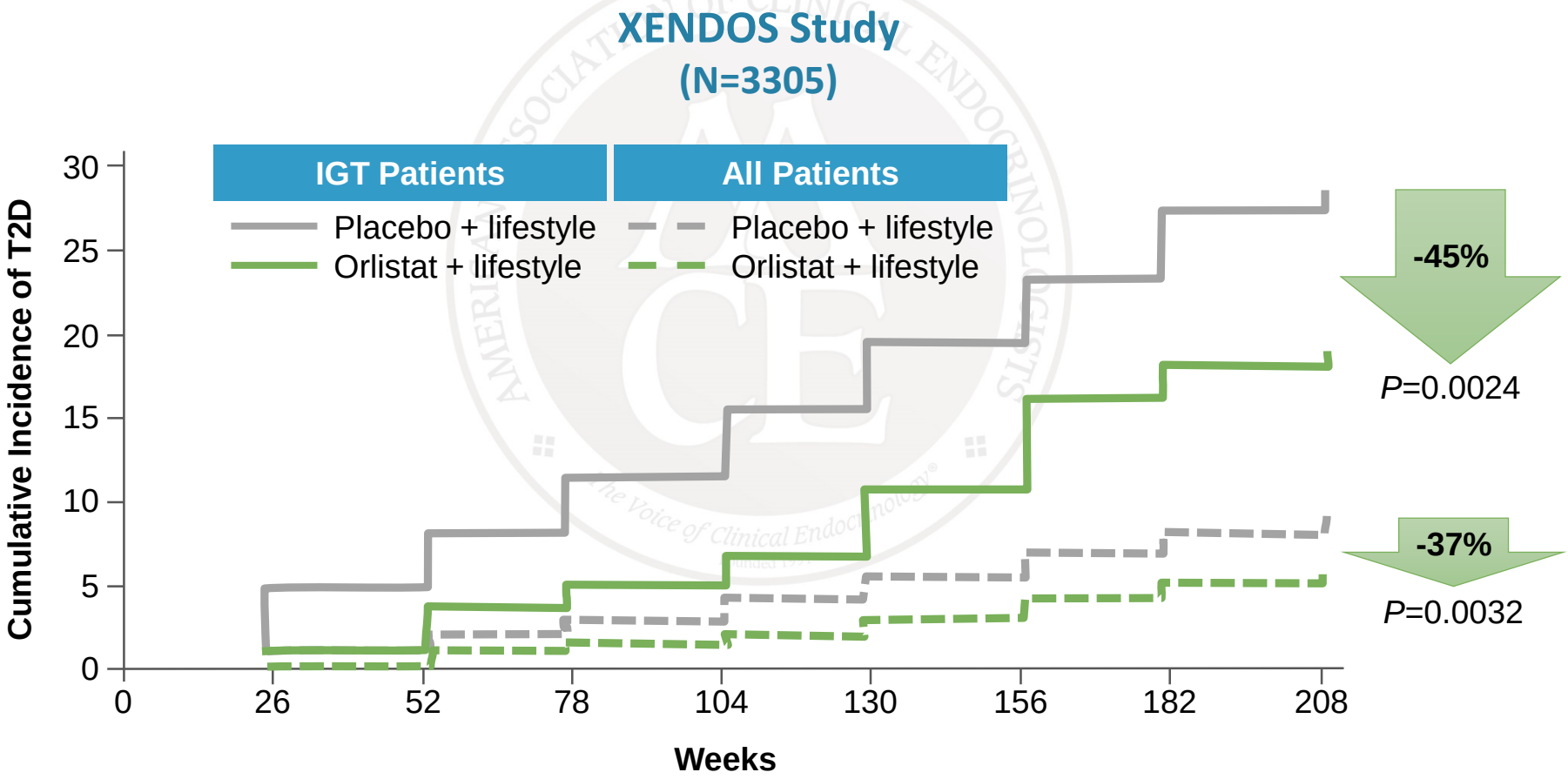
Orlistat : Clinical Efficacy



ITT = intent to treat; LOCF = last observation carried forward; TID, three times daily.

Davidson MH, et al. *JAMA*. 1999;281:235-242.

Effect of Orlistat on Incidence of Diabetes in Obese Patients with Normal and Impaired Glucose Tolerance



IGT = impaired glucose tolerance; XENDOS = Xenical in the prevention of Diabetes in Obese Subjects.

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

Orlistat Adverse Events

Event occurring in ≥5% of patients and occurring at least twice as often with orlistat as placebo, %	Year 1		Year 2	
	Orlistat 120 mg TID (N=1913)	Placebo (N=1466)	Orlistat 120 mg TID (N=613)	Placebo (N=524)
Oily spotting	26.6	1.3	4.4	0.2
Flatus with discharge	23.9	1.4	2.1	0.2
Fecal urgency	22.1	6.7	2.8	1.7
Fatty/oily stool	20.0	2.9	5.5	0.6
Oily evacuation	11.9	0.8	2.3	0.2
Increased defecation	10.8	4.1	2.6	0.8
Fecal incontinence	7.7	0.9	1.8	0.2

TID = three times daily.

Xenical prescribing information. South San Francisco, CA: Genentech USA, Inc.; 2013.

Lorcaserin

Mechanism of Action

- Specific 5-HT2C (serotonin) receptor agonist

Dosing

- 10 mg twice daily
- Discontinue if 5% weight loss is not achieved within 12 weeks

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m^2
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia
    - Other
- Schedule IV Controlled Substance

See prescribing information for specific instructions

DEA = Drug Enforcement Agency; T2D = type 2 diabetes.

Belviq prescribing information. Woodcliff Lake, NJ: Eisai Inc.; 2012.

Lorcaserin: Summary of Warnings and Contraindications

Contraindications

- Pregnancy

Adverse Effects

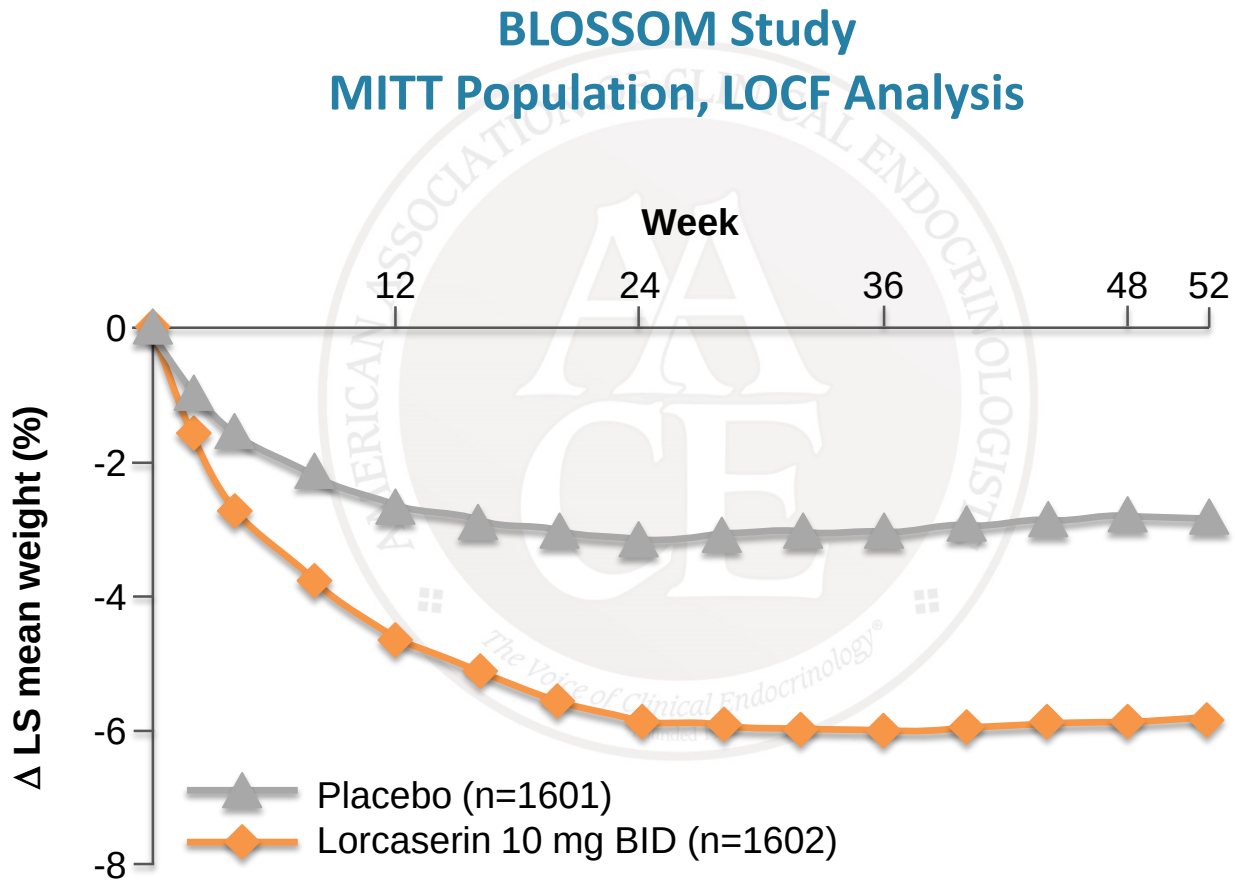
- Headache
- Dizziness
- Nausea

Warnings

- Safety of coadministration with other serotonergic or antidopaminergic agents has not been established
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders: euphoria, dissociation, suicidal thoughts, depression
- Priapism
- Increased risk of hypoglycemia with antidiabetic medications
- Leukopenia
- Prolactin elevations

Belviq prescribing information. Woodcliff Lake, NJ: Eisai Inc.; 2012.

Effect of Lorcaserin on Body Weight in Obese Adults Over 1 Year

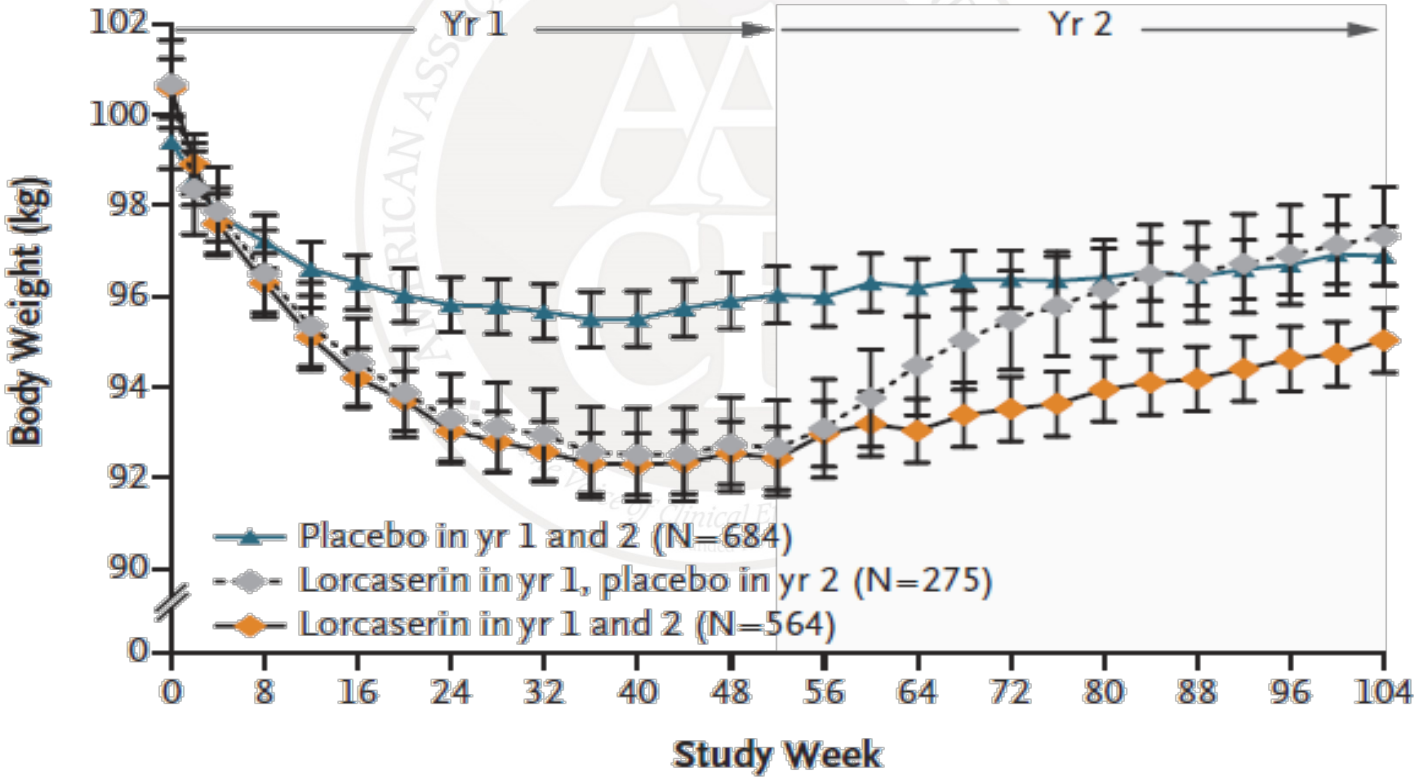


BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LOCF = last observation carried forward; LS = least squares; MITT = modified intent to treat.

Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077.

Effect of Lorcaserin on Body Weight in Obese Adults Over 2 Years

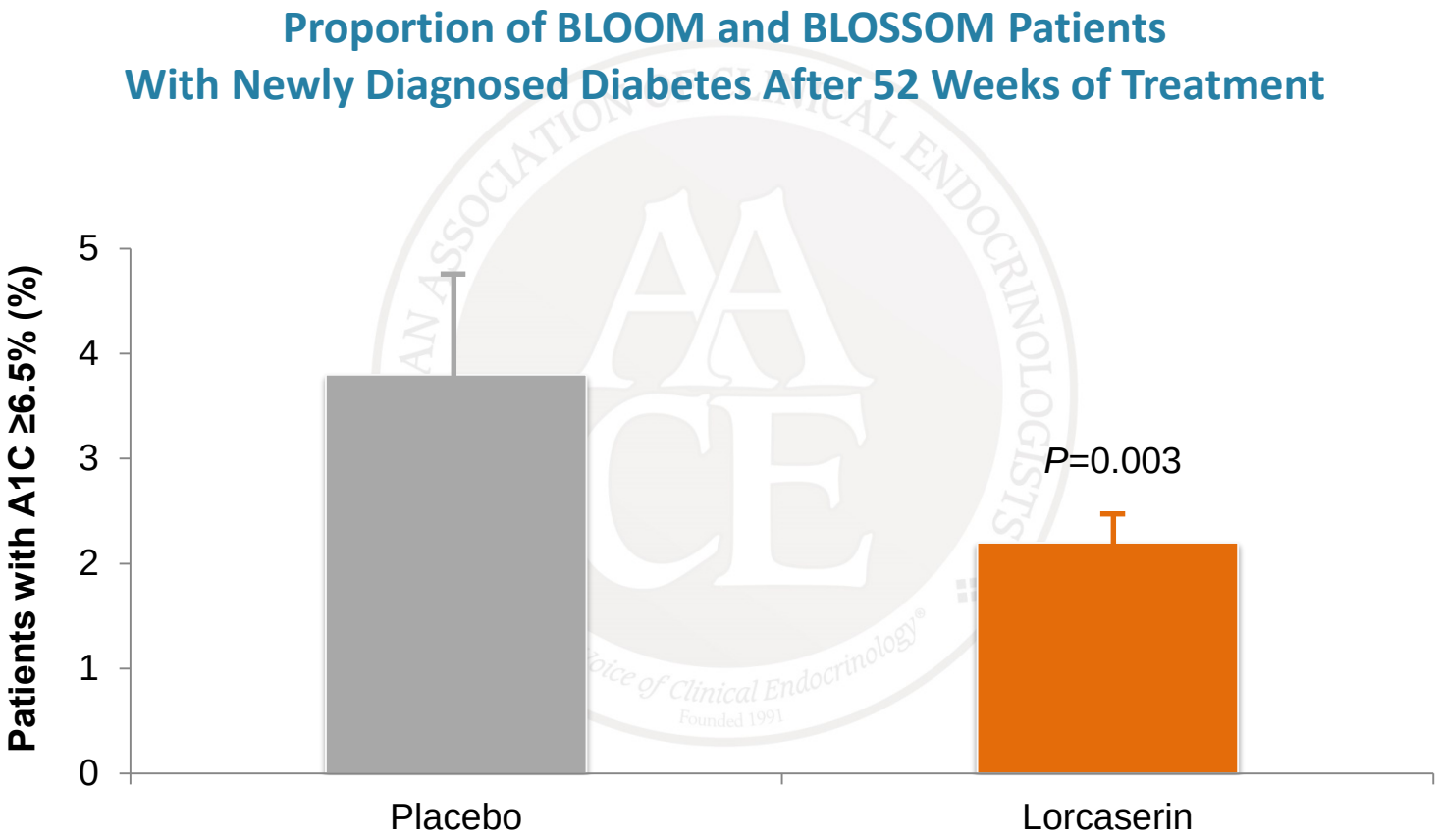
BLOOM Study
ITT Population; LOCF Analysis



BLOOM = Behavioral Modification and Lorcaserin for Overweight and Obesity Management; ITT = modified intent to treat; LOCF = last observation carried forward..

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

Effect of Lorcaserin on Progression to Type 2 Diabetes



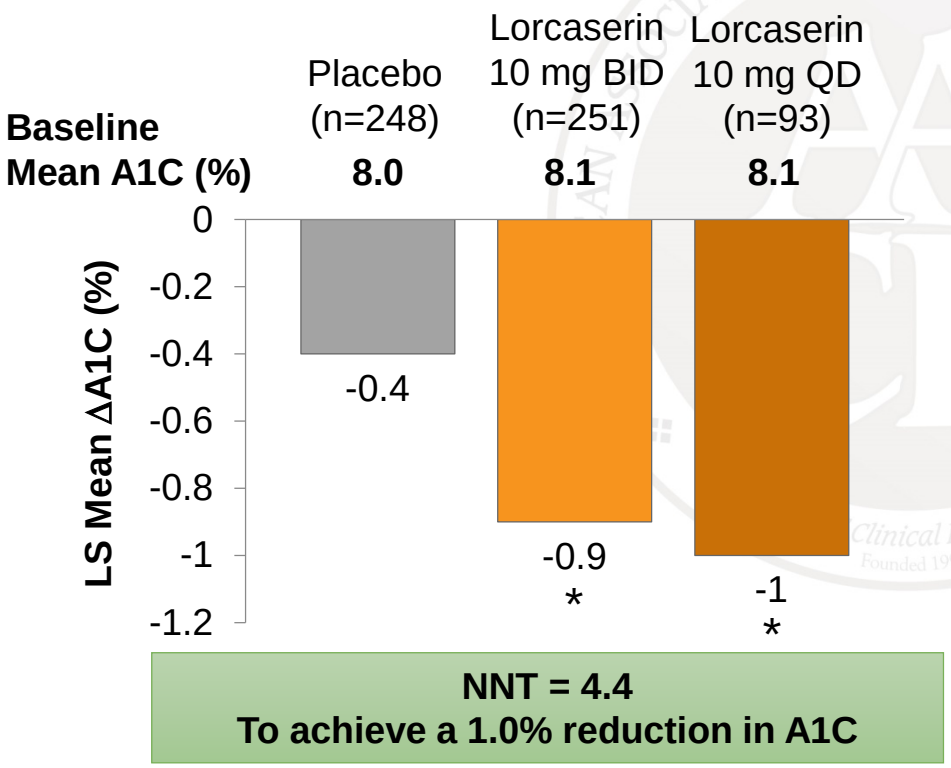
BLOOM = Behavioral Modification and Lorcaserin for Overweight and Obesity Management; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management.

Lorcaserin hydrochloride briefing document for FDA Advisory Committee. Woodcliff Lake, NJ: Eisai Inc.; 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303200.pdf.

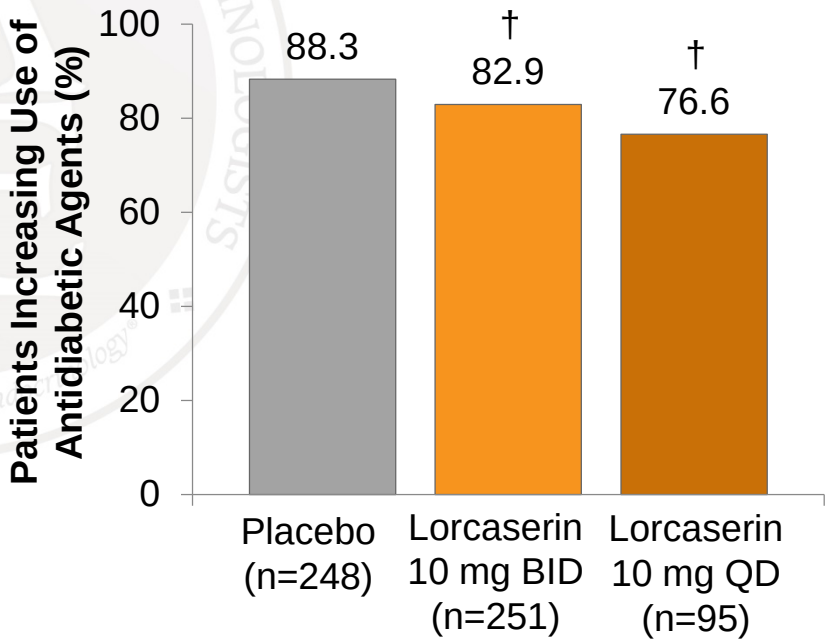
Effect of Lorcaserin on Glycemia in Type 2 Diabetes

BLOOM-DM Study

Change in A1C



Change in Diabetes Medications



*P<0.001 vs placebo. †P=0.087 vs placebo.

BLOOM-DM = Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.

O'Neil PM, et al. *Obesity*. 2012;20:1426-1436.

Handelsman Y, et al. Presented at The Obesity Society, November 2-7, 2014. Boston, MA. Abstr. # T-2576-P.

Effect of Lorcaserin on Cardiometabolic Risk Markers

BLOOM Study

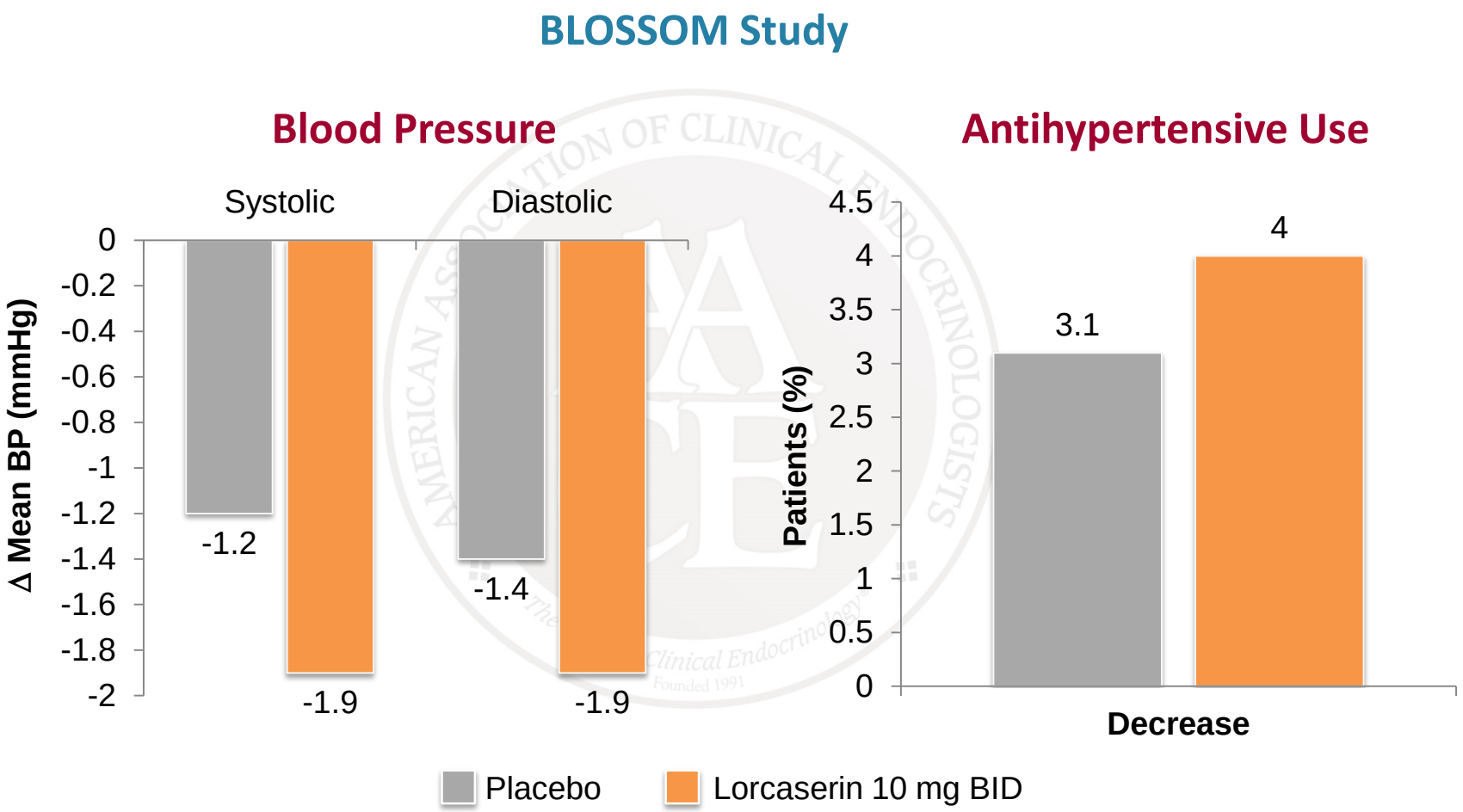
Risk Factors (Mean % Weight Loss)	Lorcaserin 10 mg (5.8%)		P value*
Systolic BP, mmHg	↓	-1.4	0.04
Diastolic BP, mmHg	↓	-1.1	0.01
Triglycerides, %	↓	-6.15	<0.001
Total cholesterol, %	↓	-0.90	0.001
LDL-C, %	↑	2.87	0.049
HDL-C, %	↑	0.05	NS
hsCRP, mg/L	↓	-1.19	<0.001
Fibrinogen, mg/dL	↓	-21.5	0.001

**P* values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

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

Effect of Lorcaserin on Hypertension

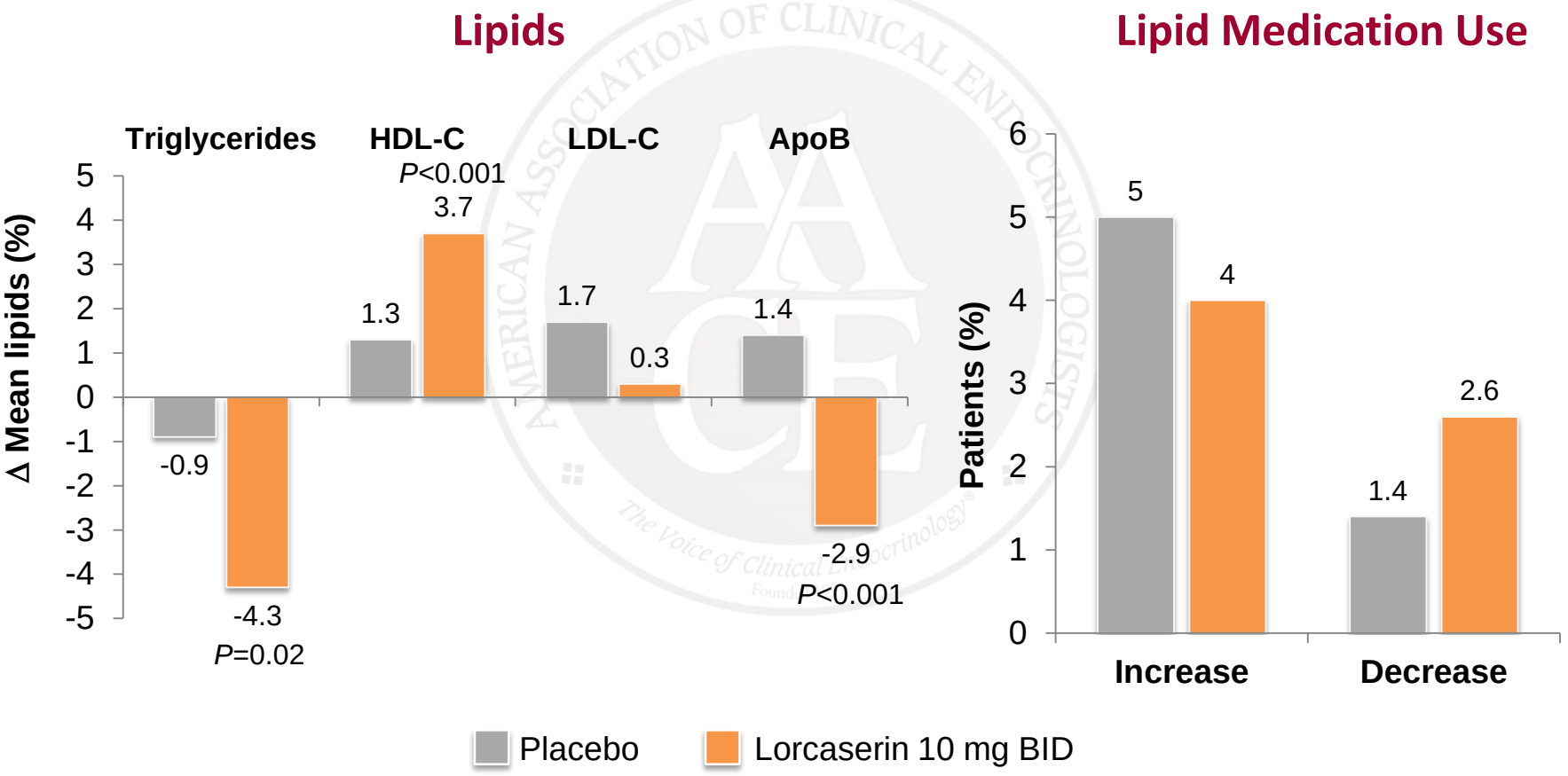


BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LS = least squares.

Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077.

Effect of Lorcaserin on Dyslipidemia

BLOSSOM Study



BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LS = least squares.

Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077.

Lorcaserin Adverse Events

Event occurring in ≥5% of patients and more frequently than with placebo, %	Lorcaserin 10 mg BID (N=3195)	Placebo (N=3185)
Headache	**16.8**	**10.1**
Upper respiratory tract infection	13.7	12.3
Nasopharyngitis	13.0	12.0
Dizziness	**8.5**	**3.8**
Nausea	**8.3**	**5.3**
Fatigue	**7.2**	**3.6**
Urinary tract infection	6.5	5.4
Diarrhea	6.5	5.6
Back pain	6.3	5.6
Constipation	**5.8**	**3.9**
Dry mouth	**5.3**	**2.3**

Belviq (lorcaserin HCl) prescribing information. Woodcliff Lake, NJ: Eisai Inc.; 2012.

Phentermine/Topiramate ER

Mechanism of Action

- Central noradrenergic effects
  - Phentermine: immediate-release sympathomimetic—affects appetite
  - Topiramate ER: delayed-release gabanergic—affects satiety

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m^2
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia

Dosing

- Once daily in morning
  - Starting dose: phentermine 3.75/topiramate ER 23 mg for 14 days
  - Usual dose: 7.5/46 mg
  - Maximum dose: 15/92 mg
- If <3% weight loss after 12 weeks on usual dose, either discontinue medication or advance to maximum dose (transition dose phentermine 11.25 mg/topiramate ER 69 mg for 2 weeks)
- If <5% weight loss after 12 weeks on maximum dose, then discontinue the medication (to discontinue take every other day for one week)
- Schedule IV Controlled Substance

See prescribing information for specific instructions

T2D = type 2 diabetes.

Qsymia prescribing information. Mountain View, CA: Vivus, Inc.; 2012.

Phentermine/Topiramate ER: Summary of Warnings and Contraindications

Contraindications

- Pregnancy
- Glaucoma
- Hyperthyroidism
- Treatment with monoamine oxidase inhibitors (MAOIs)

Adverse Effects

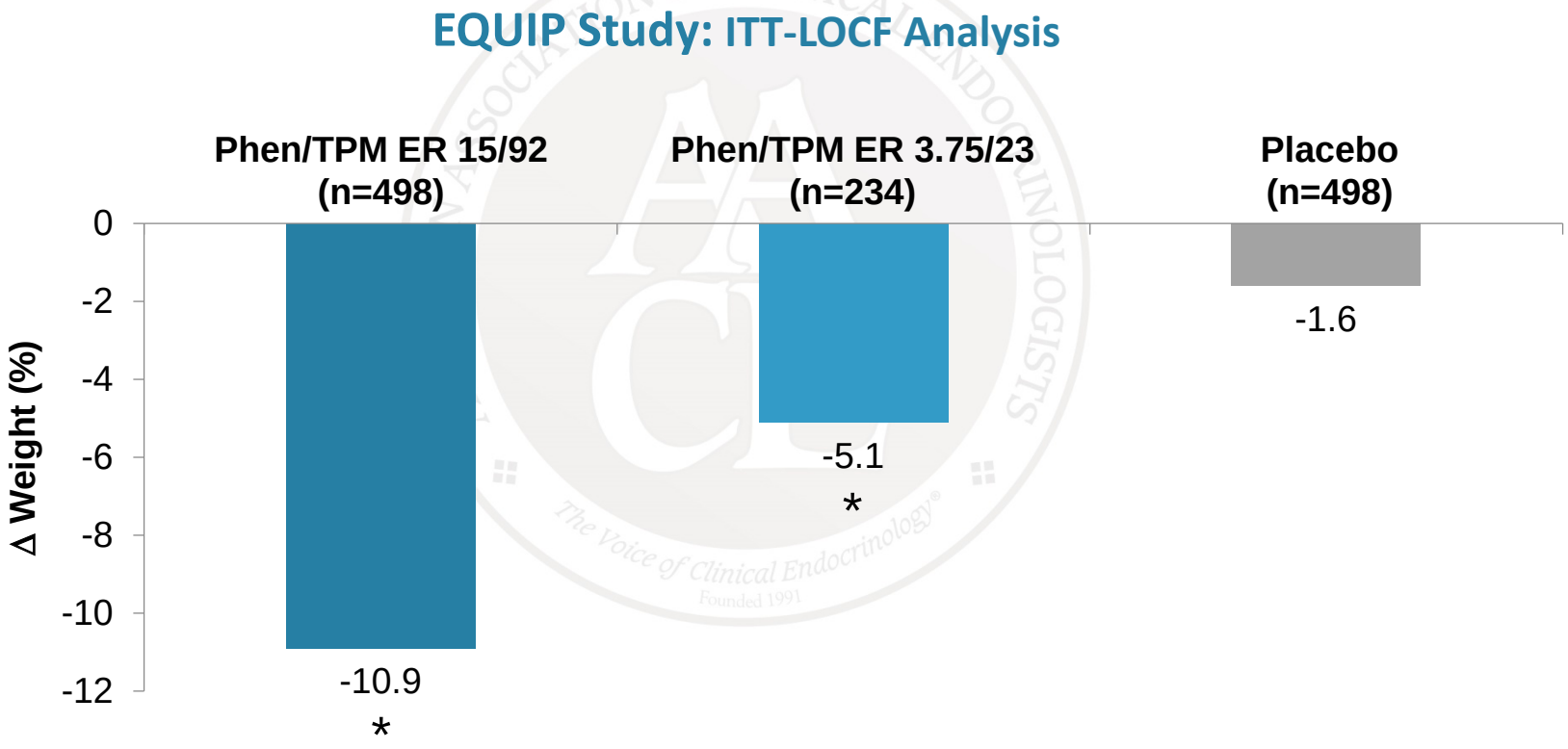
- Dry mouth
- Tingling
- Constipation
- Altered taste sensation
- Upper respiratory infection
- Insomnia

Warnings

- Fetal toxicity
- Increased heart rate
- Suicide and mood and sleep disorders
- Acute myopia and glaucoma
- Metabolic acidosis
- Creatinine elevations
- Hypoglycemia with concomitant antidiabetic therapy

Qsymia prescribing information. Mountain View, CA: Vivus, Inc.; 2012.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 1 Year

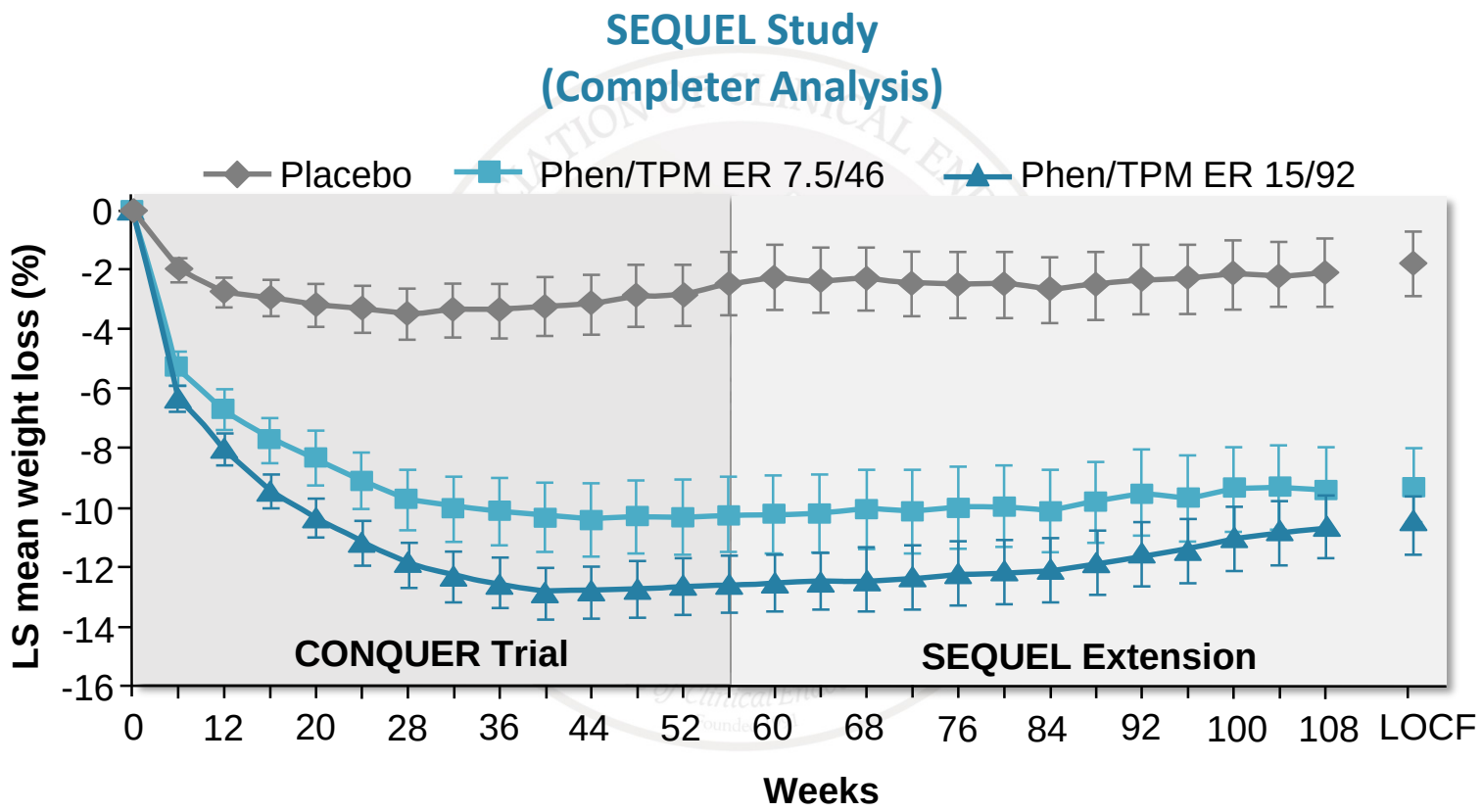


*P<0.0001 vs placebo.

ITT = intent to treat; LOCF = last observation carried forward; Phen/TPM ER = phentermine/topiramate extended release.

Allison DB, et al. *Obesity (Silver Spring).* 2012;20:330-342.

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



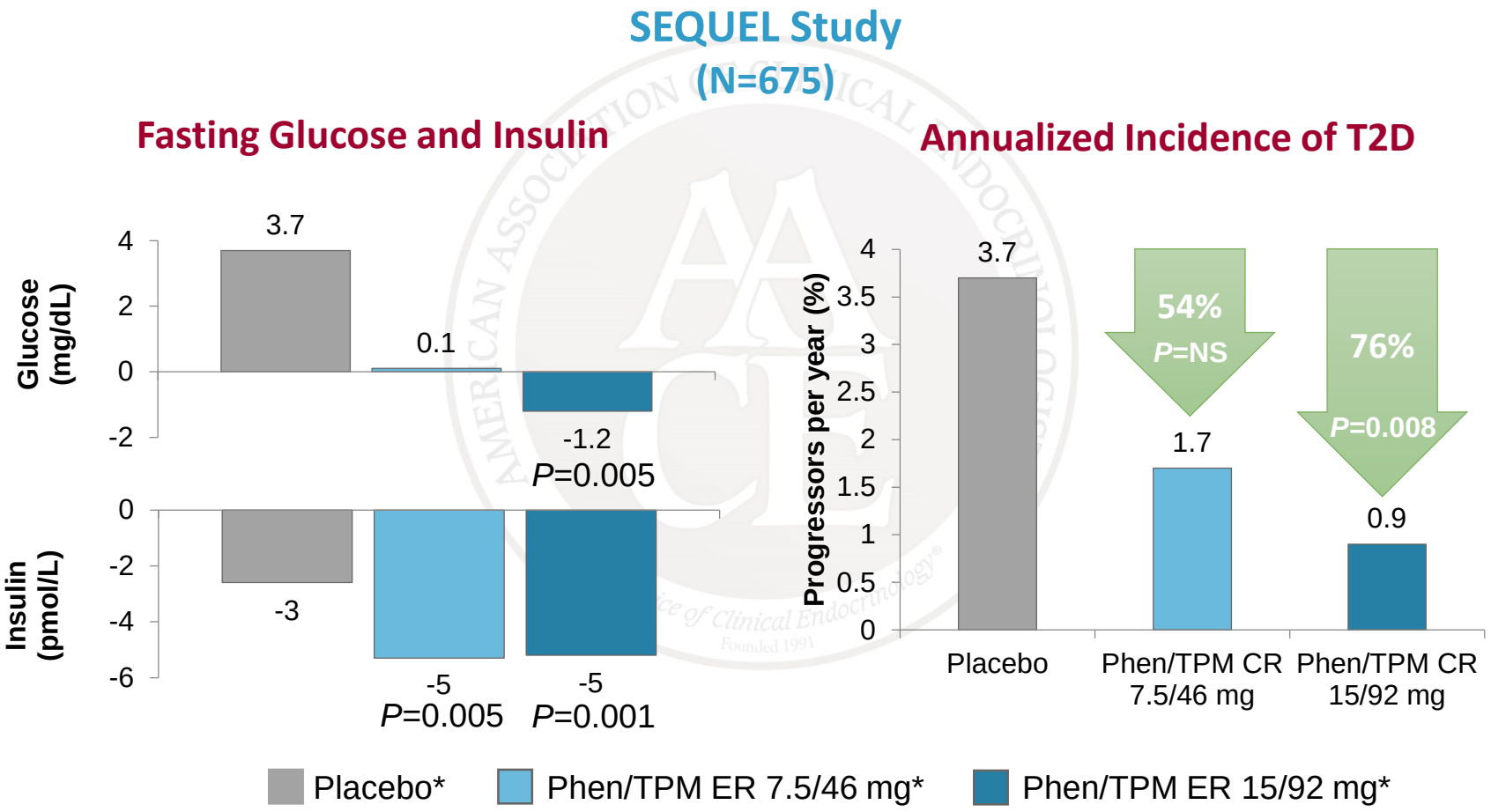
Placebo n:	227	227	227	208	197	227
Phen/TPM 7.5/46 n:	153	152	153	137	129	153
Phen/TPM 15/92 n:	295	295	295	268	248	295

Data are shown with mean (95% CI).

Phen/TPM ER = phentermine/topiramate extended release.

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

Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

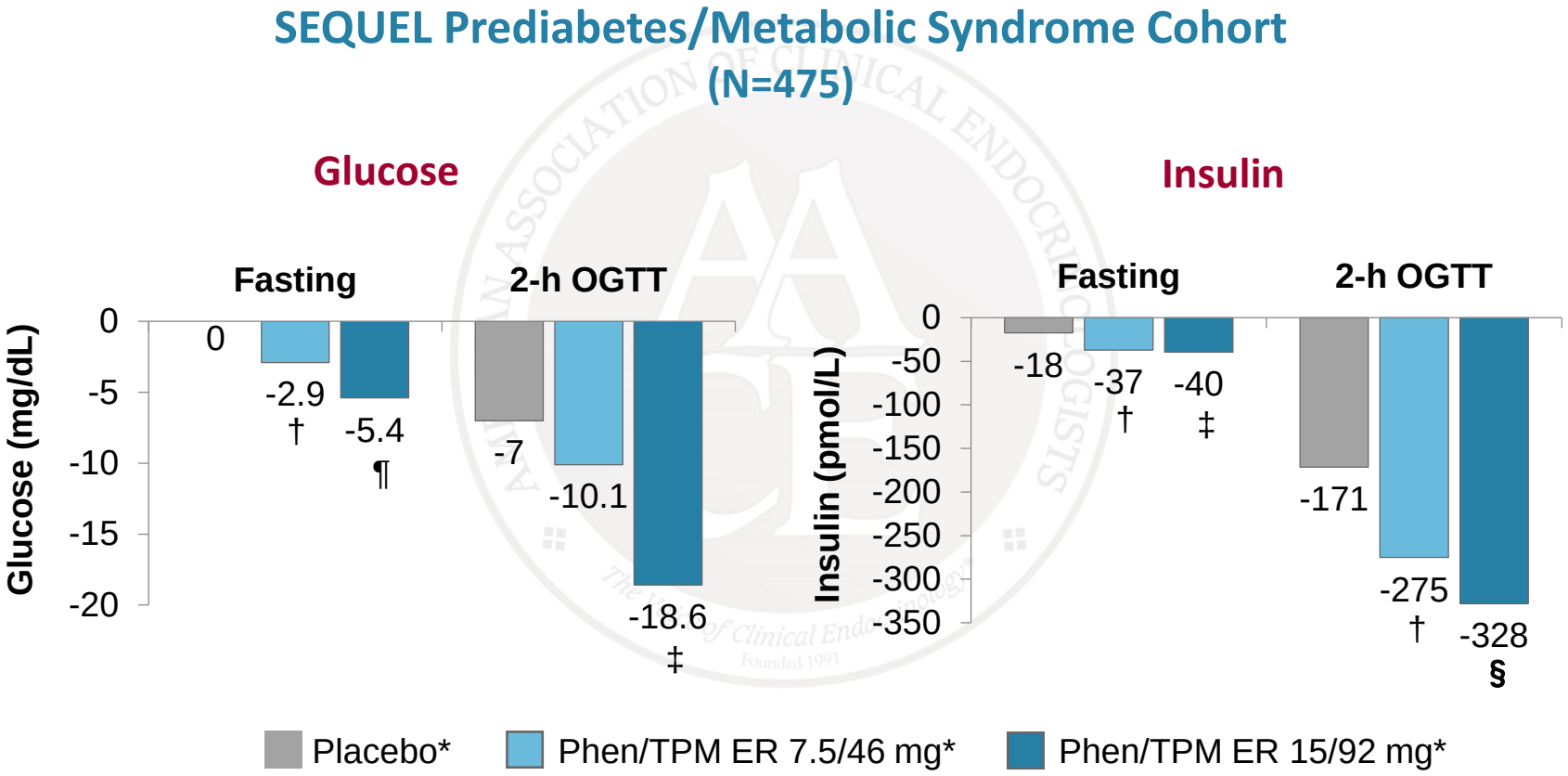


*All groups had lifestyle intervention.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

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

Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D



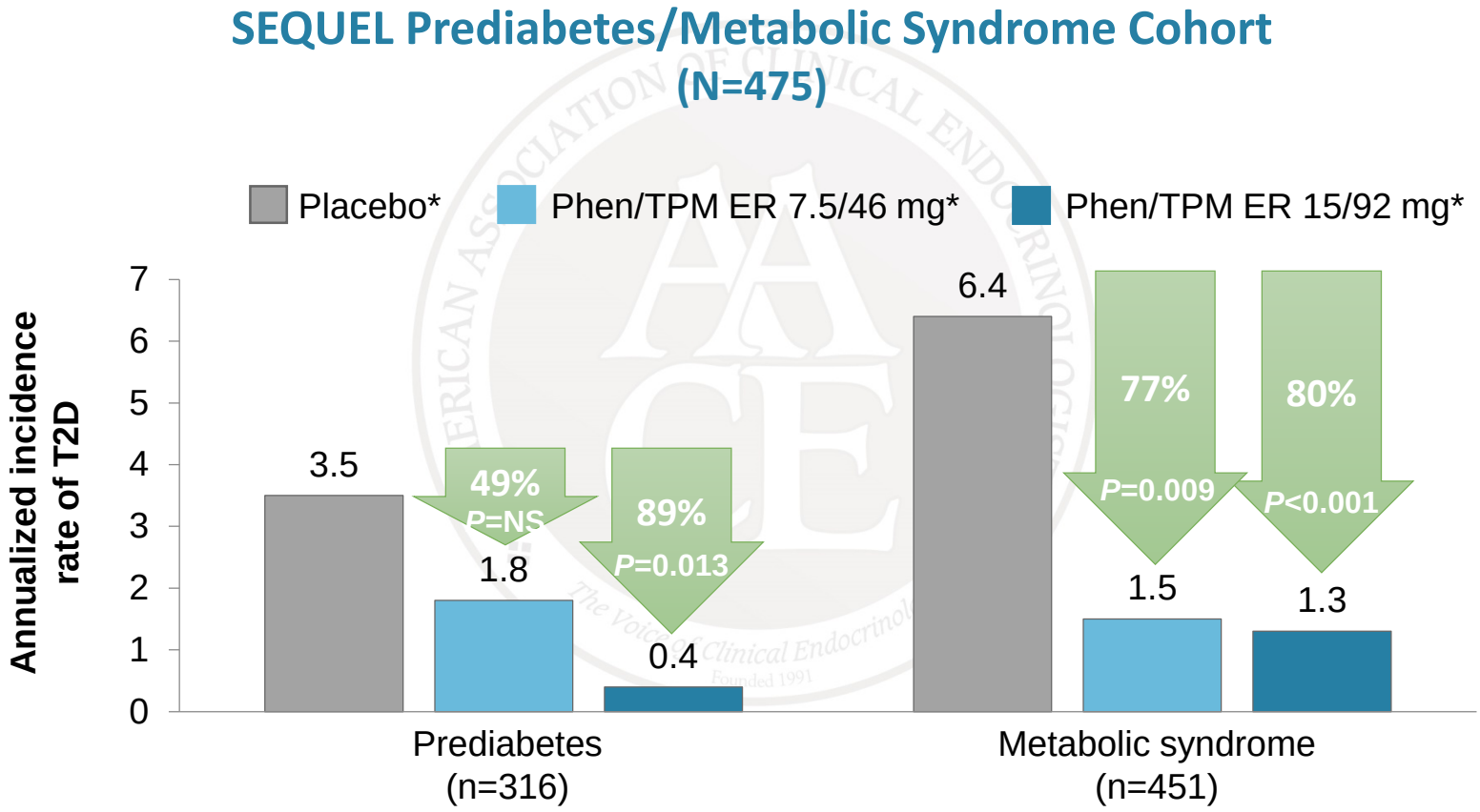
*All groups had lifestyle intervention.

†*P*<0.05. ‡*P*<0.01. §*P*<0.001. ¶*P*<0.0001.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

Effects of Phentermine/Topiramate ER in Patients at High Risk of Developing T2D

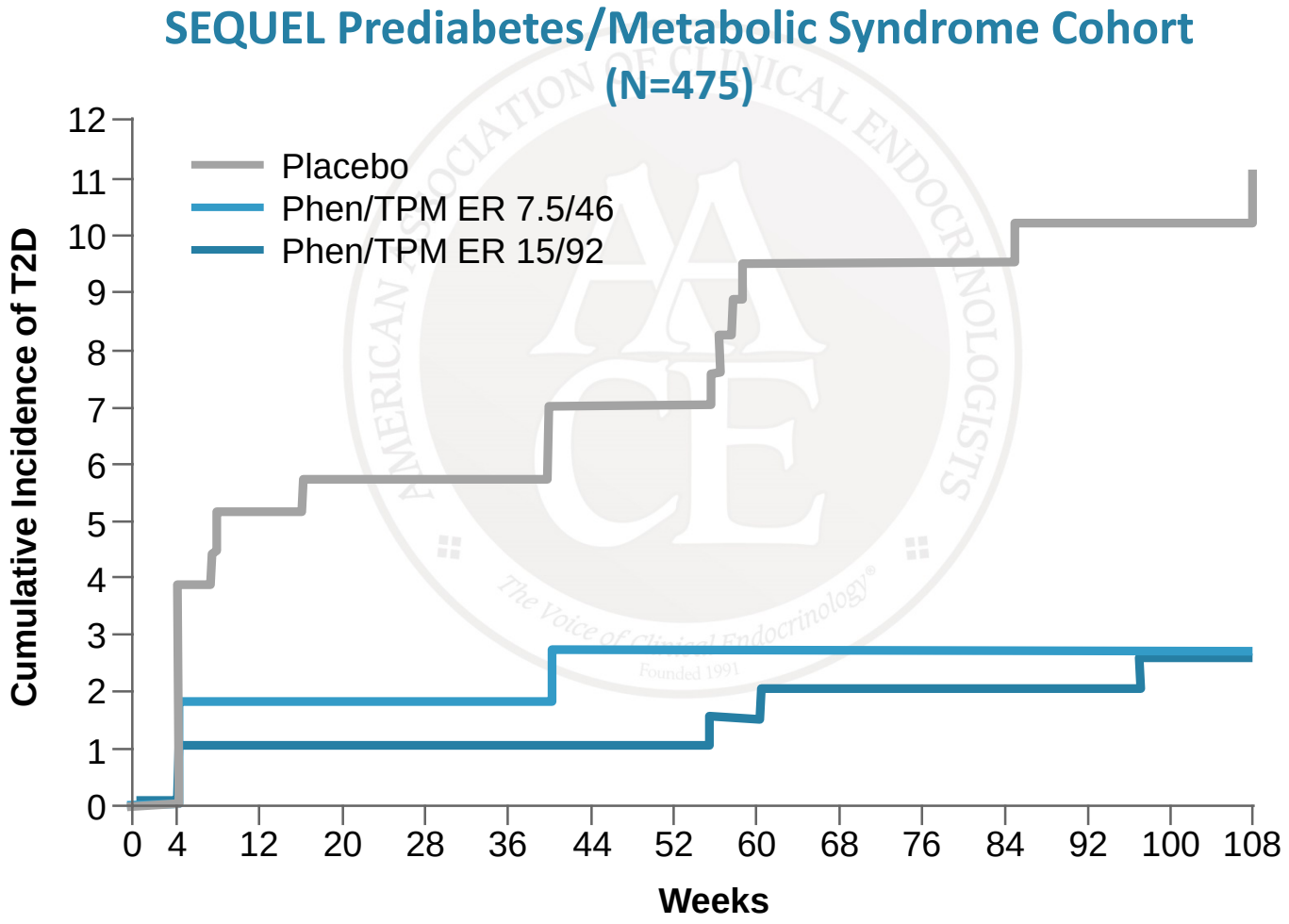


*All groups had lifestyle intervention.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

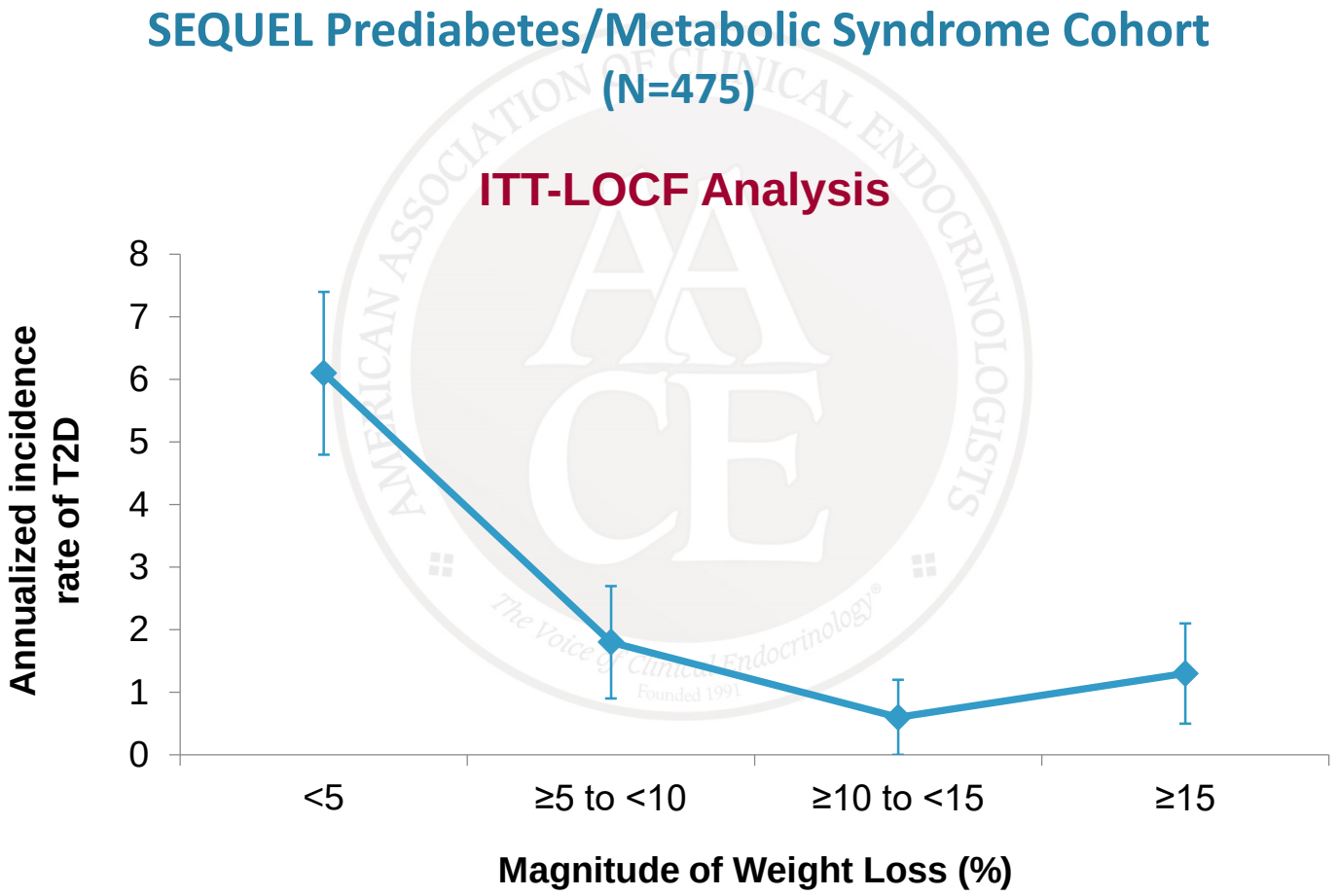
Effect of Phentermine/Topiramate ER on Incidence of Diabetes



Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

Relationship Between Weight Loss and Prevention of Type 2 Diabetes



ITT, intent to treat; LOCF, last observation carried forward.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

CONQUER Study

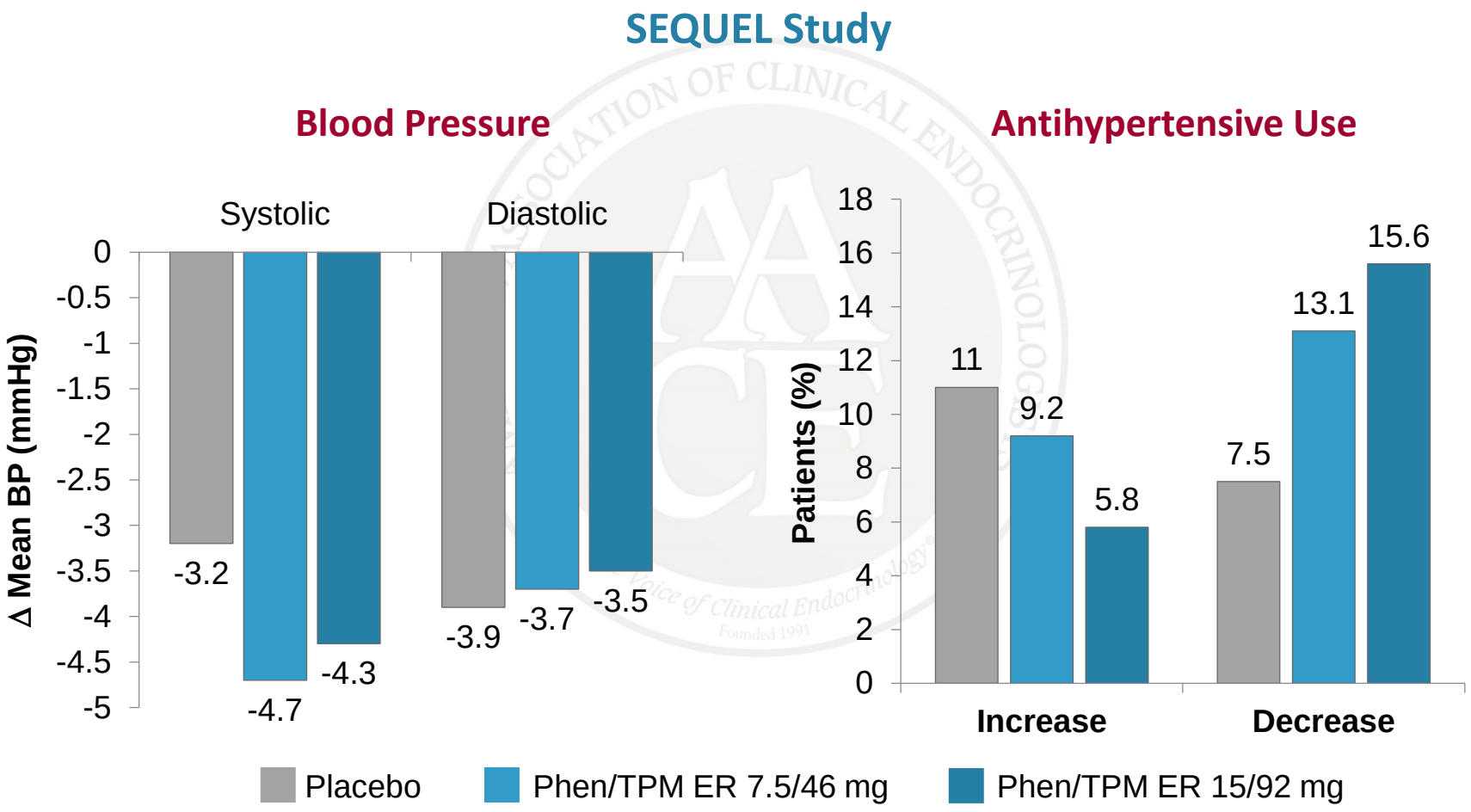
Risk Factors (Mean % Weight Loss)	Phentermine/ Topiramate ER 7.5/46 mg (8.4%)		P value*	Phentermine/ Topiramate ER 15/92 mg (10.4%)		P value*
Systolic BP, mmHg	↓	-4.7	0.0008	↓	-5.6	<0.0001
Diastolic BP, mmHg	↓	-3.4	NS	↓	-3.8	0.0031
Triglycerides, %	↓	-8.6	<0.0001	↓	-10.6	<0.0001
Total cholesterol, %	↓	-4.9	0.0345	↓	-6.3	<0.0001
LDL-C, %	↓	-3.7	NS	↓	-6.9	0.0069
HDL-C, %	↑	5.2	<0.0001	↑	6.8	<0.0001
hsCRP, mg/L	↓	-2.49	<0.0001	↓	-2.49	<0.0001
Adiponectin, µg/mL	↑	1.40	<0.0001	↑	2.08	<0.0001

*_P_ values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

Gadde KM, et al. *Lancet*. 2011;377:1341-1352.

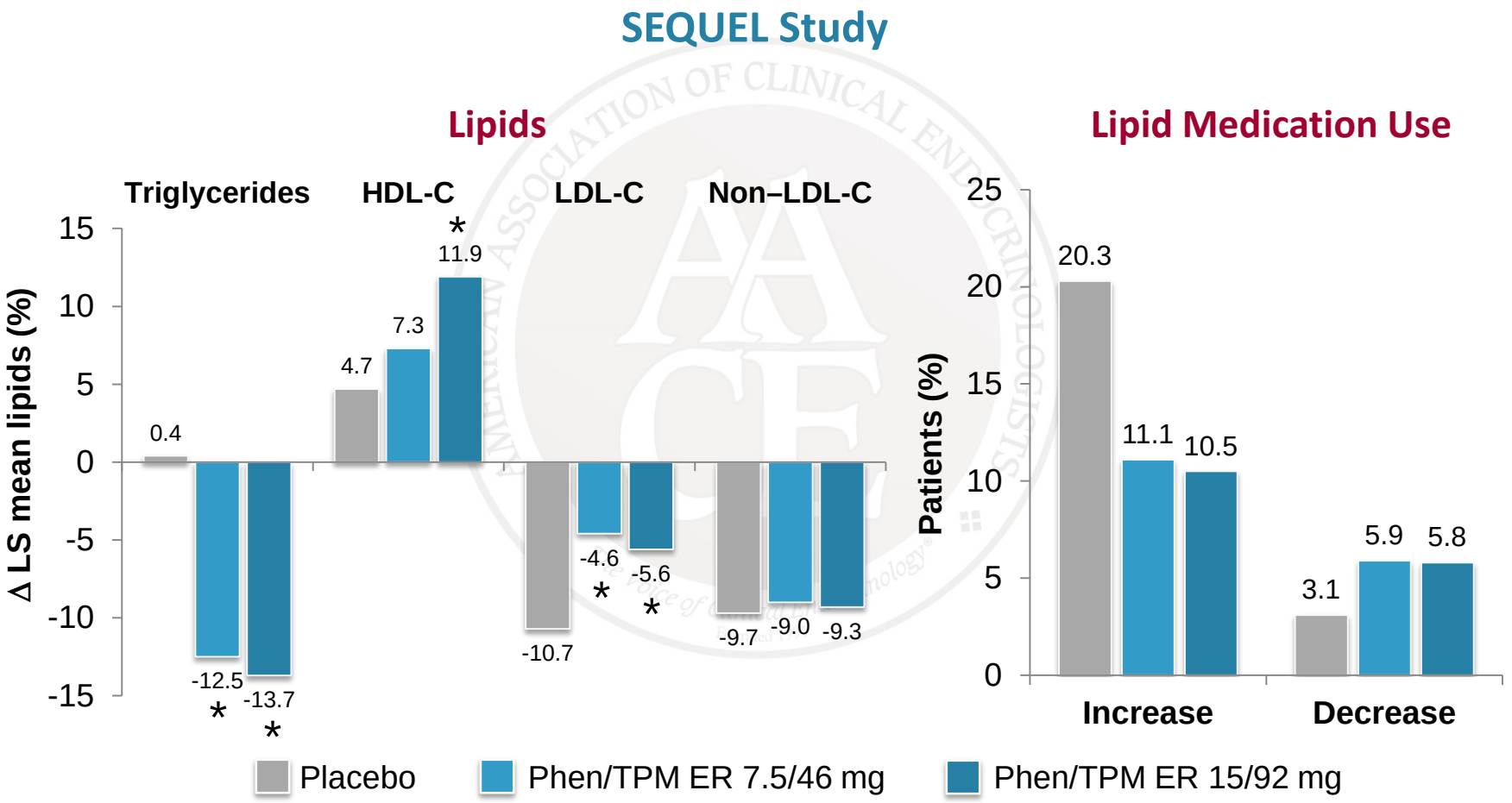
Effect of Phentermine/Topiramate ER on Hypertension



BP = blood pressure; Phen/TPM ER = phentermine/topiramate extended release.

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

Effect of Phentermine/Topiramate ER on Dyslipidemia



*P<0.01 vs placebo.

Phen/TPM ER, phentermine/topiramate extended release.

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

Selected Phentermine/Topiramate ER Adverse Events

Event occurring in ≥5% of patients and more frequently than with placebo, %	Phentermine/Topiramate			Placebo (N=1561)
	3.75 mg/23 mg (N=240)	7.5 mg/46 mg (N=498)	15 mg/92 mg (N=1580)	
Paresthesia	**4.2**	**13.7**	**19.9**	**1.9**
Dry mouth	**6.7**	**13.5**	**19.1**	**2.8**
Constipation	7.9	15.1	16.1	6.1
Upper respiratory tract infection	15.8	12.2	13.5	12.8
Headache	10.4	7.0	10.6	9.3
Nasopharyngitis	12.5	10.6	9.4	8.0
Dysgeusia	**1.3**	**7.4**	**9.4**	**1.1**
Insomnia	**5.0**	**5.8**	**9.4**	**4.7**
Dizziness	**2.9**	**7.2**	**8.6**	**3.4**
Sinusitis	7.5	6.8	7.8	6.3
Nausea	5.8	3.6	7.2	4.4
Back pain	5.4	5.6	6.6	5.1
Fatigue	5.0	4.4	5.9	4.3
Diarrhea	5.0	6.4	5.6	4.9
Bronchitis	6.7	4.4	5.4	4.2
Vision blurred	6.3	4.0	5.4	3.5
Urinary tract infection	3.3	5.2	5.2	3.6
Influenza	7.5	4.6	4.4	4.4

Qsymia prescribing information. Mountain View, CA: Vivus, Inc.; 2012.

Naltrexone/Bupropion SR

Mechanism of Action

- Naltrexone: opioid receptor antagonist
- Bupropion: norepinephrine-dopamine reuptake inhibitor

Dosing

- Titrated to 2 tablets twice a day
  - Each tablet contains naltrexone 8 mg/bupropion 90 mg

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m^2
  - BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia
    - Other

See prescribing information for specific instructions

T2D = type 2 diabetes.

Contrave prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

Naltrexone/Bupropion SR: Summary of Warnings and Contraindications

Contraindications

- Uncontrolled hypertension
- Seizures, anorexia, or discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- Chronic opioid use
- Use of other bupropion products or monoamine oxidase inhibitors
- Pregnancy

Warnings

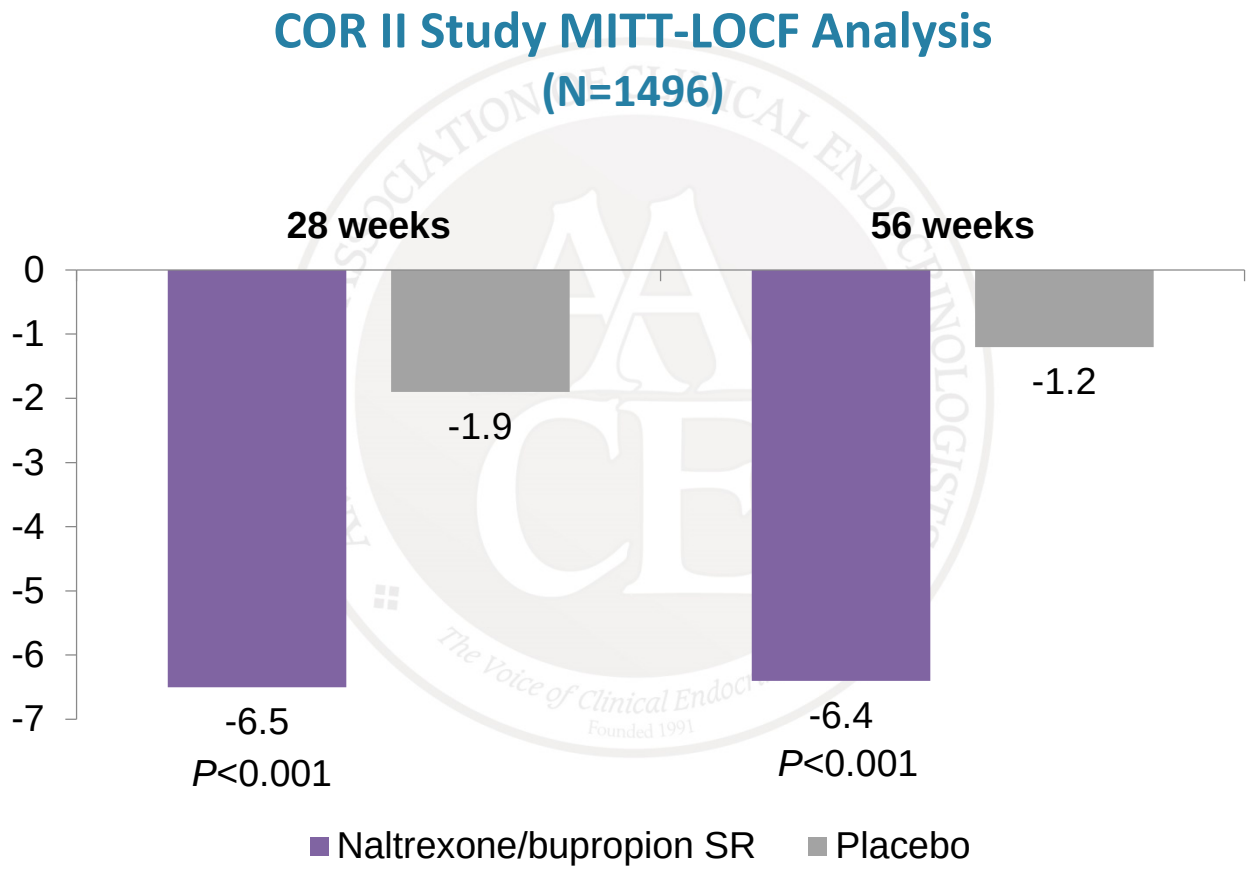
- Suicidal behavior and ideation (black box warning)
- Seizure
- Increased blood pressure and heart rate
- Hepatotoxicity
- Angle-closure glaucoma

Adverse Effects

- GI: nausea, vomiting, constipation, diarrhea
- Headache, insomnia
- Dry mouth

Contrave prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

Effect of Naltrexone/Bupropion SR on Body Weight



COR II = CONTRAVE Obesity Research II; LOCF = last observation carried forward; MITT = modified intent to treat; SR = sustained release.

Apovian C, et al. *Obesity (Silver Spring)*. 2013;21:935-943.

Effect of Naltrexone/Bupropion SR on Cardiometabolic Risk Markers

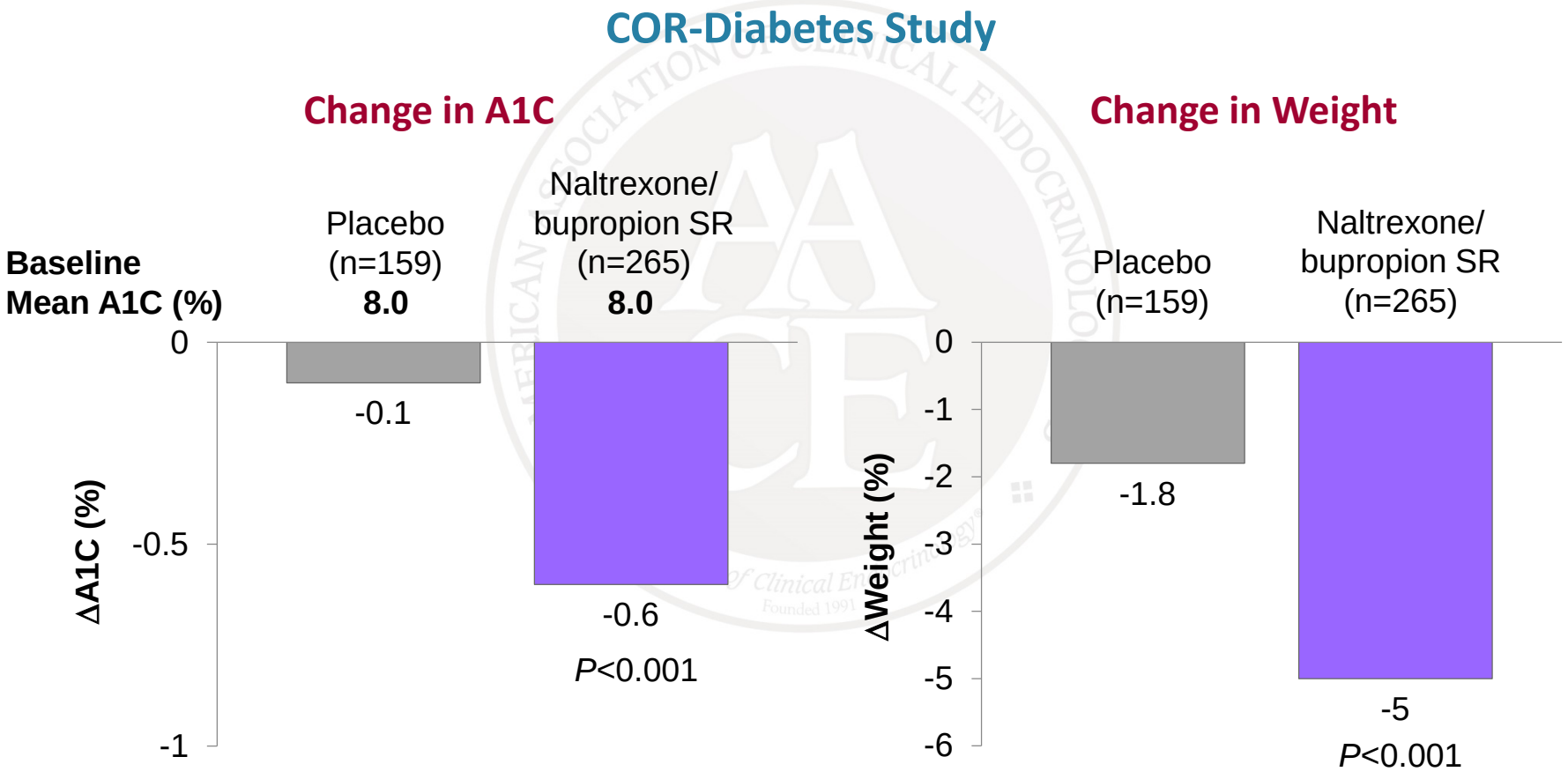
Risk Factors (Mean % Weight Loss)	Naltrexone/ Bupropion SR (6.4%)		P value*
Systolic BP, mmHg	↑	0.6	0.039
Diastolic BP, mmHg	↑	0.4	NS
Triglycerides, %	↓	-9.8	<0.001
LDL-C, %	↓	-6.2	0.008
HDL-C, %	↑	3.6	<0.001
hsCRP, mg/L	↓	-28.8	<0.001
FBG, mg/dL	↓	-2.8	NS

**P* value vs placebo.

BP, blood pressure; COR II, CONTRAVE Obesity Research II; FBG, fasting blood glucose; SR, sustained release.

Apovian C, et al. *Obesity (Silver Spring)*. 2013;21:935-943.

Effect of Naltrexone/Bupropion SR on Glycemia in Type 2 Diabetes



COR = CONTRAVE Obesity Research; LOCF = last observation carried forward; MITT = modified intent to treat; SR, sustained release.

Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

Naltrexone/Bupropion SR Adverse Events

Event occurring in ≥5% of patients and more frequently than with placebo, %	Naltrexone/Bupropion SR 32 mg/360 mg (N=2545)	Placebo (N=1515)
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
Diarrhea	7.1	5.2

Contrave prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.

Liraglutide (for Obesity)

Mechanism of Action

- GLP-1 receptor agonist

Dosing

- Titrate to 3 mg once daily subcutaneous injection

Indications

- Adjunct to diet and exercise in patients with
  - BMI ≥30 kg/m2
  - BMI ≥27 kg/m2 with ≥1 weight-related comorbidity
    - Hypertension
    - T2D
    - Dyslipidemia
    - Other

See prescribing information for specific instructions

T2D = type 2 diabetes.

Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.

Liraglutide (for Obesity): Summary of Warnings and Contraindications

Contraindications

- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Pregnancy

Warnings

- Thyroid tumors seen in rodent models
- Acute pancreatitis or gallbladder disease
- Hypoglycemia if used with sulfonylurea or glinide (in patients with T2D)
- Heart rate increase
- Renal impairment
- Suicidal behavior or ideation
- Do not use with insulin or to treat T2D

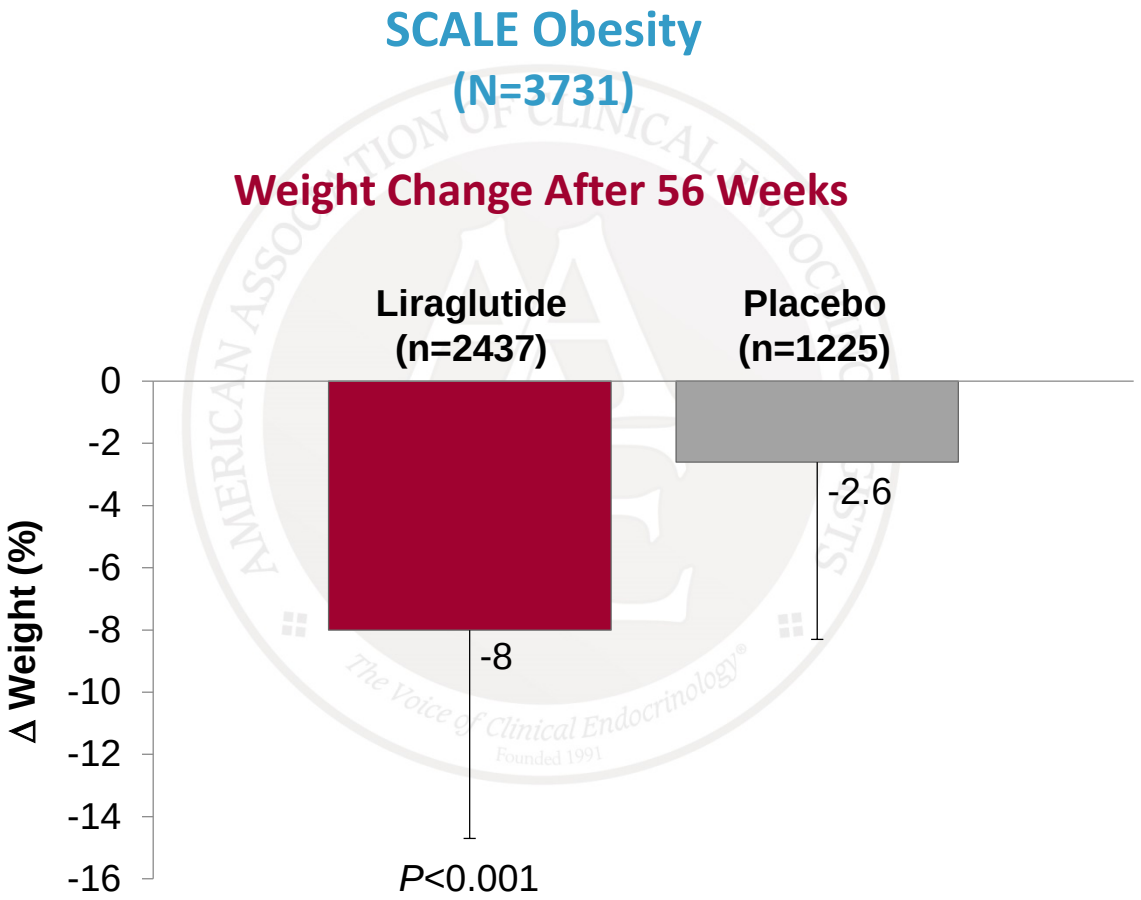
Adverse Effects

- GI: nausea, diarrhea, constipation, vomiting, decreased appetite, dyspepsia, abdominal pain
- Headache, fatigue
- Dizziness
- Increased lipase

T2D = type 2 diabetes.

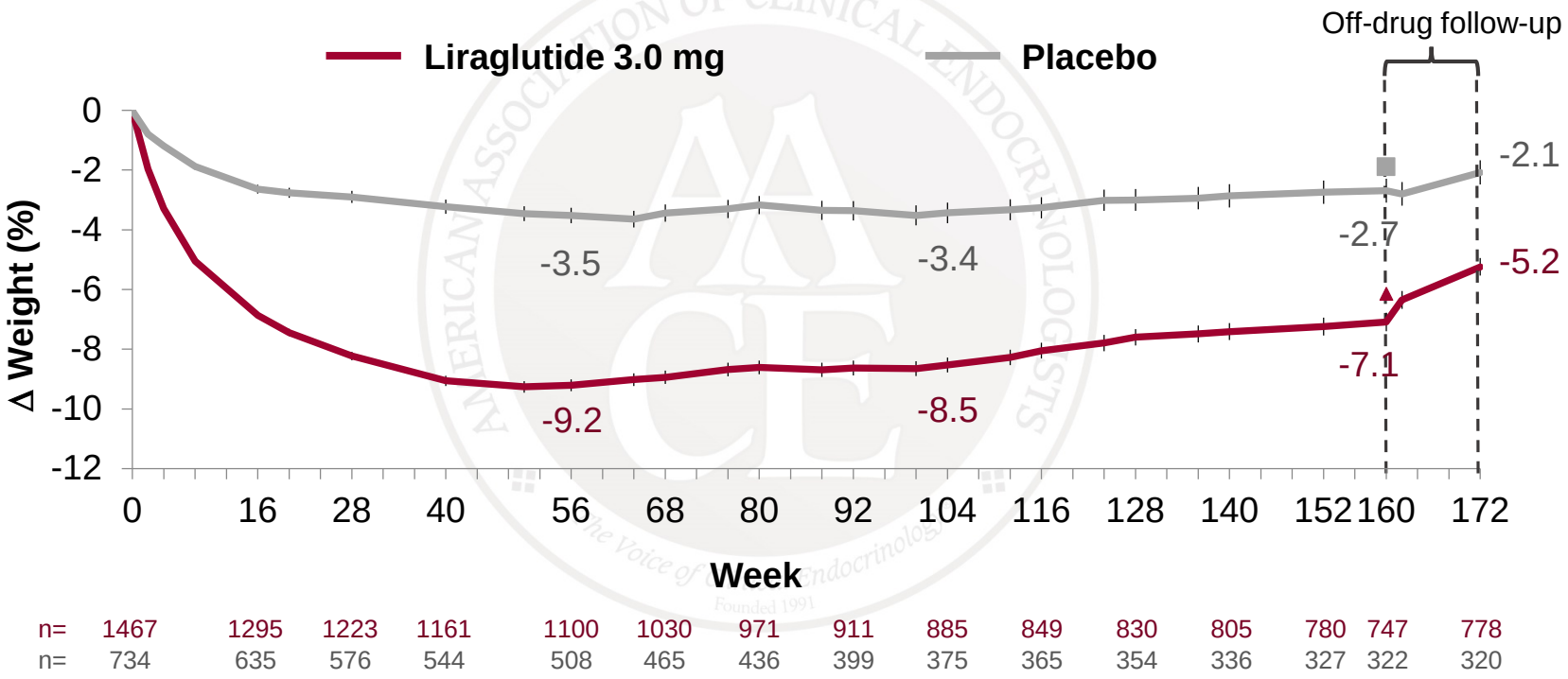
Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.

Effects of Liraglutide in Obese Patients



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

Effects of Liraglutide on Body Weight Over 3 Years



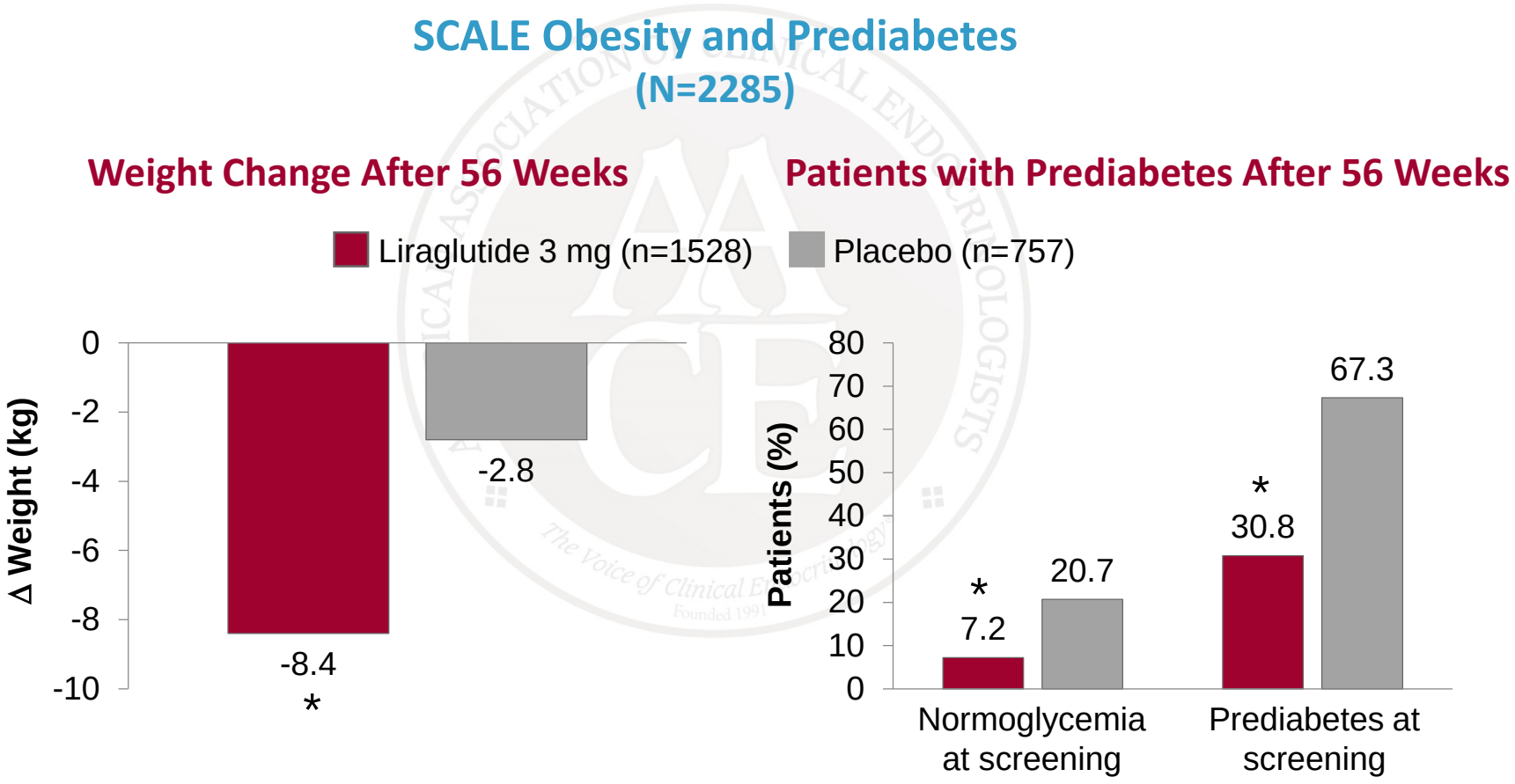
All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min/week increased physical activity.

Full analysis set, fasting visit data only. Line graphs are observed means (±SE). Points (sqaure, triangle) are observed means with last observation carried forward (LOCF).

Fujioka K, et al. ENDO 2016, April 1-4, 2016; Abstract 24365.

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=2285)



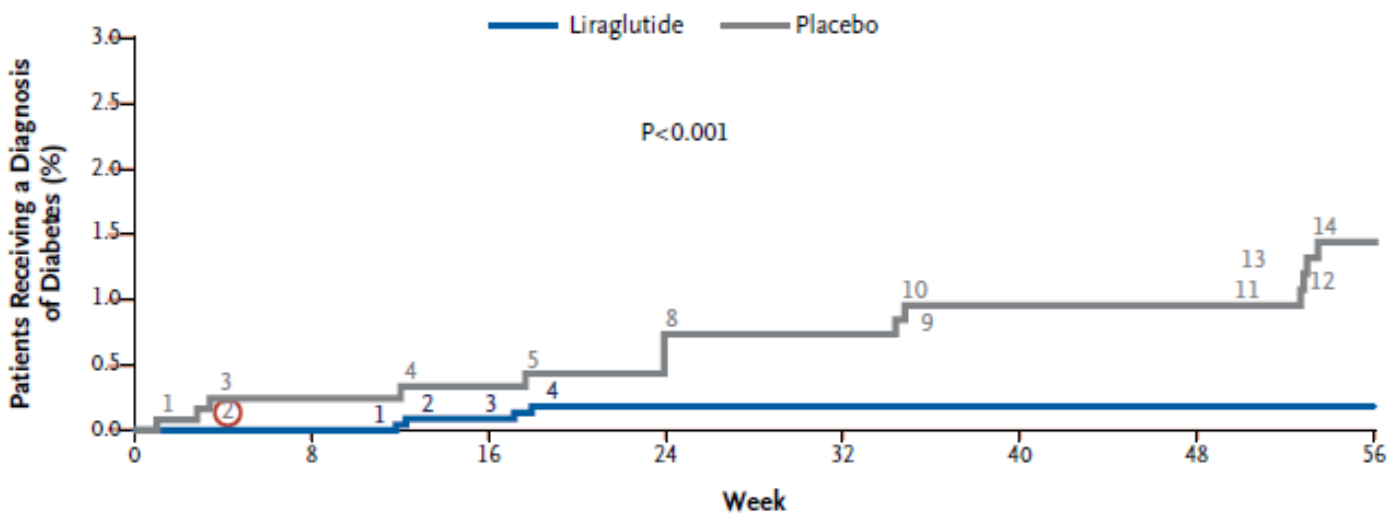
**P*<0.001 vs placebo.

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

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3731)

Cumulative Incidence of Type 2 Diabetes

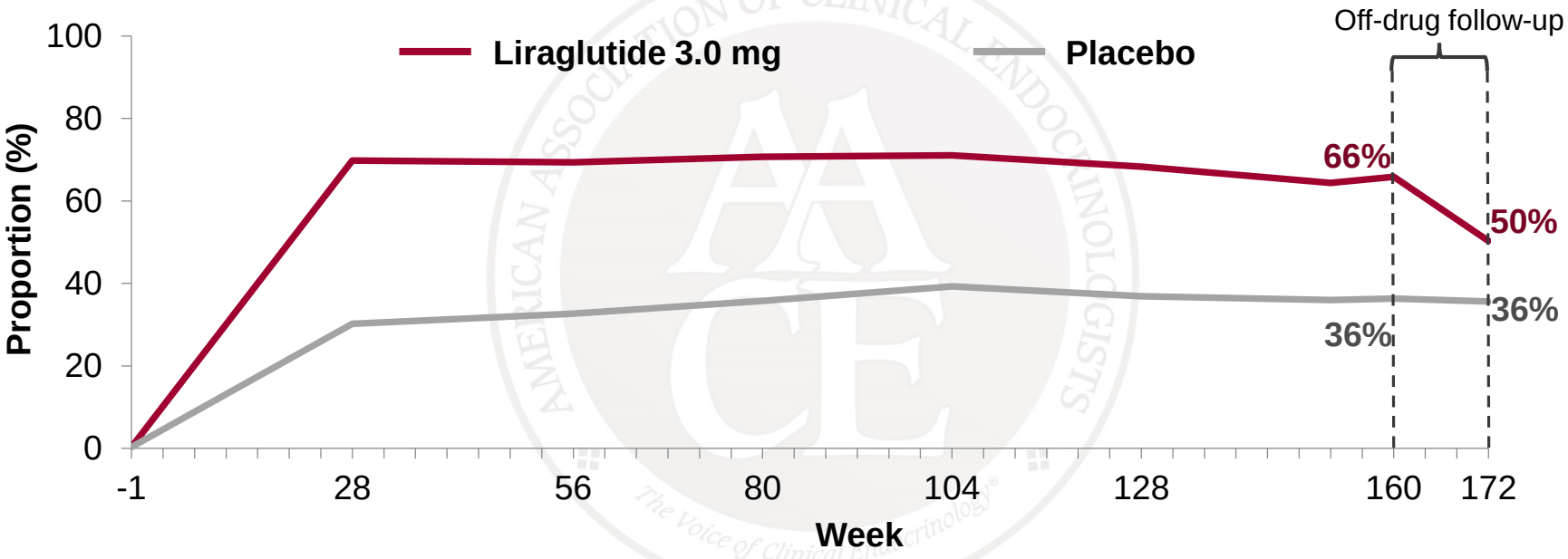


Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)

Liraglutide	1 (2219)	2 (2210)	3 (2137)	4 (2130)								
Placebo	1 (1225)	2 (1210)	3 (1204)	4 (1096)	5 (1035)	8 (984)	9 (911)	10 (908)	11 (818)	12(817)	13 (816)	14 (813)

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

Regression to Normoglycemia Among Patients with Prediabetes Treated With Liraglutide Over 3 Years



Likelihood of normoglycemia >3X higher with liraglutide 3 mg
OR = 3.6 (95% CI, 3.0 to 4.4); *P*<0.0001; NNT = ~3

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min./week increased physical activity.

Full analysis set. Statistical analysis is logistic regression.

CI = confidence interval; NNT = number needed to treat; OR = odds ratio.

Fujioka K, et al. ENDO 2016, April 1-4, 2016; Abstract 24365.

Effect of Liraglutide 3 mg on Cardiometabolic Risk Markers

SCALE Study

Risk Factors (Mean % Weight Loss)	Liraglutide 3 mg* (4.4%)	P value
Systolic BP, mmHg	↓ -2.8	<0.0001
Diastolic BP, mmHg	↓ -0.6	NS
Triglycerides, %	↓ -6.0	0.0003
Total cholesterol, %	↓ -2.0	0.03
LDL-C, %	↓ -0.9	NS
HDL-C, %	↑ 0.9	NS
VLDL-C, %	↓ -6.0	0.0002
FFAs, %	↓ -5.0	0.03
Waist circumference, cm	↓ -3.5	<0.0001

*Placebo-adjusted values; *P* values represent comparisons to placebo (ANCOVA).

Full analysis set of 3-year data.

Fujioka et al. ENDO 2016, 1–4 April 2016, Abstract 24365.

Liraglutide (for Obesity) Adverse Events

Event occurring in ≥5% of patients and more frequently than with placebo, %	Liraglutide 3 mg (N=3384)	Placebo (N=1941)
Nausea	39.3	13.8
Headache	13.6	12.6
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Decreased appetite	10.0	2.3
Dyspepsia	9.6	2.7
Dizziness	6.9	5.0
Fatigue	7.5	4.6
Abdominal pain	5.4	3.1
Increased lipase	5.3	2.2
Upper abdominal pain	5.1	2.7

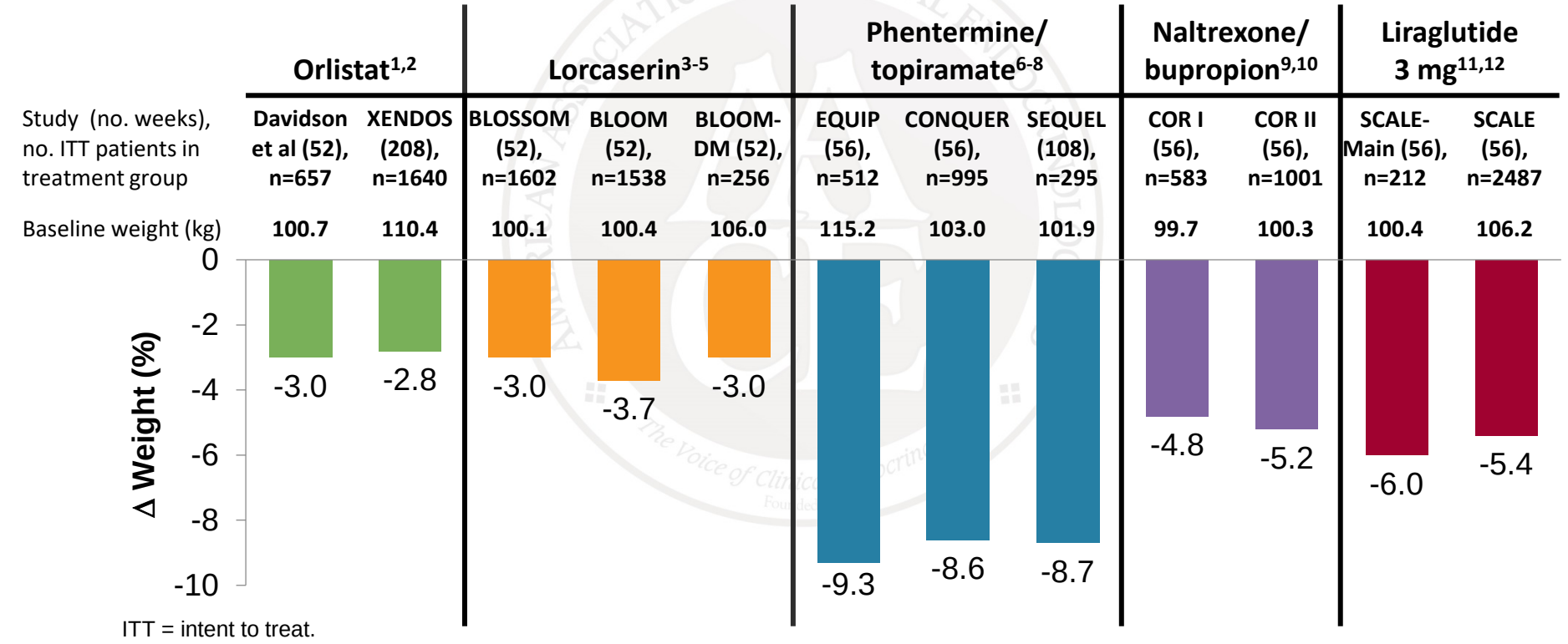
Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.

Weight Loss Medications

Efficacy Considerations

Comparison of Weight-Loss Medications Approved for Long-Term Use

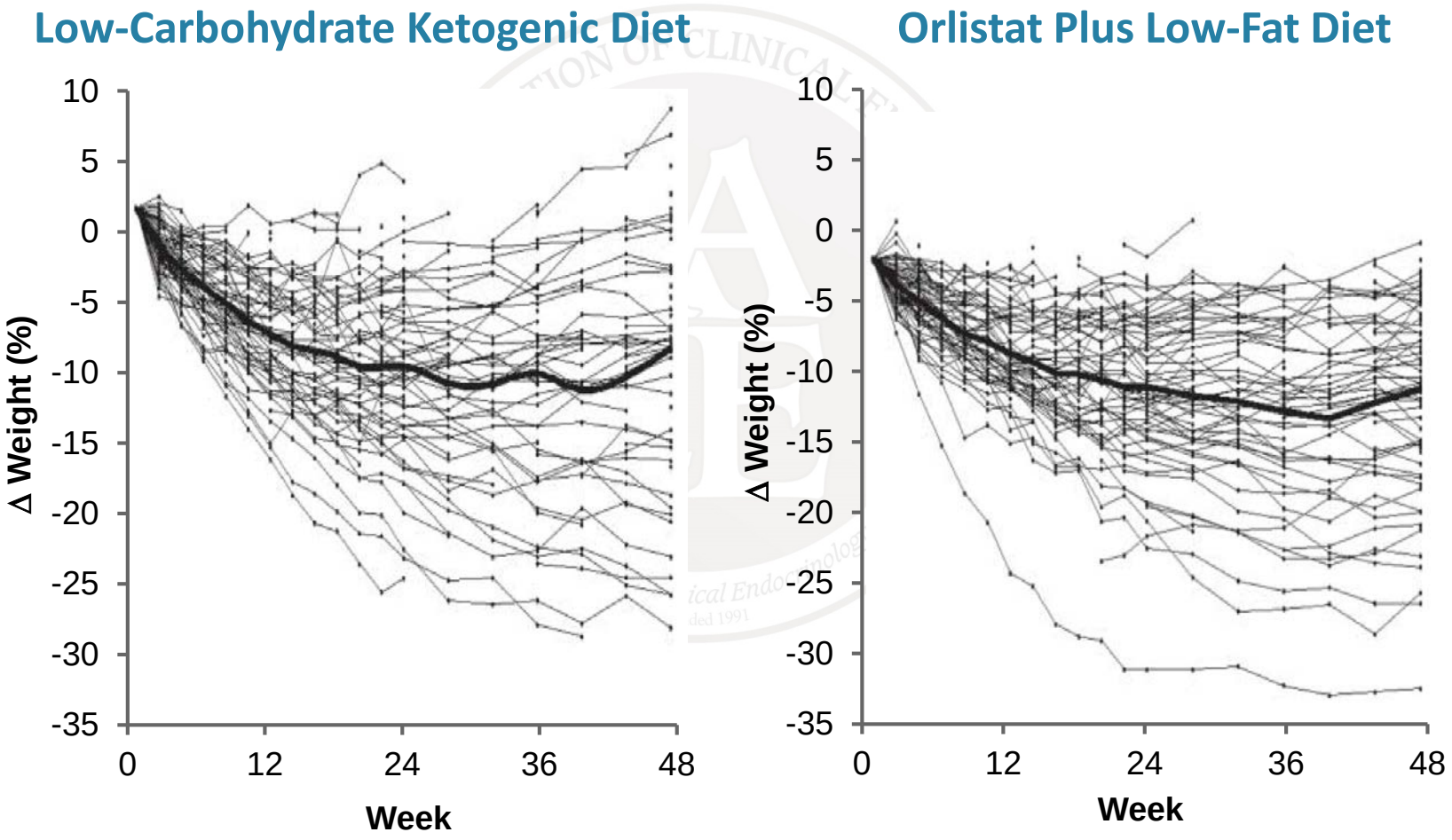
Placebo-Subtracted Changes from Baseline, Highest Approved Dose (Not Head-to-Head Trials)



ITT = intent to treat.

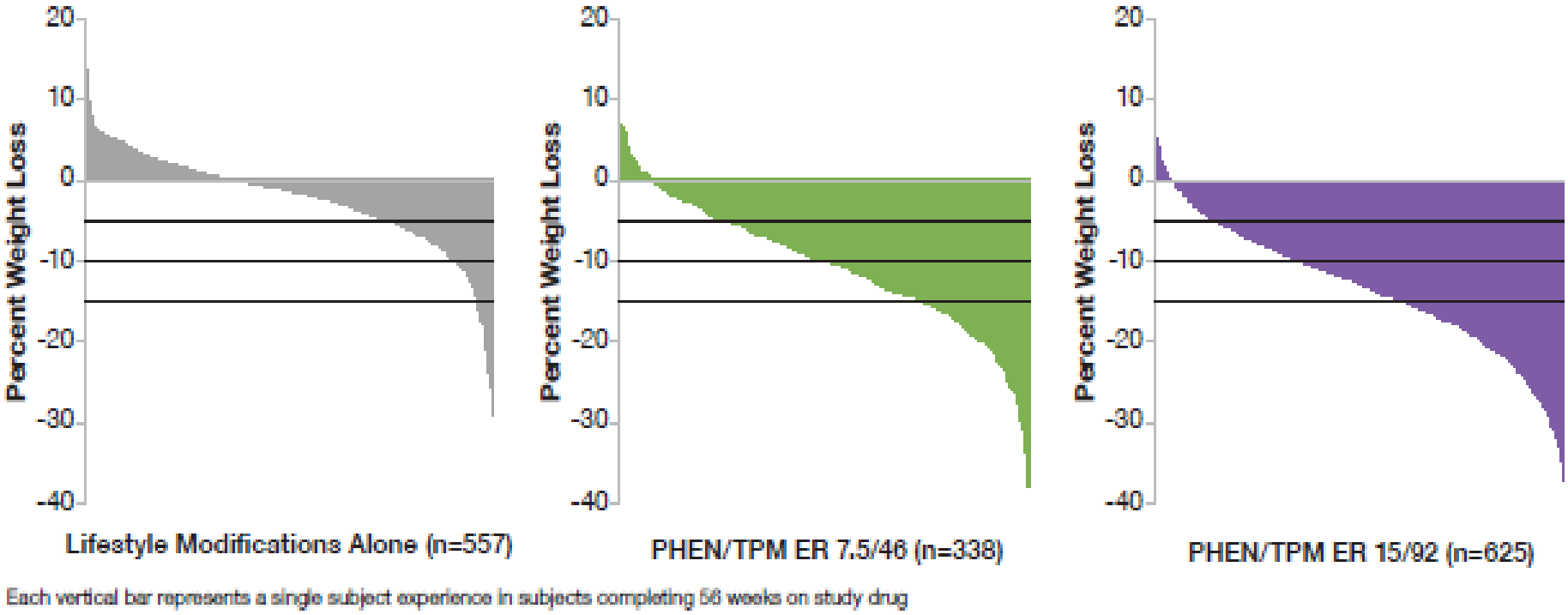
1. Davidson MH, et al. *JAMA*. 1999;281:235-242. 2. Torgerson JS, et al. *Diabetes Care.* 2004;27:155-161. 3. Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077. 4. Smith SR, et al. *N Engl J Med*. 2010;363:245-256. 5. O'Neil PM, et al. *Obesity*. 2012;20:1426-1436. 6. Allison DB, et al. *Obesity (Silver Spring).* 2012;20:330-342. 7. Gadde KM, et al. *Lancet*. 2011;377:1341-1352. 8. Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308. 9. Greenway FL, et al. *Lancet*. 2010;376:595-605. 10. Apovian CM, et al. *Obesity (Silver Spring)*. 2013;21:935–943. 11. Wadden TA, et al. *Int J Obes (Lond)*. 2013;37:1443-1451. 12. Pi-Sunyer X, et al. *N Engl J Med*. 2015;373:11-22.

Heterogeneity of Treatment Effect for Weight Loss



Yancy WS, et al. *Arch Intern Med.* 2010;170:136-145.

Variability in Weight Loss with Lifestyle Therapy and Phentermine/Topiramate ER

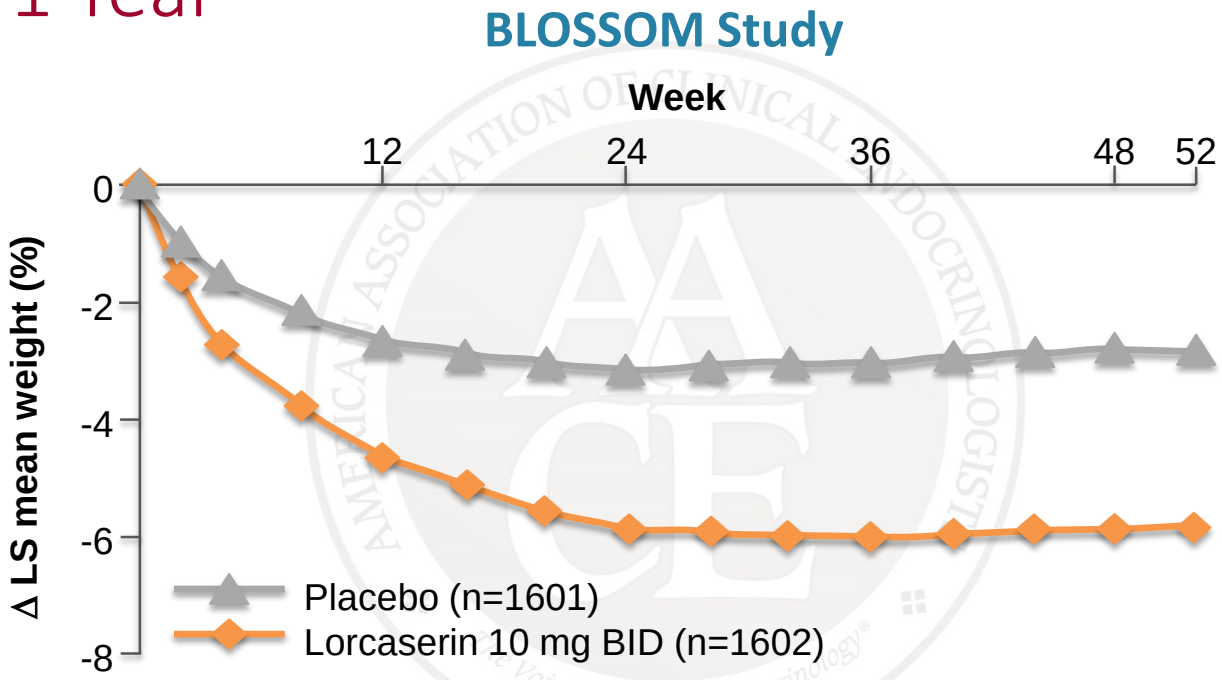


McCullough PA, et al. Poster AANP 2013.

Weight Loss Medications

Combination Therapy

Effect of Lorcaserin Combined With Intensive Lifestyle Therapy on Body Weight in Obese Adults Over 1 Year

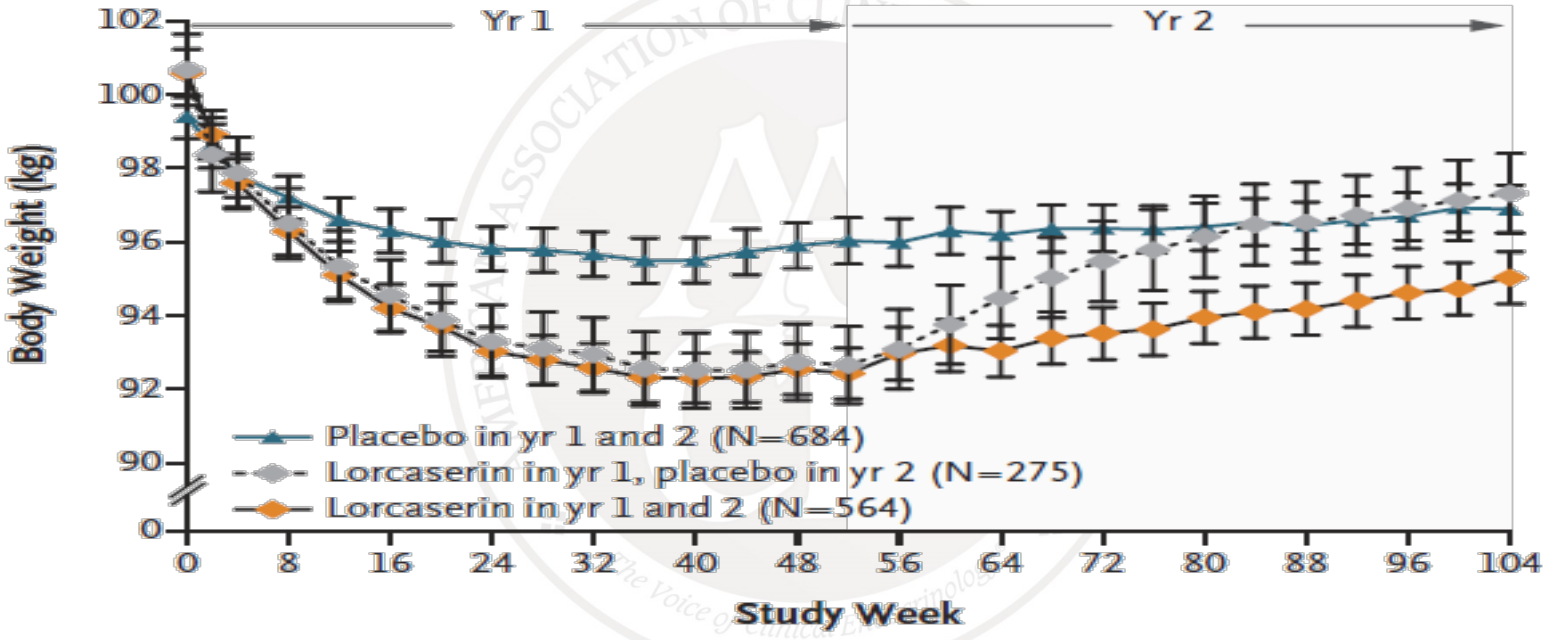


- Both the placebo and lorcaserin groups received intensive lifestyle intervention
  - Diet and exercise counseling at weeks 1, 2, 4, and monthly thereafter
  - Caloric intake 600 kcal below individual estimated energy requirements
  - 30 min moderate exercise per day

BID, twice daily; LS, least squares.

Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077.

Medication Amplifies Effects of Intensive Lifestyle Intervention



- Both the placebo and lorcaserin groups received intensive lifestyle intervention
  - Diet and exercise counseling at weeks 1, 2, 4, and monthly thereafter
  - Caloric intake 600 kcal below individual estimated energy requirements
  - 30 min moderate exercise per day

Smith SR, et al. *N Engl J Med*. 2010;363:245-256. O'Neil PM, et al. *Obesity*. 2012;20:1426-1436.

Combining Weight Loss Medications

- Combination therapy for obesity
  - Is logical
  - May target different pathways, potentially resulting in synergistic effects
- Combinations of FDA-approved weight-loss medications should only be used in a manner approved by the FDA or when sufficient safety and efficacy data are available to assure informed judgment regarding a favorable benefit-to-risk ratio

There are currently no long-term studies of weight loss drugs in non–FDA-approved combinations

Garvey TW, et al. *Endocr Pract*. 2016;22(suppl 3):1-205.

Weight Loss Medications

Individualizing Therapy According to Comorbidities

PREFERRED WEIGHT-LOSS MEDICATIONS: INDIVIDUALIZATION OF THERAPY

KEY: PREFERRED DRUG | USE WITH CAUTION | AVOID

CLINICAL CHARACTERISTICS OR COEXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	**Lorcaserin**	**Phentermine/ topiramate ER**	**Naltrexone ER/ bupropion ER**	**Liraglutide 3 mg**
Diabetes Prevention (metabolic syndrome, prediabetes)			Insufficient data for T2DM prevention		Insufficient data for T2DM prevention	
Type 2 Diabetes Mellitus						
Hypertension				Monitor heart rate	Monitor BP and heart rate. Contraindicated in uncontrolled HTN	Monitor heart rate
Cardiovascular Disease	**CAD**			Monitor heart rate	Monitor heart rate, BP	Monitor heart rate
	Arrhythmia		Monitor for bradycardia	Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Chronic Kidney Disease	**Mild (50–79 mL/min)**					
	Moderate (30–49 mL/min)			Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg bid	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis		Calcium oxalate stones		Calcium phosphate stones		
Hepatic Impairment	**Mild-Moderate (Child-Pugh 5–9)**	Watch for cholelithiasis	Hepatic metabolism of drug	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data Avoid combinations of serotonergic drugs	Avoid maximum dose: 15 mg/92 mg per day	Insufficient safety data Avoid in adolescents and young adults	

CLINICAL CHARACTERISTICS OR COEXISTING DISEASES		MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT				
		Orlistat	**Lorcaserin**	**Phentermine/ topiramate ER**	**Naltrexone ER/ bupropion ER**	**Liraglutide 3 mg**
Anxiety				Avoid max dose: 15 mg/92 mg per day		
Psychoses		Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Binge Eating Disorder			Insufficient data. Possible benefit based on reduction in food cravings	Insufficient data. Possible benefit based on studies with topiramate	Insufficient data. Possible benefit based on studies with bupropion Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder				If discontinue at dose of 15 mg/92 mg, taper slowly	Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opioid Use					Will antagonize opioids and opiates	
Women of Reproductive Potential	**Pregnancy**	Use contraception and discontinue orlistat should pregnancy occur	Use contraception and discontinue lorcaserin should pregnancy occur	Use contraception and discontinue phentermine/topiramate should pregnancy occur (perform monthly pregnacy checks to identify early pregnancy)	Use contraception and discontinue naltrexone ER/bupropion ER should pregnancy occur	Use contraception and discontinue liraglutide 3mg should pregnancy occur
	Breast-feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age ≥65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Insufficient data. Topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Post-Bariatric Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 – 3.0 mg/day

* Use medications only with clear health-related goals in mind; assess patient for osteoporosis and sarcopenia.

Abbreviations: BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; T2DM = Type 2 Diabetes Mellitus.

Weight Loss Medications

Summary

Summary

- Older obesity pharmacotherapies are limited by tolerability and dependence issues and are approved only for short-term use (≤12 weeks)
- Newer weight loss agents are typically better tolerated, have better safety profiles, and are approved for chronic weight management including weight maintenance
- Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone